MONITORING AND CONTROLLING BLOOD PRESSURE AFTER STROKE AND TRANSIENT ISCHAEMIC ATTACK



Iain McGurgan

St. Hilda's College

This dissertation is submitted for the degree of

Doctor of Philosophy

Trinity Term 2021

To Mam, Dad, Sarah & Lalis,
for their endless love and
encouragement

DECLARATION

This dissertation is of my own composition, and the research contained herein is my own original work, performed while I was a full-time student at the University of Oxford. It has not been previously submitted, in part or whole, to any university or institution for any degree, diploma, or other qualification.

ABSTRACT

Monitoring and controlling blood pressure after stroke and transient ischaemic attack

Iain McGurgan, St Hilda's College, University of Oxford

Submitted for the degree of D.Phil., Trinity Term, 2021

Despite advances in treatment, the risk of recurrent vascular events after stroke and transient ischaemic attack (TIA) remains too high. Blood pressure is the strongest modifiable risk factor, but it is frequently undertreated. Stroke guidelines recommend a target blood pressure of <130/80 mmHg to prevent recurrence, but there remains much uncertainty about in whom, when, and how this should be achieved.

This thesis aims to investigate how best blood pressure should be measured, monitored, and controlled after TIA, ischaemic stroke, and intracerebral haemorrhage, using observational and randomised controlled trial evidence of a strategy of telemetric home blood pressure monitoring-guided antihypertensive treatment.

I have found that the method of blood pressure assessment typically used in current practice, i.e. the doctor or nurse measuring blood pressure in the clinic, is inaccurate for diagnosing high blood pressure. A few days of home blood pressure monitoring immediately after someone has a stroke or TIA, and ideally repeated around the time of the one-month follow-up assessment, is much more accurate. This identifies people whose blood pressure puts them at risk of recurrent vascular events and, therefore, who should receive blood pressure-lowering medication. I also showed that home blood pressure monitoring can be used to guide treatment, and achieves bigger reductions in blood pressure than usual care. However, stopping blood pressure-lowering medications in the long-term after TIA and stroke is a problem, and I have found that this has a bad prognosis in people who had their high blood pressure well controlled initially, so some form of ongoing blood pressure monitoring at home is probably required.

ACKNOWLEDGEMENTS

I would like to offer my utmost thanks to my supervisor, Professor Peter Rothwell, for his tremendous mentorship, both academic and clinical, and for generously supporting me both in my pursuit of becoming a clinical academic and in my extracurricular endeavours. His unique ability to uncover insightful and important research questions in just about any conversation we have had means that I depart with a to-do list of ideas for further research longer than this thesis.

I am also immensely grateful to Professor Robert Clarke of the Nuffield Department of Population Health, University of Oxford, for his guidance and encouragement to follow a path of epidemiological research, to Professor Chris McGuigan of University College Dublin for his instrumental mentorship, and to the Association of British Neurologists, the Stroke Association, and The Sobell Foundation for the clinical research fellowship that funded three years of my studies.

Having witnessed three generations of clinical fellows come and go in OXVASC, I have almost mistakenly begun to consider myself as some kind of group elder, when in fact the work on the COMMIT study culminating in this thesis predates my arrival by over a decade. I would like to thank, in particular, Louise Silver, Linxin Li, Fiona Cuthbertson, Michelle Wilson, Josephine Edens, Gary Lau, Alastair Webb, Nicola Lovett, Nicola Paul, Urs Fischer, and Brett Nicolle (and his colleagues at OBS Medical Ltd.). Rose Wharton, who contributed to the statistical analysis at the beginning of the COMMIT study, sadly died before seeing it completed, and has been sorely missed. For the PROHIBIT-ICH trial, my gratitude goes to Michelle Wilson, Josephine Edens, Louise Silver, Emily-Rose Vaughan-Fowler, and Bethan Reade, and to David Werring, Jo Hornby, and Maja Dabagh of UCL Queen Square Institute of Neurology, as well as to the research teams at each of the sixteen trial sites. I would also like to thank all of my colleagues at the Wolfson Centre for Prevention of Stroke and Dementia for their invaluable help, including but not limited to the administrators, data managers, statisticians, building managers, and research fellows, nurses, and therapists. In particular, I would like to thank Linxin Li, Ramon Luengo-Fernandez, Rob Hurford, Dearbhla Kelly, Aubretia McColl, Gary Lau, Cyrus Daruwalla, Louise Silver, and Joanna Moschandreas for their kind support and friendship.

Finally, I appreciate the generosity of all the Oxford Vascular Study and PROHIBIT-ICH trial volunteers and their families, who selflessly dedicated their time during what was a difficult and often frightening period in their lives to participate in research to advance the prevention of stroke in others.

'The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it.'

Professor John Hay, BMJ, 1931[1]

Table of Contents

DECLARATION ..... **iii**
ABSTRACT ..... **iv**
ACKNOWLEDGEMENTS ..... **v**
Table of Contents ..... **vii**
Glossary ..... **x**
List of Tables ..... **xiii**
List of Figures ..... **xviii**
Chapter 1: Introduction **1**

1.1 Blood pressure and the risk of recurrent stroke 2
1.1.1 The burden of the problem 2
1.1.2 Blood pressure lowering to reduce the risk of stroke recurrence 3
1.2 Treatment considerations in TIA and ischaemic stroke 6
1.2.1 Which patients should start antihypertensive treatment? 6
1.2.2 How soon after TIA/stroke should antihypertensive treatment be started? 7
1.2.3 What target blood pressure should we aim for? 9
1.3 Treatment considerations in intracerebral haemorrhage 9
1.3.1 The burden of ICH 12
1.3.2 Blood pressure and the risk of recurrent ICH 12
1.3.3 How soon after ICH should antihypertensive treatment be started? 13
1.3.4 Evidence for intensive and sustained blood pressure control after ICH 14
1.4 Practicalities of blood pressure management for secondary prevention after TIA, ischaemic stroke, and ICH 16
1.4.1 Choice of antihypertensive agents 16
1.4.2 Time of day of blood pressure-lowering drug dosing 17
1.4.3 Is there a role for fixed low-dose combination therapy? 18
1.4.4 Targeting blood pressure variability in addition to mean blood pressure 20
1.5 How should blood pressure be assessed and monitored? 22
1.5.1 Office blood pressure measurement 22
1.5.2 Automated office blood pressure measurement 22
1.5.3 Ambulatory blood pressure monitoring 23
1.5.4 Home blood pressure monitoring 24
1.5.5 Which measurement modality is superior? 24
1.5.6 Blood pressure monitoring to guide long-term control 25
1.6 Blood pressure-lowering treatment adherence 27
1.7 The Oxford Vascular Study 29
1.7.1 Study population 29
1.7.2 Case ascertainment and follow-up 29
1.7.3 Definitions of stroke and TIA in OXVASC 32
1.7.4 Diagnostic work-up, aetiological classification, and management of TIA and stroke in OXVASC 32
1.7.5 Patient consent and approval 34
1.8 Telemetric home blood pressure monitoring methodology 35
1.9 Thesis aims 36
1.9.1 Observational data 36

1.9.2 Clinical trial data 37
1.10 Tables 39
1.11 Figures 54

Chapter 2: Early assessment of blood pressure after TIA and minor stroke (Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study) 60

2.1 Abstract 61
2.2 Introduction 63
2.3 Methods 65
2.3.1 Study design and participants 65
2.3.2 Procedures 65
2.3.3 Statistical analysis 67
2.4 Results 69
2.5 Discussion 73
2.6 Tables 77
2.7 Figures 90

Chapter 3: Office, ambulatory, and telemetric home blood pressure monitoring: comparative predictive value for vascular events in a high-risk, treated population (Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study) 104

3.1 Abstract 105
3.2 Introduction 107
3.3 Methods 109
3.3.1 Study design and participants 109
3.3.2 Procedures 109
3.3.3 Statistical analysis 110
3.4 Results 114
3.5 Discussion 119
3.6 Tables 123
3.7 Figures 139

Chapter 4: Prognostic value of residual hypertension one month after TIA and stroke: clinic versus home-telemetric and ambulatory blood pressure monitoring (Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study) 154

4.1 Abstract 155
4.2 Introduction 157
4.3 Methods 159
4.3.1 Study design and participants 159
4.3.2 Procedures 159
4.3.3 Statistical analysis 161
4.4 Results 163
4.5 Discussion 167
4.6 Tables 171
4.7 Figures 184

Chapter 5: Home telemonitoring-guided blood pressure control after TIA and stroke: Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study 192

5.1 Abstract 193
5.2 Introduction 195

5.3 Methods 197
5.3.1 Study design and participants 197
5.3.2 Procedures 197
5.3.3 Statistical analysis: 199
5.4 Results 201
5.5 Discussion 206
5.6 Tables 210
5.7 Figures 219
Chapter 6: PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage (PROHIBIT-ICH): an interim report of a pilot randomised trial of home telemetry-guided treatment 229
6.1 Abstract 230
6.2 Introduction 232
6.3 Methods 234
6.3.1 Study design and participants 234
6.3.2 Approvals 235
6.3.3 Randomisation 235
6.3.4 Procedures and intervention 235
6.3.5 Outcomes 238
6.3.6 Statistical analysis 239
6.4 Results 240
6.5 Discussion 243
6.6 Tables 246
6.7 Figures 254
Chapter 7: Durability of telemonitoring-guided blood pressure control after TIA and stroke: long-term treatment adherence and recurrent vascular events (Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study) 257
7.1 Abstract 258
7.2 Introduction 260
7.3 Methods 262
7.3.1 Study design and participants 262
7.3.2 Procedures 262
7.3.3 Statistical analysis 264
7.4 Results 267
7.5 Discussion 274
7.6 Tables 280
7.7 Figures 293
Chapter 8: Conclusions and future directions 304
8.1 Introduction 305
8.2 Key findings and implications for clinical practice 306
8.3 Future research directions 308
8.3.1 Acute phase blood pressure after TIA and minor stroke 308
8.3.2 Clinical outcomes in COMMIT and PROHIBIT-ICH 310
8.3.3 Target blood pressure in stroke secondary prevention; evidence for a J-curve 311
8.4 Figures 316
References 321
Appendix 342

Glossary

ABPM	Ambulatory blood pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE-I	Angiotensin-converting-enzyme inhibitor
AHA/ ASA	American heart association/ American stroke association
AOBP	Automated office blood pressure
ARB	Angiotensin II receptor antagonist/blocker
ARV	Average real variability
A&E	Accident & Emergency
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CCF	Congestive cardiac failure
CE	Cardioembolic
CI	Confidence interval
COMMIT	Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment
CSVD	Cerebral small vessel disease
CT	Computed tomography
CTA	CT angiography
CV	Coefficient of variation
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DWI	Diffusion-weighted imaging
ECG	Electrocardiogram

ESC/ESH	European Society of Cardiology / European Society of Hypertension
HBPM	Home blood pressure monitoring
HR	Hazard ratio
HTN	Hypertension
ICD	International classification of disease
ICH	Intracerebral haemorrhage
IHD	Ischaemic heart disease
IQR	Interquartile range
ISH	International Society of Hypertension
LAD	Large artery disease
MAP	Mean arterial pressure
MI	Myocardial infarction
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MVE	Major vascular events
NASCET	North American symptomatic carotid endarterectomy trial
NHS	National health service
NICE	National institute for health and care excellence (UK)
NIHSS	National institutes of health stroke scale
OR	Odds ratio
OXVASC	Oxford vascular study
PP	Pulse pressure
PROGRESS	Perindopril protection against recurrent stroke study
PRoFESS	Prevention regimen for effectively avoiding second strokes
PROHIBIT-ICH	PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage
PVD	Peripheral vascular disease
QUARTET	Quadruple ultra-low-dose treatment for hypertension

RMSE	Root mean square error
SAH	Subarachnoid haemorrhage
SD	Standard deviation
SAMMPRIS	Stenting versus aggressive medical management therapy for intracranial arterial stenosis
SBP	Systolic blood pressure
SPRINT	Systolic blood pressure intervention trial
SPS3	Secondary Prevention of Small Subcortical Strokes Trial
TCD	Transcranial Doppler ultrasound
TIA	Transient ischaemic attack
TOAST	Trial of org 10172 in acute stroke treatment
TRIDENT	Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial
UPSTF	US Preventive Services Task Force
WHO	World health organisation
WMH	White matter hyperintensities

List of Tables

Table 1-1 Recommendations on BP lowering after TIA/stroke in major international clinical guidelines 40

Table 1-2 Main randomised controlled trials of BP lowering and secondary stroke prevention 44

Table 1-3 Use of various blood pressure measurement modalities in primary prevention hypertension guidelines 46

Table 1-4 Studies of ambulatory blood pressure monitoring in secondary stroke prevention 49

Table 1-5 Studies of home blood pressure monitoring in secondary stroke prevention 52

Table 2-1 Characteristics of participants according to antihypertensive treatment status at baseline 78

Table 2-2 Prevalence of masked and transient post-event hypertension using the first one and three days of telemetric HBPM 80

Table 2-3 Prevalence of transient post-event hypertension on 3-day HBPM by clinic systolic blood pressure, according to treatment status at baseline clinic (i.e. before HBPM readings were available) 81

Table 2-4 Diagnostic classification on HBPM by aetiology of TIA/stroke 82

Table 2-5 Clinic and pre-hospital BP, by BP diagnostic classification on HBPM 83

Table 2-6 Prevalence of masked and transient post-event hypertension, defined using pre-hospital/emergency department BP, using the first one and three days of telemetric HBPM 84

Table 2-7 Clinic and premorbid BP, by BP diagnostic classification on HBPM 85

Table 2-8 Prevalence of hypertension and risk of recurrent MVE (combined stroke, myocardial infarction, peripheral vascular events, vascular death) on clinic BP and HBPM 86

Table 2-9 The risk of vascular events associated with a diagnosis of hypertension (130/80) and for a 20/10 mmHg higher SBP and DBP, respectively, on HBPM and baseline clinic BP post-TIA/stroke 87

Table 2-10 The risk of recurrent MVE (combined stroke, myocardial infarction, peripheral vascular events, vascular death) associated with a diagnosis of residual hypertension on clinic BP and HBPM by different hypertension thresholds 88

Table 2-11 Risk of recurrent MVE (combined stroke, myocardial infarction, peripheral vascular events, vascular death) on clinic and HBPM SBP, by time to assessment ... 89

Table 3-1 Participant characteristics 123

Table 3-2 Characteristics of participants for whom there was disagreement between HBPM and awake ABPM in the diagnosis of hypertension 124

Table 3-3 Blood pressure and hypertension on HBPM, ABPM, and clinic BP based on antihypertensive use at one-month follow-up 126

Table 3-4 Baseline characteristics and BP of patients based on 24-hour ABPM dipping status 127

Table 3-5 Hypertension diagnostic categories based on clinic BP vs HBPM or awake ABPM 129

Table 3-6 Associations of masked and white-coat hypertension, defined by awake ABPM and HBPM, with vascular risk factors 130

Table 3-7 The risk of recurrent major vascular events in relation to clinic BP, HBPM, and ABPM one month after TIA/stroke 132

Table 3-8 The risk of recurrent vascular events and mortality associated with hypertension or per standard deviation higher SBP or DBP, respectively, on clinic BP, HBPM, and ABPM at one-month post-TIA/stroke 133

Table 3-9 The risk of recurrent vascular events and mortality associated with hypertension or per standard deviation higher SBP or DBP, respectively, on clinic BP and HBPM in patients who refused or did not tolerate ABPM 135

Table 3-10 The risk of recurrent major vascular events in relation to clinic BP, HBPM, and ABPM one month after TIA/stroke 136

Table 3-11 The risk of recurrent major vascular events in relation to clinic BP, HBPM, and ABPM one month after TIA/stroke; mutually adjusted models and goodness of fit 137

Table 3-12 The risk of recurrent major vascular events in relation to clinic BP and residual out-of-office BP, and goodness of fit of sequentially adjusted models 138

Table 4-1 Characteristics and blood pressure of patients, by completion of HBPM and ABPM at one-month follow-up 171

Table 4-2 Differences in baseline characteristics of patients based on their completion of ABPM and HBPM at one-month follow-up 173

Table 4-3 Clinic, HBPM, and ABPM mean blood pressure of patients based on their completion of ABPM and HBPM at one-month follow-up 174

Table 4-4 Blood pressure and hypertension on HBPM, ABPM, and clinic BP based on antihypertensive use at one-month follow-up 175

Table 4-5 The risk of recurrent MVE in relation to clinic BP, HBPM, and ABPM one month after TIA/stroke 176

Table 4-6 The risk of recurrent vascular events associated with hypertension or a 20 or 10 mmHg higher SBP or DBP, respectively, on clinic BP, HBPM, and ABPM at one month post-TIA/stroke 177

Table 4-7 The risk of recurrent vascular events associated with hypertension or a 20 or 10 mmHg higher SBP or DBP, respectively, on clinic BP, HBPM, and ABPM at one month post-TIA/stroke, in patients with all three measurements at one month 179

Table 4-8 The risk of recurrent vascular events associated with hypertension or per standard deviation higher SBP or DBP, respectively, on clinic BP, HBPM, and ABPM at one month post-TIA/stroke, in patients with all three measurements at one month 181

Table 4-9 The risk of recurrent vascular events associated with hypertension or a 20 or 10 mmHg higher SBP or DBP, respectively, on clinic BP and HBPM in patients who refused or did not tolerate ABPM 183

Table 5-1 Characteristics of patients according to antihypertensive treatment status between baseline assessment and one-month follow-up 211

Table 5-2 Blood pressure of participants between baseline and follow-up 213

Table 5-3 Blood pressure reduction between baseline and follow-up according to BP-lowering treatment status during intensive monitoring 214

Table 5-4 Summary of results from patient HBPM satisfaction questionnaire..... 215

Table 5-5 Primary care physicians' HBPM satisfaction questionnaires..... 216

Table 5-6 Characteristics of OXVASC patients in the pre-COMMIT study period (6 years) and the first 6 years of the COMMIT study 217

Table 5-7 Baseline and follow-up clinic blood pressure of OXVASC patients in the pre-COMMIT study period (6 years) and the first 6 years of the COMMIT study..... 218

Table 6-1 Baseline characteristics 246

Table 6-2 Mean blood pressure at baseline, 3-month, and 12-24-month follow-up... 248

Table 6-3 Blood pressure medication use at baseline, 3-month, and 12-24-month follow-up 249

Table 6-4 Full dose equivalent adjustment table for included participants 250

Table 6-5 Adverse events during follow-up 251

Table 6-6 Feasibility issues regarding home BP monitoring 252

Table 6-7 Feasibility issues regarding 24-hour ambulatory BP monitoring 253

Table 7-1 Characteristics and blood pressure of patients, by decreases in BP-lowering, lipid-lowering, and antithrombotic drugs after the intensive BP-monitoring period 280

Table 7-2 Initiator and rationale for antihypertensive medication discontinuation/reduction after the intensive BP monitoring period..... 282

Table 7-3 Characteristics of patients prescribed secondary prevention medications by the end of the intensive BP monitoring period, by decreases in any of these drugs during follow-up 283

Table 7-4 Characteristics of patients with decreases in BP-lowering versus lipid-lowering/antithrombotic drugs, but not both, after the intensive BP-monitoring period 285

Table 7-5 Recurrent major vascular events and secondary prevention medication reduction/withdrawal by follow-up interval 286

Table 7-6 Associations of secondary prevention medication discontinuation with accurately-characterised hypertension at baseline and the end of the HBPM period, stratified by recurrent major vascular events 287

Table 7-7 Risk of recurrent major vascular events associated with reduction in secondary prevention medications 288

Table 7-8 Follow-up blood pressure by reduction in antihypertensive medications... 290

Table 7-9 Risk of recurrent vascular events associated with reduction in antihypertensive medications after the intensive monitoring period, in sequentially-adjusted models 291

Table 7-10 Risk of recurrent vascular events associated with reduction in antihypertensive medications after the intensive monitoring period, by timing of medication reduction fitted as a time-varying covariate to different points during each follow-up interval 292

List of Figures

Figure 1-1 Reduction in haemorrhagic stroke in clinical trials (from the UK TRIDENT HBPM sub-study protocol (see Appendix 3.1), courtesy of the TRIDENT investigators) 54

Figure 1-2 Normal 'dipping' profile (top) and abnormal 'non-dipping' profile (bottom) on 24-hour ambulatory BP monitoring after stroke 55

Figure 1-3 Masked and white-coat hypertension in the COMMIT population, as defined by disagreement between home BP monitoring and clinic BP 56

Figure 1-4 Oxford Vascular Study primary care practices 57

Figure 1-5 A sample real-time blood pressure tracing from the secure server used for the COMMIT and PROHIBIT-ICH studies 58

Figure 1-6 Home blood pressure monitoring-guided blood pressure management programme schema 59

Figure 2-1 Flowchart of study inclusion and exclusion 90

Figure 2-2 Distribution and scatter plots of mean blood pressure on home monitoring with baseline clinic BP 91

Figure 2-3 Masked hypertension and transient post-event hypertension by clinic systolic blood pressure (top), and by number of cardiovascular risk factors at baseline (bottom) 92

Figure 2-4 Blood pressure diagnostic categorisation by vascular risk factors 93

Figure 2-5 Home blood pressure over one month of monitoring, by TOAST classification 94

Figure 2-6 Clinic (day 0) and home (day 1-28) systolic BP, by categorisation of BP on baseline clinic and three-day HBPM, and by the commencement of treatment among hypertensive participants at baseline clinic 95

Figure 2-7 Clinic (day 0) and home (day 1-28) blood pressure, by categorisation of blood pressure on baseline clinic and three-day HBPM 96

Figure 2-8 Clinic (day 0) and home (day 1-28) blood pressure in patients with transient post-event hypertension who were not prescribed antihypertensive treatment at baseline clinic 97

Figure 2-9 Clinic (day 0) and home (day 1-28) blood pressure, by categorisation of blood pressure on baseline clinic and three-day HBPM 98

Figure 2-10 Hazard ratios (95% CI) for major vascular events, by tertiles of systolic blood pressure on clinic and home measurement, plotted against the mean systolic BP in each tertile. 99

Figure 2-11 Cumulative incidence of major vascular events by diagnostic category of hypertension based on 3-day HBPM..... 100

Figure 2-12 Survival curves and numbers at risk, by categorisation of blood pressure on baseline clinic and three-day HBPM..... 101

Figure 2-13 Survival curves and numbers at risk, by categorisation of blood pressure on baseline clinic and three-day HBPM, using different BP thresholds and by treatment status..... 102

Figure 2-14 Survival curves and numbers at risk, by categorisation of blood pressure on baseline clinic and three-day HBPM, based on TOAST classification 103

Figure 3-1 Flowchart of study inclusion and exclusion 139

Figure 3-2 Change in the number of prescribed antihypertensive drugs between baseline and one-month follow-up 140

Figure 3-3 Distribution of mean systolic and diastolic blood pressure on 7-day HBPM, awake, asleep and 24-hour ABPM, and clinic recordings at one-month follow-up.... 141

Figure 3-4 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on seven-day HBPM and awake ABPM..... 142

Figure 3-5 Blood pressure measured in the office, on awake ABPM, and on 7-day HBPM, according to age categories..... 143

Figure 3-6 Differences in systolic BP between office BP and out-of-office measures, according to age categories 144

Figure 3-7 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on clinic assessment and seven-day HBPM at one month 145

Figure 3-8 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on clinic assessment and awake ABPM at one month 146

Figure 3-9 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on seven-day HBPM and 24-hour ABPM at one month 147

Figure 3-10 Prevalence of masked and white-coat hypertension, defined by HBPM and ABPM, according to age categories 148

Figure 3-11 Hazard ratios (95% CI) for major vascular events, by tertiles of systolic blood pressure on office, home and awake ambulatory measurement, plotted against the mean systolic BP in each tertile and stratified by age category 149

Figure 3-12 Absolute risk of recurrent major vascular events, stroke, and mortality, according to 24-hour ABPM BP dipping pattern, stratified by hypertension on ABPM and HBPM 150

Figure 3-13 Absolute risk of recurrent major vascular events according to 24-hour ABPM BP dipping pattern, stratified by hypertension on ABPM/HBPM and age category 151

Figure 3-14 Absolute risk (A) and cumulative incidence (B) of recurrent major vascular events according to diagnostic agreement between HBPM and awake ABPM, stratified by age 152

Figure 3-15 Meta-analysis of studies reporting risk of vascular events by continuous systolic BP recorded on office BP, HBPM and ABPM 153

Figure 4-1 Flowchart of study inclusion and exclusion 184

Figure 4-2 Change in the number of prescribed antihypertensive medications between baseline clinic and the arrival to the one-month follow-up clinic 185

Figure 4-3 Distribution of mean systolic and diastolic blood pressure on 7-day HBPM, daytime, night-time and 24-hour ABPM, and clinic recordings at one-month follow-up 186

Figure 4-4 Scatter plots of mean systolic blood pressure on seven-day HBPM with daytime ABPM, 24-hour ABPM, and clinic BP at one month 187

Figure 4-5 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on seven-day HBPM and 24-hour ABPM at one month 188

Figure 4-6 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on clinic assessment and daytime ABPM at one month 189

Figure 4-7 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on clinic assessment and seven-day HBPM at one month 190

Figure 4-8 Risk of recurrent major vascular events associated with white-coat hypertension versus correctly diagnosed hypertension at one-month clinic assessment, according to HBPM and ABPM 191

Figure 5-1 Flowchart of study inclusion and exclusion 219

Figure 5-2 Changes in antihypertensive treatment use during and following the intensive monitoring period 220

Figure 5-3 Home BP during three months of intensive monitoring and guided treatment, by categories of mean systolic and diastolic BP on the first day of monitoring 221

Figure 5-4 Home BP during one month of intensive monitoring and guided treatment, stratified by a net antihypertensive dosage increase during this time 222

Figure 5-5 Mean daily individual coefficient of variation (%) of blood pressure during one month of intensive HBPM and guided treatment 223

Figure 5-6 Mean daily individual coefficient of variation (%) of blood pressure during one month of intensive HBPM and guided treatment, stratified by a net antihypertensive dosage increase during this period 224

Figure 5-7 Telemetric home blood pressure monitoring-guided management programme patient satisfaction questionnaire 225

Figure 5-8 One-year follow-up clinic systolic blood pressure of OXVASC patients during the pre-COMMIT study period (6 years) and the first 6 years of the COMMIT study 226

Figure 5-9 One-year follow-up clinic systolic blood pressure of OXVASC patients during the pre-COMMIT study period (6 years) and the first 6 years of the COMMIT study, standard average 227

Figure 5-10 Reduction in blood pressure from baseline to one-year follow-up in OXVASC patients during the pre-COMMIT study period (6 years) and during the first 6 years of the COMMIT study 228

Figure 6-1 PROHIBIT-ICH trial procedure 254

Figure 6-2 PROHIBIT-ICH trial sites and recruitment 255

Figure 6-3 PROHIBIT-ICH interim trial profile 256

Figure 7-1 Flowchart of study inclusion and exclusion 293

Figure 7-2 Change in antihypertensive use during and following the intensive HBPM-guided treatment phase 294

Figure 7-3 Home BP over three months of intensive monitoring and guided treatment, by categories of mean systolic and diastolic BP on the first day of monitoring 295

Figure 7-4 Timing of discontinuation of secondary prevention medications after the intensive monitoring period, and timing of recurrent major vascular events in all patients who discontinued treatment 296

Figure 7-5 Discontinuation of secondary prevention medications after the intensive monitoring period, by age category 297

Figure 7-6 Timing of discontinuation of secondary prevention medications after the intensive monitoring period, relative to the timing of recurrent major vascular events during follow-up 298

Figure 7-7 Timing of discontinuation of antihypertensive medication after the intensive monitoring period relative to the timing of recurrent major vascular events during follow-up, by hypertension on 3-day home blood pressure monitoring 299
Figure 7-8 Risk of recurrent major vascular events after the intensive monitoring period by hypertension on baseline 3-day HBPM, according to antihypertensive medication reduction during follow-up 300
Figure 7-9 Risk of recurrent major vascular events after the intensive monitoring period by antihypertensive medication dose reduction/discontinuation versus persistence with the initial prescribed dose (or dose increase) during follow-up 301
Figure 7-10 Risk of recurrent major vascular events after the intensive monitoring period by hypertension on baseline 3-day HBPM, according to antihypertensive medication reduction in patients who remained fully adherent to lipid-lowering and antithrombotic drugs 302
Figure 7-11 Risk of recurrent major vascular events after the intensive monitoring period by antihypertensive medication dose reduction/discontinuation versus persistence with the initial prescribed dose (or dose increase), in patients who remained fully adherent to lipid-lowering and antithrombotic drugs 303
Figure 8-1 Scatterplot of first post-event systolic blood pressure (SBP) versus the most proximal premorbid SBP recording from primary care, in the OXVASC population .. 316
Figure 8-2 The cumulative incidence of recurrent major adverse cardiovascular events (MACE) in three phases of the OXVASC study 317
Figure 8-3 Risk of recurrent major vascular events (log scale) plotted against the mean of each 10 mmHg category of daytime and night-time mean systolic blood pressure (SBP) on 24-hour ambulatory blood pressure monitoring (ABPM), in the COMMIT study population. 318
Figure 8-4 Hazard ratio of recurrent vascular events (95% CI shaded) plotted on a log scale against mean one-month follow-up clinic blood pressure fitted as a continuous variable in the COMMIT study, using a restricted cubic spline (3 knots) 319

Figure 8-5 Hazard ratios of all recurrent vascular events (all outcomes), all-cause mortality, stroke, and myocardial infarction / sudden cardiac death (MI & SCD) plotted on a log scale against mean 7-day blood pressure on home blood pressure monitoring immediately preceding the one-month follow-up clinic, fitted as a continuous variable *320*

Chapter 1: Introduction

1.1 Blood pressure and the risk of recurrent stroke 2
1.1.1 The burden of the problem 2
1.1.2 Blood pressure lowering to reduce the risk of stroke recurrence 3
1.2 Treatment considerations in TIA and ischaemic stroke 6
1.2.1 Which patients should start antihypertensive treatment? 6
1.2.2 How soon after TIA/stroke should antihypertensive treatment be started? . 7
1.2.3 What target blood pressure should we aim for? 9
1.3 Treatment considerations in intracerebral haemorrhage 9
1.3.1 The burden of ICH 12
1.3.2 Blood pressure and the risk of recurrent ICH 12
1.3.3 How soon after ICH should antihypertensive treatment be started? 13
1.3.4 Evidence for intensive and sustained blood pressure control after ICH 14
1.4 Practicalities of blood pressure management for secondary prevention after TIA, ischaemic stroke, and ICH 16
1.4.1 Choice of antihypertensive agents 16
1.4.2 Time of day of blood pressure-lowering drug dosing 17
1.4.3 Is there a role for fixed low-dose combination therapy? 18
1.4.4 Targeting blood pressure variability in addition to mean blood pressure ... 20
1.5 How should blood pressure be assessed and monitored? 22
1.5.1 Office blood pressure measurement 22
1.5.2 Automated office blood pressure measurement 22
1.5.3 Ambulatory blood pressure monitoring 23
1.5.4 Home blood pressure monitoring 24
1.5.5 Which measurement modality is superior? 24
1.5.6 Blood pressure monitoring to guide long-term control 25
1.6 Blood pressure-lowering treatment adherence 27
1.7 The Oxford Vascular Study 29
1.7.1 Study population 29
1.7.2 Case ascertainment and follow-up 29
1.7.3 Definitions of stroke and TIA in OXVASC 32
1.7.4 Diagnostic work-up, aetiological classification, and management of TIA and stroke in OXVASC 32
1.7.5 Patient consent and approval 34
1.8 Telemetric home blood pressure monitoring methodology 35
1.9 Thesis aims 36
1.9.1 Observational data 36
1.9.2 Clinical trial data 37
1.10 Tables 39
1.11 Figures 54

1.1 Blood pressure and the risk of recurrent stroke

1.1.1 The burden of the problem

Stroke is the second leading cause of mortality worldwide, accounting for about 6.5 million deaths each year.[2] Elevated blood pressure is the strongest modifiable risk factor, with over half of the global burden of stroke being attributable to high systolic blood pressure.[3] There is a continuous positive association between mean blood pressure and stroke risk in observational studies,[4, 5] and meta-analyses of randomised controlled trials of blood pressure-lowering drugs have demonstrated substantial decreases in first-ever stroke risk with reductions in mean blood pressure in the general population.[6, 7]

The risk of stroke is particularly high in people with previous stroke or transient ischaemic attack (TIA), with almost a third of all strokes occurring in those with a previous cerebrovascular event.[8-10] Randomised trials have established that lowering blood pressure reduces this risk,[11] but long-term blood pressure control after stroke in practice remains poor, due in part to widespread under-treatment and under-adherence.[12-14] In practice, only a third of patients achieve guideline blood pressure targets[15-17] and over 20% discontinue their antihypertensive drugs within the first year after stroke,[18] and there is a high risk of recurrent stroke in those with insufficient blood pressure control.[19]

The work detailed in this thesis is an attempt to address a seemingly solvable problem that remains unsolved; at least 80% of recurrent strokes could be avoided with existing and widely accessible secondary prevention strategies, of which blood pressure treatment plays a leading role,[20] but the current risk remains too high as strategies to control blood pressure in the real world elude us. We are either measuring blood pressure unreliably, diagnosing high levels incorrectly, monitoring it inconsistently, or treating it inadequately, or as is perhaps more likely the case, doing all of these to some degree. In the following sections, and through presenting both observational and randomised controlled trial data, I will address some of the pitfalls of measurement of blood pressure in the early stages after TIA and stroke, how we can improve this, how

we should assess blood pressure in the longer term to guide treatment, and the impact of treatment withdrawal.

1.1.2 Blood pressure lowering to reduce the risk of stroke recurrence

Evidence from observational studies and randomised trials suggests that the relationship between blood pressure and stroke in the general population is even stronger than that for ischaemic heart disease; with each 10 mmHg lower systolic blood pressure being associated with a decrease in first-ever stroke risk of approximately one third.[6, 21-23] Systolic blood pressure is more strongly predictive of stroke risk than diastolic blood pressure, and although the association is steeper at younger ages, absolute risk reductions with blood pressure lowering are greater at older ages because of the higher incidence of stroke, underlying the importance of isolated systolic hypertension in the elderly.[5, 24] There also appear to be racial differences in the impact of BP on stroke risk, with a 10 mmHg higher systolic BP in blacks being associated with a three times greater stroke risk than that in whites.[25]

Although observational evidence is more scarce in a secondary prevention setting, a continuous association between blood pressure and stroke risk of comparable strength appears to exist in people with a recent history of TIA or stroke, down to a blood pressure of at least 130/80 mmHg.[26] There are also fewer randomised trials investigating blood pressure lowering after stroke than in a primary prevention setting, but a reduction in recurrent stroke risk in the region of 20-30% for antihypertensive therapy versus placebo was found in meta-analyses,[11, 27] with an apparent linear relationship on meta-regression.[11] A limited number of randomised trials have compared intensive BP lowering (<130 mmHg systolic BP) with less aggressive targets,[28-31] all reporting non-significant trends towards reductions in recurrent stroke risk in the intensive treatment groups. Meta-analyses of these trials[11, 27, 28] have formed the basis for recommendations of a systolic BP target of <130 mmHg after TIA/stroke,[32] but these studies had some limitations, and the potential for harm at lower achieved BP is a contentious issue.

The type and aetiology of stroke also appear to be important determinants of the relationship between blood pressure and recurrence risk. Blood pressure is more strongly associated with the risk of spontaneous intracerebral haemorrhage (ICH) than ischaemic stroke,[33] and is significantly higher immediately before and in the acute phase after ICH than after ischaemic stroke.[34] Accordingly, the effects of blood pressure lowering on risk reduction of recurrent stroke appear to be greater after ICH than after ischaemic stroke.[35] For ischaemic stroke, blood pressure appears to be particularly strongly associated with small vessel disease (SVD)-related stroke than other subtypes.[36] Mean pre-event blood pressure is substantially higher in SVD-related stroke/TIA than non-SVD-related events, accounted for by higher mean blood pressure during the years prior and a rising trend toward higher blood pressure leading up to the event,[37] but evidence is conflicting on whether this might have implications for targeted prevention.[29, 38, 39]

High blood pressure is also observed in the majority of cases of TIA, and despite uncertainty as to whether this is a consequence or trigger of the event,[40, 41] prompt introduction of secondary prevention treatment including blood pressure-lowering therapy after TIA results in an 80% reduction in 90-day stroke risk,[42] although most early benefit is probably due to antithrombotic therapy.[43]

Although I concentrate on secondary prevention of stroke and other major vascular events in this thesis, cognitive impairment and dementia are highly prevalent after stroke,[44, 45] and the incidence of dementia after major stroke is almost 50 times higher in the year after a major stroke compared with that in the general population.[46] High systolic BP is also a risk factor for vascular dementia,[47] and this association persists after TIA or stroke.[48] Several trials of antihypertensive medications have included secondary cognitive outcomes, and despite mostly non-significant findings in individual trials, BP lowering was associated with reduced cognitive decline (reduction in Mini-Mental Stroke Examination [MMSE]) in a meta-analysis (OR 0.92, 95% CI 0.85–1.00,

p=0.04). In a Cochrane review restricted to two of these trials with cognitive secondary endpoints that were performed in stroke patients, there was a non-significant trend towards a reduced risk of dementia during follow-up (RR 0.88, 95% CI 0.73 to 1.06).[27] In a non-stroke population, a large trial (SPRINT MIND) of intensive versus standard BP lowering did not find a significantly reduced risk of dementia with intensive BP control but did for mild cognitive impairment (HR 0.81, 95%CI 0.69-0.95).[49] In the absence of sufficient evidence to support BP lowering to reduce the risk of post-stroke dementia at present, there is at least some evidence from the Prevention of Decline in Cognition after Stroke Trial (PODCAST) that intensive BP lowering is not harmful from a cognitive standpoint.[31]

The focus of my thesis is the monitoring and medical treatment of blood pressure after cerebrovascular events, but lifestyle modification is an important aspect of hypertension management and stroke prevention more generally. In a cohort study of health professionals, around half of all ischaemic stroke was attributable to a lack of adherence to a 'low-risk lifestyle.[50] Although there is limited evidence concerning the effectiveness of lifestyle interventions versus pharmacological therapy for vascular risk reduction, dietary salt restriction or adoption of the Dietary Approaches to Stop Hypertension (DASH) diet, regular physical activity, limitation of alcohol intake, and weight loss have all been independently associated with some degree of blood pressure lowering and should be recommended in addition to any drug treatment.[51-57] Indeed, compliance with a telephone-administered lifestyle modification program as part of the Stenting Aggressive Medical Management for Prevention of Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial was associated with better risk factor control, including blood pressure.[58]

1.2 Treatment considerations in TIA and ischaemic stroke

1.2.1 Which patients should start antihypertensive treatment?

Clinical guidelines unanimously advocate commencement or resumption of antihypertensive treatment after TIA/stroke in anyone with a history of hypertension or elevated blood pressure readings on assessment (Table 1-1). Some recommend commencement of treatment in those who are classified as 'normotensive', based on the results of some trials of blood pressure lowering in secondary prevention that included participants with lower baseline blood pressure.[32, 59, 60] The perindopril protection against recurrent stroke study (PROGRESS) in particular, which randomised patients regardless of baseline blood pressure, reported a 43% (95% CI 30-45%) risk reduction of recurrent stroke for a 12/5 mmHg lower blood pressure, achieved with combination perindopril and indapamide therapy.[61] Meta-analyses of all primary and secondary prevention blood pressure-lowering trials also support treatment irrespective of baseline blood pressure for vascular risk reduction,[22, 62] consistent with the findings of PROGRESS.[61]

However, treatment initiation regardless of baseline systolic blood pressure may not be an entirely appropriate interpretation of the available evidence. For example, the definition of 'non-hypertensive' used in PROGRESS was clinic blood pressure <160/90 mmHg,[61] and a post hoc analysis suggested that the effectiveness of the intervention diminished with lower baseline blood pressure, with little evidence of benefit at systolic blood pressure <140 mmHg.[63] In the Prevention Regimen for Effectively Avoiding Second Stroke (PRoFESS) trial, where mean baseline blood pressure was only 144/84 mmHg, telmisartan was not associated with a reduction in risk of recurrent stroke or major vascular events during 2.5-year mean follow-up,[64] and a lower achieved blood pressure (systolic blood pressure <120 mmHg) was associated with an increased risk of recurrent stroke and vascular events in a post hoc analysis.[19]

In practice, clinicians are cautious about lowering blood pressure in certain groups, such as those with flow-restricting vascular stenosis.[65, 66] Rapid initiation or titration of blood pressure-lowering medication in older people with multiple comorbidities may increase the risk of falls.[67, 68] In the following chapters, I consider the potential safety concerns of intensive blood pressure lowering early after TIA, minor stroke and ICH, as well as the utility of conventional blood pressure measurement used in current practice to guide decisions about which patients should commence treatment.

1.2.2 How soon after TIA/stroke should antihypertensive treatment be started?

Over 80% of people with acute stroke are hypertensive at the time of hospital admission.[69] It has been consistently demonstrated in observational studies that blood pressure in patients with acute stroke is higher than in matched controls with other acute illnesses but frequently resolves spontaneously in the days and weeks that follow.[70-72] The cause of this transient rise in blood pressure ('post-stroke hypertension') is largely unknown. Premorbid hypertension itself is associated with high post-stroke blood pressure.[70, 73, 74] A specific physiological reaction to the stroke has been postulated, possibly due to disturbed cerebral autoregulation,[75] but it remains uncertain whether post-stroke hypertension is a specific response to cerebral injury, anxiety, or the remnant of a premorbid surge in blood pressure.[34, 76] High blood pressure in acute ischaemic stroke has been associated with poor outcome (death or early deterioration) in observational studies.[77, 78]

Despite this, there have been concerns for many years that high blood pressure in the acute phase of a stroke may be necessary to ensure adequate cerebral perfusion, and that aggressively treating it might cause harm. Indeed, acute systolic blood pressure <150 mmHg also appears to be associated with poor outcome,[78] and trials of blood pressure lowering in the acute phase after major ischaemic stroke demonstrate little benefit or even harm.[79-87] The timing of treatment initiation is likely to be an important

factor, however, with larger blood pressure reductions achieved in trials with earlier treatment initiation, and some evidence of improved functional outcome in trial subgroups with administration within 6 hours.[88] Some have even proposed that therapeutically-induced *hyper*tension should be considered to improve cerebral perfusion in ischaemic stroke,[89-91] and the first trials of acute administration of phenylephrine have had promising results in carefully selected patients with non-cardioembolic stroke.[92, 93]

Most guidelines recommend delaying commencement of blood pressure-lowering treatment for several days after major ischaemic stroke unless blood pressure is extremely elevated (systolic blood pressure ≥220 mmHg) or patients are candidates for thrombolysis/thrombectomy (to reduce the risk of secondary ICH, Table 1-1). Similar rates of hypertension in the acute phase of TIA and minor stroke are observed,[94] and there is some evidence that this might be a similarly transient phenomenon.[70]

There is little evidence to guide the timing of treatment commencement in acute minor stroke or TIA, however, as the main secondary prevention trials of blood pressure-lowering agents recruited patients well after the acute phase.[29, 61, 64] Guidelines provide conflicting recommendations for TIA, with European guidelines advocating immediate treatment and US guidelines recommending a delay of a few days (Table 1-1).[59, 95] Motivation to start and adhere to secondary prevention treatment might be stronger closer to the event, however, so initiating treatment after stabilisation but before hospital discharge, or shortly after acute outpatient assessment, might be optimal.[96]

In Chapter 2:, I examine the utility of measuring clinic blood pressure early after TIA and minor stroke to guide treatment decisions and raise the question of whether there might be merit in delaying the commencement of blood pressure-lowering treatment, as is recommended for major ischaemic stroke,[59, 95] which would permit better characterisation of blood pressure.

1.2.3 What target blood pressure should we aim for?

A continuous linear relationship between usual blood pressure and coronary artery disease and stroke mortality has been shown in prospective cohort studies in the general population, with decreases in vascular death observed with blood pressure down to 115/75 mmHg and no evidence of a floor effect.[5, 23] Meta-analyses of trials of antihypertensive agents also support the benefit of treatment even after stratification by baseline blood pressure,[22, 62] although risk reduction is somewhat less impressive when restricting to trials that selected people with a history of cerebrovascular disease.[97] The majority of clinical guidelines stipulate a blood pressure target of 130/80 mmHg or lower for long-term secondary prevention, at least for patients with previous hypertension (Table 1-1). However, this blood pressure target after TIA/stroke has rarely been achieved in any of the main secondary prevention trials.[98]

In the Systolic Blood Pressure Intervention Trial (SPRINT), a mean systolic blood pressure of 121 mmHg was achieved in the intensive treatment arm, and there was a 25% (95% CI 11-36%) reduction in major vascular events compared to the standard treatment arm (mean systolic blood pressure 136 mmHg), but this trial excluded patients with previous stroke.[68] In addition, unattended automatic office blood pressure measurement was predominantly used in SPRINT, which results in lower blood pressure values than conventional blood pressure measurement used in previous trials, thus the achieved blood pressure in SPRINT might correspond to a higher blood pressure level in usual practice.[99] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, performed in people with type 2 diabetes, intensive blood pressure lowering (mean achieved systolic blood pressure 119 mmHg) did not result in a reduced risk of a composite of major vascular events compared to standard therapy (mean systolic blood pressure 134 mmHg).[100] Although the risk of stroke was significantly reduced in the intensive blood pressure-lowering arm (HR 0.59, 95% CI 0.39-0.89, p=0.01), this was a secondary outcome based on a very low number of events.

Very few trials have investigated the effect of different blood pressure targets on the risk of *recurrent* stroke. The Secondary Prevention of Small Subcortical Strokes Trial (SPS3), an open-label randomised trial performed in lacunar stroke, showed that a lower blood pressure target (mean achieved systolic blood pressure 127 mmHg) was associated with a non-significant risk reduction (HR 0.81, 95% CI 0.64-1.03, p=0.08) compared to a standard target (mean systolic blood pressure 138 mmHg) during 3.7-year mean follow-up.[29] In a meta-analysis including all systolic blood pressure low-target trials after stroke (SPS3, PODCAST, PAST-blood pressure, RESPECT), the risk of recurrent stroke was reduced by 22% (HR 0.78, CI 0.64-0.96, p=0.02) by treatment to lower targets.[28] However, this finding is driven predominantly by the Recurrent Stroke Prevention Clinical Outcome (RESPECT) trial, which was performed in a Japanese population,[28] and the Secondary Prevention of Small Subcortical Strokes Trial (SPS3), an open-label randomised trial performed only in lacunar stroke,[29] so generalisability of the results to the wider stroke population might be problematic. Indeed, there are limited subgroup analyses among any trials to derive conclusions about disparities in the safety and efficacy of BP lowering across different stroke subtypes.[11] Moreover, there is limited information relating to the safety of the intervention in these trials, particularly in older adults who were excluded from some,[28] and a lack of reporting of adverse events relative to achieved BP precludes accurate evaluation of the risks of intensive BP lowering after stroke.

While a linear association of blood pressure with vascular events may be true in the general population, this might not be the case for people with existing vascular disease. The potential existence of a 'J-curve' in the association of blood pressure with stroke, i.e. a plateau in the beneficial effect (or harmful effects) when blood pressure is lowered below a critical nadir, might limit the utility of aggressive blood pressure treatment. The much weaker association of blood pressure reduction and recurrent stroke risk in SPS3 (19 [-3 to -36]% relative risk reduction for 11 mmHg lower systolic blood pressure)

compared with PROGRESS (43 [30-45]% for 12 mmHg), for example, might hint at a J-shaped association.[29, 61] I discuss this in more detail in Chapter 8:, where I provide some provisional data on the association of intensively treated low blood pressure with vascular risk from the Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study.

1.3 Treatment considerations in intracerebral haemorrhage

1.3.1 The burden of ICH

Intracerebral haemorrhage (ICH) is the most severe form of stroke and is a major cause of severe disability and death worldwide. Spontaneous ICH results from rupture of blood vessels in the brain that is not caused by trauma, causing bleeding within the brain parenchyma. The rupturing of these vessels is a consequence of cerebral small vessel disease; blood vessels are damaged by hypertension-related degenerative changes (arteriosclerosis), or cerebral amyloid angiopathy (CAA).[101]

ICH accounts for 10-15% of the 20 million new strokes in the world each year and has a high case fatality rate; the one-month rate is about 40%, higher than that for ischaemic stroke or subarachnoid haemorrhage.[102-104] Long term outcome after ICH is also poor; less than half of patients survive one year and less than a third survive five years, while survivors have substantial cognitive and physical impairments.[105] Despite the absolute number of incident ICH being around half that of ischaemic stroke globally, the burden of ICH in terms of 'loss of productive life years' is substantially greater as ICH tends to affect people at earlier ages.[106] Additionally, a meta-analysis demonstrated that both ICH incidence and one-month case fatality rates remained relatively constant between 1980 and 2008,[102] making ICH a persistent challenge for stroke research.

1.3.2 Blood pressure and the risk of recurrent ICH

Survivors are at high risk of recurrent ICH and other serious cerebrovascular and cardiovascular events, with annual rates of up to 10%,[105] and recurrent strokes result in higher mortality and disability than the first occurrence.[107] There is also a high risk of dementia after spontaneous ICH, with an incidence of almost 30% at four years, likely higher than that for ischaemic stroke.[108]

Elevated blood pressure is a particularly strong risk factor for ICH. People with hypertension have almost six times the risk of ICH compared to those without, after

adjustment for other risk factors.[109] This association might be explained by the effect of poorly controlled hypertension on small blood vessel walls, leading to hypertensive arteriopathy. Observational research suggests a strong association between hypertension and ICH recurrence for both non-lobar and lobar bleeds, with associations found even at 'pre-hypertensive levels' (systolic blood pressure 120-139 mm Hg and diastolic blood pressure 80-89 mm hg) and stronger associations with higher levels of blood pressure, suggesting that prolonged aggressive blood pressure control may substantially lower risk.[110]

1.3.3 How soon after ICH should antihypertensive treatment be started?

Observational data suggest that blood pressure is very high in the acute phase after ICH, significantly higher than that after ischaemic stroke.[34] High blood pressure in acute ICH is associated with haematoma expansion and poor clinical outcome.[111, 112] There have been concerns that high blood pressure may be necessary to ensure adequate cerebral perfusion after ICH, and that aggressively treating it may cause harm. Such concerns have been assuaged by evidence that suggests that adequate cerebral blood flow is maintained after acute blood pressure reduction in ICH.[113, 114] However, results of the two largest trials of intensive blood pressure lowering early after ICH[115, 116] have renewed uncertainty. Meta-analyses of these trials and other smaller studies demonstrated that early intensive blood pressure lowering was safe, but without functional or mortality benefit.[117-121] In contrast, a linear association between systolic blood pressure achieved in the first 24 hours and functional status was found in a recent individual participant data meta-analysis of the two largest trials, with improvements in functional recovery seen for blood pressure as low as 120-130 mmHg.[122] These trials excluded patients with large and severe haematomas, however, so their findings may not be readily generalisable to these patients.[123, 124] Most guidelines cautiously advise lowering blood pressure immediately in ICH if blood pressure is severely elevated (Table 1-1).

1.3.4 Evidence for intensive and sustained blood pressure control after ICH

Sustained post-acute blood pressure management arguably holds the most potential to improve long-term prognosis and recurrence following an ICH, but there have been no dedicated trials targeting long-term blood pressure reduction after ICH. The main prospective randomised data on the effects of long-term blood pressure lowering after ICH also come from PROGRESS.[61] Among 660 participants with a history of ICH at baseline, there was a mean difference of 11 mm Hg systolic and 4 mm Hg diastolic blood pressure between perindopril- and indapamide-treated and placebo arm participants, with a reduction in the absolute rate of ICH from 2% to 1% over 3.9 years of follow-up. This 50% relative risk reduction for ICH was higher than the 24% reduction in ischaemic stroke.[35] The stronger treatment effect in patients with ICH as compared to ischaemic stroke is consistent with the larger reductions of ICH as compared to ischaemic stroke outcomes in randomised trials of blood pressure-lowering in patients with hypertension.[24]

Consistent with this substantial risk reduction in ICH, the SPS3 trial in 3020 patients with recent subcortical infarction (presumed due to small vessel disease, the main cause of ICH) showed that the risk of future ICH was significantly reduced (by 63%) by intensive blood pressure lowering (target systolic blood pressure <130 mm Hg compared with 130-139 mm Hg).[29] PRoFESS, on the other hand, showed no significant benefits of early initiation of treatment with an angiotensin receptor antagonist (telmisartan) on top of usual care for total stroke or ICH in 20,332 patients with recent ischaemic stroke.[64]

However, a meta-regression analysis (Figure 1-1) of these three randomised trials, which included an assessment of ICH as an endpoint, suggests that the discrepant findings in PRoFESS might have been due to the smaller achieved blood pressure reduction, with evidence of a dose-response association between blood pressure and ICH risk overall.

As is the case for ischaemic stroke, there are also concerns that intensive blood pressure lowering after ICH might have an adverse impact in older populations by reducing cerebral perfusion, causing cerebral ischaemia, progression of cognitive impairment and falls.[125] Thus, although intensive blood pressure lowering is a very promising secondary prevention intervention in ICH, the optimum long term target blood pressure remains uncertain.

I sought to address these questions regarding intensive blood pressure control for secondary prevention of ICH in two randomised trials; PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment (PROHIBIT-ICH, currently recruiting, Chapter 6:), and a telemetric blood-pressure monitoring UK sub-study of the Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial (TRIDENT, study disbanded by the TRIDENT investigators before recruitment commencement due to COVID-19 recruitment concerns, protocol outlined in Appendix 3.1).

1.4 Practicalities of blood pressure management for secondary prevention after TIA, ischaemic stroke, and ICH

1.4.1 Choice of antihypertensive agents

Most stroke guidelines recommend dual antihypertensive therapy with a renin-angiotensin-system acting agent plus either a calcium channel antagonist or a thiazide/thiazide-like diuretic (Table 1-1). Five classes of blood pressure-lowering drugs have been investigated in stroke secondary prevention trials: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARB), β-adrenergic antagonists, calcium channel antagonists, and diuretics (Table 1-2). Most of these trials compared a single agent with a placebo,[64, 126-128] precluding reliable comparisons of different classes.

PROGRESS showed much greater reductions in blood pressure and stroke risk among subjects randomised to combination therapy with perindopril plus indapamide than in those randomised to perindopril alone, such that there was no significant reduction in recurrent stroke in the monotherapy group.[61] The conclusion that a 'perindopril-based regimen' was effective in reducing stroke risk has therefore been questioned.[129, 130] In the MOSES trial, blood pressure reductions were similar between nitrendipine (a calcium channel antagonist) and eprosartan (an ARB), but there was a 25% (95% CI 3-42%) lower risk of recurrent cerebrovascular events with eprosartan.[131] However, the trial had an open-label design, and most of the overall risk reduction was attributable to a reduction in TIA risk, with no significant benefit for the ARB for recurrent ischaemic stroke or on time-to-event analysis.

A network meta-analysis of all secondary prevention stroke trials to try to estimate comparative effectiveness showed that a diuretic-based regimen was possibly superior,[132]. This is consistent with the results of more recent observational data, which found that thiazide or thiazide-like diuretics showed better effectiveness for stroke risk

reduction than ACE inhibitors.[133] Calcium channel antagonists have not been investigated in large randomised trials in secondary stroke prevention (Table 1-2), but their effects on stroke risk reduction appear to be similar to those of ACE inhibitors in meta-analyses of trials in primary prevention and smaller secondary prevention trials.[132, 134]

A proportion of the risk-reducing benefits of some antihypertensive drugs is likely attributable to reducing blood pressure variability.[135-137] β-adrenergic antagonists, therefore, which increase variability,[136, 137] should probably be avoided as first-line treatment, and thiazide/thiazide-like diuretics and/or calcium channel antagonists might be preferable to ACE inhibitors or ARBs. In the COMMIT and PROHIBIT-ICH studies, outlined in subsequent chapters, the choice of antihypertensive agent was tailored to the individual patient, but usual first-line treatment was a combination of an ACE inhibitor and thiazide-like diuretic, the regimen of the PROGRESS trial,[61] followed by a dihydropyridine calcium channel antagonist.

1.4.2 Time of day of blood pressure-lowering drug dosing

It is well established that blood pressure follows a clear pattern of circadian variation in the general population, with the highest readings in the mid-morning that fall progressively during the day and night, before rising again in the early hours of the morning.[138] Interruptions of this usual circadian pattern, especially where the normal nocturnal blood pressure 'dipping' profile (a nocturnal mean blood pressure reduction of ≥10% of mean awake blood pressure) is absent on ambulatory blood pressure monitoring (Figure 1-2), are associated with an increased risk of vascular events that is possibly independent of 24-hour mean blood pressure.[139] Alternatively, it has been argued that a non-dipping profile might just be a marker of pre-existing disease, or even of daytime administration of antihypertensive agents, rather than having independent prognostic value for vascular events.[140]

In any case, the circadian pattern of blood pressure represents an interesting additional treatment target that is theoretically modifiable by adjusting the timing of antihypertensive drug dosing. Moving ingestion of antihypertensive therapy from the morning to bedtime appears to reduce the prevalence of non-dipping and was associated with a lower risk of vascular events in the Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC) study,[141] as well as in the more recent Hygia Chronotherapy Trial,[142] where bedtime dosing almost halved the risk of vascular events. However, these two trials (performed by the same group) have been subject to much criticism regarding their methodology and findings.[143-146] In light of this, and the potential risks of a more pronounced treatment-induced dip in nocturnal blood pressure, especially in the elderly,[147-149] routine bedtime dosing of all antihypertensive therapy should only be considered with caution until the results of the ongoing Treatment In Morning versus Evening (TIME) study (UKCRN17071)[150] are published.

In the COMMIT and PROHIBIT-ICH studies, outlined in subsequent chapters, time-of-day of blood pressure-lowering treatment was used as an important blood pressure management tool, with adjustments made according to the circadian profile of each patient identified using ABPM and HBPM.

1.4.3 Is there a role for fixed low-dose combination therapy?

The combination of two or more fixed-dose antihypertensive agents (polypill), with or without a statin and antiplatelet drug, is a promising strategy in stroke prevention, particularly in low- and middle-income settings where the burden of uncontrolled hypertension is highest.[151, 152] Early trials of polypills showed inconclusive effects on vascular risk, but treatment adherence and risk factor control generally improved, although this was sometimes at the expense of a higher burden of adverse effects.[153] An individual participant data meta-analysis of three recent large trials found that polypill use versus usual care/placebo resulted in a 41% (95% CI 22-55%) reduction in first-ever stroke during five-year follow-up, with better results observed with the inclusion of

aspirin.[154] However, the magnitude of systolic blood pressure reduction between baseline and follow-up attributable to the polypill was modest (4.7 [95% CI 4.2-5.2] mmHg), much less than what was expected in each constituent trial.

Quadruple ultra-low-dose treatment for hypertension (QUARTET), a recently published, double-blinded, randomised trial of subtherapeutic dose combination antihypertensive therapy (irbesartan 37·5 mg, amlodipine 1·25 mg, indapamide 0·625 mg, bisoprolol 2·5 mg), showed improved blood pressure control (6.9 [95% CI 4.9-8.9] mmHg lower systolic blood pressure at 12 weeks) and equal tolerability for the polypill versus a monotherapy control (irbesartan 150mg) among otherwise healthy people with untreated/minimally-treated hypertension.[155] No long-term data on vascular outcomes were provided, however, and a fairer comparator group for determining efficacy versus usual care in a secondary stroke prevention setting would be dual therapy, such as the regimen used in the PROGRESS trial,[61] since virtually all secondary prevention guidelines recommend this (Table 1-1).

For all the promise of fixed-dose combination antihypertensive treatment in early trials, the polypill could be considered the antithesis of individualised risk reduction that is sought in other aspects of stroke prevention. The flexibility of dosing of different agents at different times of day would also be precluded, and therapeutic inertia (failure to intensify therapy when blood pressure is not controlled) is a theoretical concern. Although improved treatment adherence to a less complex regimen might be a benefit of using a polypill after TIA/stroke, this could be offset by higher rates of adverse events, even if these have not been encountered in non-generalisable healthy trial populations.[155] Many polypills have included ACE inhibitors and β-adrenergic antagonists,[156] which may increase blood pressure variability,[157] and would be inappropriate for those with bradykinin-induced cough or previously diagnosed asthma, respectively, both present in at least 4% of this population.[158, 159] While thiazide/thiazide-like diuretics are highly effective for secondary stroke prevention,[61] so would likely be

included in any polypill designed for this population, they are associated with the highest rates of discontinuation due to their side-effect profiles, particularly electrolyte disturbances in older patients.[160]

In terms of randomised evidence to support the use of blood pressure-lowering polypills in a stroke-specific setting, TRIDENT, a trial of the effects of a fixed-dose combination of telmisartan 20mg, amlodipine 2.5mg, and indapamide 1.25mg versus placebo on recurrent stroke risk in patients with recent ICH, is outlined in my sub-study protocol in Appendix 3.1, and the main trial is currently recruiting.

1.4.4 Targeting blood pressure variability in addition to mean blood pressure

There exists a very weak correlation between blood pressure measurements at separate clinic visits in people with prior stroke or TIA.[161] Such visit-to-visit blood pressure variability was previously regarded as purely random error that was clinically unimportant, other than in posing a barrier to the accurate determination of an individual's underlying 'usual blood pressure', but this assumption has been questioned.[135]

Indeed, blood pressure variability is reproducible and therefore non-random, especially in people with cerebrovascular disease,[162, 163] who have higher visit-to-visit blood pressure variability than the general population.[161] Furthermore, visit-to-visit blood pressure variability is a strong predictor of future stroke, even after adjustment for mean blood pressure, especially in those at high vascular risk.[164-170] This might account for the observation that patients with normal mean systolic blood pressure but high variability are at considerably greater risk than those with consistently stable normotension, as well as for the disparity between the large relative risk reductions for stroke in trials of antihypertensive medications in older people despite the diminishing predictive value of mean systolic blood pressure at older ages.[135, 164]

Consistent with this, antihypertensive trial data suggest medication class effects on stroke risk reduction that persist even when decreases in mean systolic blood pressure are the same, which are accounted for by different actions on blood pressure variability, with calcium channel blockers and non-loop diuretics having the largest variability-reducing effects.[136, 137, 171, 172] Importantly, short-, medium-, and long-term blood pressure variability can be accurately quantified using out-of-office blood pressure measurement, repeated at intervals as necessary. In addition, beat-to-beat blood pressure variability, which can be assessed rapidly and easily, also predicts recurrent stroke independently of mean blood pressure, has similar prognostic value to day-to-day blood pressure variability on HBPM, and might be affected by antihypertensive medication class in the same way as longer-term blood pressure variability.[173] Taken together, these findings may have important implications for secondary stroke prevention. The use of calcium channel antagonists and thiazide/thiazide-like diuretics after TIA and stroke leads to reductions in systolic blood pressure variability, which has prognostic importance and which can be quantified using HBPM[174] and potentially by clinic/bedside reductions in beat-to-beat variability over minutes, thereby representing an additional blood pressure control target to further reduce residual risk.

In Chapter 5:, I establish the effects of HBPM-guided antihypertensive treatment on both mean blood pressure and blood pressure variability, with the use of drug classes specifically chosen for their effects on both.

1.5 How should blood pressure be assessed and monitored?

1.5.1 Office blood pressure measurement

Within three decades of the advent of the sphygmomanometer in the late 19th century, US medical insurance firms began to incorporate blood pressure measurement into their assessments, such was the appreciation of its value in risk prediction.[175] For many decades, 'office' or clinic blood pressure (these terms are used interchangeably in this thesis) measurement using a manual sphygmomanometer, or more recently, oscillometric devices, was the only technique available. Although compelling evidence has been amassed on the association of clinic blood pressure with vascular risk,[176] and despite most antihypertensive treatment trials having used 'traditional' clinic blood pressure measurement,[95] it is now recognised that clinic blood pressure is intrinsically inaccurate in the diagnosis of hypertension.[177] Clinic readings are subject to a plethora of sources of measurement error and observer bias,[178] and single clinic readings are subject to random error, so clinic blood pressure is likely to be poorly representative of people's underlying usual blood pressure.[177]

'Masked hypertension', where clinic blood pressure is within normal limits but out-of-office readings are high, occurs in at least 10-15% of the general population.[179] In addition, a systematic error caused by a pressor reaction to the blood pressure measurement procedure and setting, known as the 'white-coat effect', leads to overdiagnosis of hypertension and underestimation of treatment effects,[180] and is highly prevalent (Figure 1-3).[181] In Chapter 2:, I investigate the prevalence of masked and white-coat hypertension after TIA and stroke, and the implications of these phenomena in the acute phase for subsequent risk prediction and management.

1.5.2 Automated office blood pressure measurement

The advent of automated blood pressure measurement devices has given rise to the development of strategies to circumvent some of the pitfalls of clinic blood pressure

assessment. Automated office blood pressure (AOBP) monitors record multiple readings over time with a single activation, so can be performed unattended in clinic to mitigate some of the white-coat effect.[182] AOBP was the basis of blood pressure measurement in SPRINT,[183] it appears to correlate better with subclinical vascular disease than conventional clinic blood pressure,[184, 185] and it is the first-line measurement modality in Canadian hypertension guidelines (Table 1-3).[186] However, few data are available on the reproducibility of readings,[187] overdiagnosis of hypertension is still frequent,[188] and it is probably not suitable as an alternative to home blood pressure assessment.[189] The main value of the development of such automated techniques has been their application to out-of-office blood pressure measurement, namely ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM).

1.5.3 Ambulatory blood pressure monitoring

ABPM is usually performed over 24 hours and provides mean daytime, night-time, and 24-hour blood pressure. ABPM has several advantages over clinic blood pressure; it is performed in a real-life setting, it is observer-independent, it is theoretically free from the white-coat effect, it provides data on diurnal variation and short-term blood pressure variability, and it is a stronger predictor of target organ damage[190] and vascular events.[191-197] Accordingly, most major hypertension guidelines now endorse ABPM to diagnose hypertension,[59, 95, 186, 187, 198-205] with the US Preventive Services Task Force Recommendation Statement[198] and the UK National Institute for Clinical Excellence Guidelines[199] recommending ABPM as the first-line reference standard for confirming a diagnosis of hypertension suggested on clinic blood pressure (Table 1-3).

However, ABPM is expensive,[206-208] can be uncomfortable and is frequently poorly tolerated,[209] has poor intra-individual reproducibility over time (as bad as that for clinic blood pressure),[206-208] and may not be appropriate for monitoring long-term blood pressure control due to resistance from some patients to having repeat ABPM.[210]

1.5.4 Home blood pressure monitoring

HBPM uses much cheaper and more widely available devices than ABPM, is preferred by patients,[211] and is ideally suited for long-term blood pressure monitoring and assessing the blood pressure response to antihypertensive medication changes. Blood pressure measurements are taken over several days (or longer), so clinical information on day-to-day and longer-term blood pressure variability are also available.

As is the case for ABPM, HBPM is superior to clinic blood pressure for the prediction of target organ damage[212] and vascular events[213-215] in a primary prevention setting, where it has been investigated. It does not usually provide nocturnal blood pressure data, which is an important limitation. However, the recent advent of night-time HBPM is gaining popularity due to the development of silent wrist-based monitors that are purported to not interrupt sleep or disturb sleeping partners.[216] Nocturnal blood pressure measured on HBPM seems to be comparable to nocturnal blood pressure measured by ABPM,[217] and also appears to have predictive value for vascular events.[218, 219] Self-recorded HBPM can be subject to imprecise recordings because of under/over-reporting and inaccurate or illegible readings[220-223] but these can be avoided with the use of monitors with digital storage or telemetric devices.[221, 224-227]

1.5.5 Which measurement modality is superior?

In view of the evidence summarised above, most primary prevention hypertension guidelines now acknowledge that diagnosis of hypertension is sub-optimal when based only on clinic blood pressure, and require diagnostic confirmation by out-of-office measures (Table 1-3).[59, 95, 186, 187, 198-205] Some primary prevention guidelines favour ABPM over HBPM for hypertension diagnosis (Table 1-3),[199, 204] but there is no strong empiric evidence to support this, with few studies comparing the relative prognostic value of ABPM and HBPM.[228] Some cost-effectiveness analyses also favoured ABPM over HBPM, but optimistically assumed that ABPM had 100% sensitivity and specificity for the

identification of clinically relevant hypertension due to a lack of comparative prognostic studies of clinical outcomes.[229-231]

In the secondary prevention of stroke, clinic blood pressure might be even less reliable for diagnosing and managing hypertension, as it is well recognised that people with TIA/stroke have increased background visit-to-visit variability in clinic blood pressure,[162, 232] which can produce chance 'low' or 'high' single readings.[161] Despite this, current stroke secondary prevention guidelines base their recommendations about hypertension diagnosis, blood pressure treatment targets, and long-term control upon clinic blood pressure assessment (Table 1-1).[59, 60, 95, 186, 200, 202, 233-235] This stark contrast between primary and secondary prevention stroke practice may reflect the lack of evidence in secondary prevention; only one randomised trial of blood pressure lowering in secondary prevention of stroke included any kind of out-of-office blood pressure measurement (Table 1-2).[131] Moreover, only a few studies have examined the use of ABPM for the secondary prevention of stroke (Table 1-4) and none for HBPM. A few studies of HBPM in primary care included stroke patients (Table 1-5), but these found no benefit in this subset. Indeed, a small study of 80 participants examining diagnosis of hypertension using ABPM and telemetric HBPM in treated stroke and TIA patients suggests that these should not be considered interchangeable methods of blood pressure evaluation in this population.[236]

In Chapter 3: and Chapter 4:, I compare the diagnostic accuracy and risk prediction of clinic, home, and ambulatory blood pressure measurement in a secondary prevention cohort, in order to address some of this lingering uncertainty.

1.5.6 Blood pressure monitoring to guide long-term control

In addition to its improved accuracy for diagnosis of hypertension, the use of HBPM is gaining popularity as evidence has emerged that it can additionally be used to guide treatment and improve long-term blood pressure control in primary prevention when combined with co-interventions such as systematic antihypertensive medication titration

or patient education.[227, 237, 238] This holds promise for addressing the problems of under-treatment and poor long-term blood pressure control in the secondary prevention of stroke.

However, in the very few of the trials of HBPM for long-term blood pressure control that included participants with a history of stroke, HBPM did not appear to be effective in terms of blood pressure lowering, with or without telemonitoring and co-interventions, and this was not explained by more intensive treatment prior to randomisation in these patients.[238-241] In Chapter 5: and Chapter 6:, I investigate the role of long-term out-of-office blood pressure monitoring in an observational study and randomised controlled trial, respectively, for guiding treatment decisions and recurrent stroke prevention.

1.6 Blood pressure-lowering treatment adherence

Consistently adhering to a regimen of secondary prevention medications and lifestyle changes after TIA and stroke should result in up to an 80% relative risk reduction of recurrent events.[20] blood pressure control is a crucial component of this, but although guidelines recommend a strict blood pressure target, they provide no recommendations on how this should be achieved in the real world.[59, 60, 95] In practice, up to a third of patients discontinue their antihypertensive treatment within the first year or two after stroke.[18, 242-244]

Most published research on the factors determining poor adherence after TIA and stroke focuses on patient- and drug-specific influences, with post-stroke cognitive impairment, disability, medication side-effects, and patient beliefs about treatment all being implicated.[245] However, institutional factors also play a role,[246] and an observational study based on registry data found that the majority of so-called 'non-adherence' to secondary prevention medications might represent purposeful discontinuation by health care providers after discharge from hospital.[243] Given this finding, coupled with the wide variation across centres in antihypertensive prescribing after stroke,[247] at least a proportion of treatment discontinuation might be a justified response to better characterisation of blood pressure after the acute phase, using repeat multiple repeat clinic measures or out-of-office assessment, for example.

For the proportion of blood pressure-lowering treatment discontinuation that is truly down to poor adherence, no single intervention has proved to be a panacea. Drug adherence should be assessed in all cases of inadequate blood pressure control at follow-up after a stroke while bearing in mind that asking about missed doses or using basic questionnaires probably only identifies those who are the least adherent, and even then may fail to identify even completely non-adherent patients.[248-253] More sophisticated direct methods of ascertaining treatment adherence have been tested, such as measuring drug metabolites/ drug-associated biological markers in serum or urine, direct

observation of medication-taking behaviour, and the use of integrated microsensors that measure pill ingestion,[250, 254] but despite some promising results for improving in resistant hypertension,[255, 256] these are burdensome, expensive,[257] raise some ethical concerns,[258] and might be more suitable in a research setting for validating other strategies. Once a non-judgemental dialogue about medication-taking behaviour has been started, there are several possible strategies with varying degrees of success, for example including the patient in the decision making process about antihypertensive treatment choice,[259] using motivational interviewing techniques,[260] employing technologies such as pill dispensers and text message reminders,[261, 262] and, as previously discussed, encouraging regular HBPM.[221, 224-226, 237]

In Chapter 7:, I discuss the impact of poor adherence to antihypertensive treatment on the long-term risk of recurrent vascular events after TIA and stroke, in a population with otherwise well-managed risk factors and excellent initial control of blood pressure.

1.7 The Oxford Vascular Study

The COMMIT study, detailed in Chapter 2: Chapter 3: Chapter 4: Chapter 5: and Chapter 7:, is an observational cohort of intensive HBPM nested within the overarching Oxford Vascular Study (OXVASC). OXVASC is an ongoing, longitudinal, population-based cohort study of all incident acute vascular events (TIA, stroke, coronary, and peripheral vascular events) in Oxfordshire, UK, and has been operational since 1st April 2002. This section details the methodology of OXVASC, to provide context for the COMMIT study chapters that follow.

1.7.1 Study population

The OXVASC population comprises approximately 93,000 individuals, registered with over 100 general practitioners, defined by registration with one of nine primary care practices in Oxfordshire (Figure 1-4). The practices were chosen to represent the urban/rural mix and deprivation range of the Oxfordshire population[263] and all refer patients with acute vascular events to a single centre (Oxford University Hospitals NHS Trust; John Radcliffe Hospital). All participating practices provide accurate age-sex patient registers and hold individual lifelong records of all medical consultations, prescribed medications, and blood pressure measurements / other investigations. An estimated 97% of the study residential population is registered with a primary care practice; the majority of unregistered people are young University students who reside in Oxford during term-time. The OXVASC population is approximately 94% White, 3% Asian, 2% Chinese, and 1% Afro-Caribbean.[264]

1.7.2 Case ascertainment and follow-up

Multiple overlapping methods of 'hot' and 'cold' pursuit are used to achieve near-complete ascertainment of all individuals in the study population with acute vascular events.[265]

'Hot' pursuit includes:

1. A rapid-access daily (weekday) clinic receiving referrals of suspected minor stroke or TIA from participating general practitioners, the local emergency department, other outpatient clinics, or other hospitals (e.g. the local eye hospital). Weekend clinics are run by the John Radcliffe Hospital stroke service and patients are identified by the OXVASC team the following week. Domiciliary visits are arranged for patients unable to attend clinic.
2. Daily searches and case note reviews of admissions to the emergency assessment unit, medical short stay unit, and acute medicine, stroke, neurology, and other relevant hospital wards at the John Radcliffe Hospital.
3. Daily searches of the local emergency department and eye casualty attendance register.
4. Daily searches of in-hospital death records via the Bereavement Office.
5. Daily assessment of all patients undergoing diagnostic coronary, carotid, and peripheral angiography, angioplasty, stenting, or other vascular surgical procedures.

'Cold' pursuit includes:

1. Monthly searches of all death certificates and coroner's reports for out-of-hospital deaths.
2. Monthly searches of general practitioner diagnostic coding and hospital discharge codes.
3. Monthly searches of all brain and vascular imaging referrals.
4. Practice-specific listings of all *International Classification of Disease* (ICD) 10 death codes from centralised registration with the Office for National Statistics.

Patients with events occurring out-of-area (often identified through GP practice searches on ‘cold’ pursuit) are included, but temporarily registered patients and those who were not registered with an OXVASC practice at the time of their event are excluded.

Patients are assessed as soon as possible following referral or hospital admission in a face-to-face interview conducted by a study clinician. Structured, event-specific forms are used to collect data. The information recorded from the patient and their hospital/ general practice records includes patient demographics, details of the event, past medical history (including vascular risk factors), medications, social and family history, clinical examination including stroke severity assessment using the *National Institutes of Health Stroke Scale* [NIHSS]) and at least three clinic blood pressure measures (detailed descriptions are provided in subsequent chapters), all pre-morbid blood pressure measurements, investigation results, and relevant subsequent interventions. Information obtained in the interview is cross-referenced with primary care records.

In the case of death prior to assessment, eye-witness accounts, hospital records, and autopsy reports (when performed) are obtained. Primary care records are obtained for all cases of death due to a vascular aetiology.

All surviving patients are followed up face-to-face at one, six, 12, 60, and 120 months after the vascular event by a study nurse or physician to identify further vascular events, relevant diagnoses (such as atrial fibrillation or dementia), and to ensure medication compliance and adequate blood pressure control. This is supplemented by the review of primary care records. Patients who have moved out of the study area (or are unwilling/ unable to have face-to-face follow-up) are followed up via telephone at the same time-points. Telephone follow-up was used exclusively during the COVID-19 lockdown, and telephone versions of cognitive assessments were used (further details in subsequent chapters). If a patient has a recurrent event during follow-up, they re-assessed and investigated as necessary by a study physician.

1.7.3 Definitions of stroke and TIA in OXVASC

The definitions of stroke and TIA in OXVASC conform to the older *World Health Organisation* (WHO) criteria.[266] Stroke is defined as an acute onset neurological deficit persisting for more than 24 hours or leading to death, with no apparent cause other than of vascular origin. TIA is defined using the same WHO criteria for stroke but with complete resolution of symptoms and signs within 24 hours. Minor stroke is defined as an NIHSS $\leq$3 at assessment. For the COMMIT study chapters of this thesis, both first-in-OXVASC-study period cerebrovascular events and recurrent events are included, as some existing OXVASC participants entered the COMMIT sub-study at the time of a recurrent event.

1.7.4 Diagnostic work-up, aetiological classification, and management of TIA and stroke in OXVASC

All patients with TIA and stroke undergo a standardised investigation protocol including brain imaging (generally MRI, or contrast CT if MRI is contraindicated or unavailable, see further notes below), vascular imaging (extra- and intracranial vascular imaging with CT/MR-angiography and/or carotid Doppler imaging), 12-lead electrocardiography (ECG), and screening blood tests (full blood count, coagulation factors, urea and electrolytes, liver function tests, C-reactive protein, erythrocyte sedimentation rate, thyroid-stimulating hormone, calcium, magnesium, and a lipid profile). From 1st April 2010, transthoracic echocardiography and five-day R-test ECG monitoring have been performed in all ischaemic stroke and TIA patients; previously they were performed when clinically indicated, such as for undetermined events, multi-territory infarcts, patients at high risk of endocarditis or known valvular disease, or other relevant cardiac pathology. Thrombophilia and autoimmune antibody screening and genetic testing are conducted when clinically indicated.

OXVASC neuroimaging protocols have evolved during the study. From 1st April 2002 to 31st March 2007, CT brain and carotid Doppler ultrasound were the first-line modalities. From 1st April 2007, MRI and MR-angiography became first-line imaging modalities for posterior circulation events and for all events from 1st April 2010. Computed CT and CT-angiography is performed in the case of standard contraindications to MRI, such as a cardiac pacemaker, other MRI-unsafe implantable devices, or claustrophobia. Transcranial Doppler ultrasound of the intracranial arteries (TCD; Doppler Box, Compumedics DWL, Singen Germany) is performed in all patients attending clinic for one-month follow-up. Carotid Doppler ultrasound is undertaken in those in whom CT/MR-angiography is contraindicated, for example, patients with a low estimated glomerular filtration rate, and for further characterisation of stenosis if carotid endarterectomy or stenting is indicated.

Upon completion of relevant investigations, all recruited ischaemic stroke and TIA patients are reviewed in a monthly departmental meeting. A senior study neurologist (Professor Peter Rothwell) classifies the event aetiology according to modified TOAST criteria: cardioembolic, large artery disease, small vessel disease, undetermined, unknown (incomplete investigation), multiple, and other.[267, 268] Events are classified as undetermined if no aetiology is identified with the minimum diagnostic workup of brain imaging (CT or MRI), carotid imaging, ECG, and blood tests, and as unknown if investigations were incomplete.

Patients received intensive medical management, including dual anti-platelet therapy (aspirin and clopidogrel) for the first month with aspirin or clopidogrel monotherapy thereafter, and anti-coagulation for patients with atrial fibrillation, high-dose lipid-lowering treatment (a statin in the vast majority of patients), and treatment of hypertension (a detailed explanation is provided in subsequent chapters). Patients were also provided with dietary, exercise, and smoking cessation (where relevant) advice.

1.7.5 Patient consent and approval

All patients eligible for OXVASC are provided with a detailed booklet sheet about the study, and after having time to read this and ask questions, are asked to complete a consent form. If the patient is unable to provide informed consent, then written assent is obtained from their next of kin. If a patient does not wish to attend follow-up visits, then permission to use their clinical records is sought. OXVASC is approved by *Oxfordshire Clinical Research Ethics Committee* (OREC A: 05/Q1604/70).

1.8 Telemetric home blood pressure monitoring methodology

Detailed methods of telemetric HBPM are included in each chapter of this thesis, whereby specific aspects of monitoring and recorded data were used for different purposes. Here, I will briefly outline some of the technical procedures involved.

Consenting participants in the COMMIT study or ICH survivors randomised to the intervention group in the PROHIBIT-ICH trial were provided with a Bluetooth-enabled, regularly-calibrated, telemetric blood pressure monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT. Measurements were automatically transmitted by Bluetooth either to a mobile phone (older version) or a Raspberry Pi microcomputer hub, for secure transmission via a cellular network to a server hosting a password-protected website for review and download (OBS Medical, Abingdon, UK). A sample blood pressure tracing of a patient in the COMMIT study on the secure website is shown in Figure 1-5.

A similar monitoring protocol was in place for both the COMMIT study and the PROHIBIT-ICH trial. I obtained and reviewed the blood pressure of all patients in the COMMIT study each working day from 03/11/2016 to 31/03/2019, and all patients in the PROHIBIT-ICH trial intervention group (from 11/04/2019 to present), and updated a spreadsheet for each to indicate blood pressure control. If readings were absent, the patient was phoned to check if the blood pressure was measured and the Bluetooth kit was working. Technical problems were resolved with the patient by phone where possible, or reported to OBS medical as required, for next working day support. If required, a replacement kit was sent by courier, and the data from each account were merged. In the case of unexpected readings (e.g. high peaks or unexpected low readings), the patient was phoned to check if there is anything which may account for them (Figure 1-6). Further details of HBPM and ABPM, and relevant patient instruction forms and standard operating procedures are included in the Appendix.

1.9 Thesis aims

Despite overwhelmingly clear evidence from randomised trials that antihypertensive therapy substantially reduces the risk of stroke in primary prevention, uncertainty still surrounds the issue of blood pressure lowering after cerebrovascular events, blood pressure control in practice is often insufficient, and the risk of recurrent stroke, coronary events, and vascular death remains substantial. A lack of clarity surrounding best practice for assessment and control of blood pressure in secondary prevention of stroke might be a contributing factor. The overarching aim of this thesis, therefore, is to address the uncertainty surrounding how best to measure, monitor, and guide the treatment of blood pressure in individuals who are most vulnerable to vascular events. Each chapter is intended to largely stand alone to address a specific research question, so although I have endeavoured to minimise repetition, some overlap is inevitable.

This thesis uses both observational and randomised controlled trial data centred on these areas of uncertainty, to achieve the following specific aims:

1.9.1 Observational data

To characterise blood pressure after TIA or stroke using telemetric home blood pressure monitoring (HBPM) as part of the COMMIT study. The objectives are:

(i) To assess the utility of clinic blood pressure versus telemetric HBPM to diagnose hypertension and to ascertain the extent of misdiagnosis using clinic blood pressure in the early stages after TIA and minor stroke (Chapter 2:)

(ii) To compare the prognostic value of early clinic blood pressure versus early HBPM after TIA and minor stroke (Chapter 2:)

(iii) To explore differences in the data captured by contemporaneous clinic, 24-hour ABPM, and telemetric HBPM, which might explain differences in

predictive value for recurrent vascular events in a secondary prevention cohort with a high rate of vascular events (Chapter 3:)

(iv) To directly compare the utility of clinic blood pressure, HBPM, and ABPM after the acute phase of TIA and minor stroke for the diagnosis of residual hypertension and prediction of recurrent vascular events over long-term follow-up (Chapter 4:)

(v) To determine whether a programme of telemetric HBPM-guided blood pressure treatment be used to achieve the guideline blood pressure target (<130/80 mmHg) after TIA/stroke (Chapter 5:)

(vi) To determine the effects of targeted HBPM-guided blood pressure treatment on day-to-day blood pressure variability (Chapter 5:)

(vii) To determine whether a programme of telemetric HBPM-guided blood pressure treatment is feasible, safe, and acceptable to patients and their general practitioners (Chapter 5:)

(viii) To ascertain the effects on risk of recurrent vascular events, if any, of poor long-term adherence to antihypertensive treatment prescribed during the COMMIT study (Chapter 7:)

1.9.2 Clinical trial data

To characterise blood pressure after ICH and to definitively determine the efficacy of telemetric HBPM-guided blood pressure treatment, as part of the PROHIBIT-ICH trial, and the development of a trial protocol for a blood pressure monitoring sub-study of an international randomised controlled trial.

(i) PROHIBIT-ICH is a multi-site, randomised controlled trial in 112 adult survivors of spontaneous ICH that is investigating whether intensive lowering of blood pressure using telemetric home monitoring in ICH survivors is feasible, safe and effective in reducing brain injury. I developed the trial protocol, and I run the day-to-day management of the blood

pressure part of the trial. Interim results of the blood pressure aspect of the trial ate outlined in Chapter 6:.

(ii) Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial, UK Telemetric Home Blood Pressure Monitoring Sub-Study (TRIDENT UK HBPM) was a planned home telemetric blood pressure monitoring observational sub-study of a multicentre, double-blinded, placebo-controlled, randomised controlled trial of a fixed low-dose combination blood-pressure-lowering pill ('Triple Pill') on top of standard of care, in patients with a history of acute spontaneous ICH and hypertension. Unfortunately, due to reasons beyond my control, the trial sub-study was cancelled just before approval was granted. The protocol and main study documents, which I wrote in their entirety, are included in Appendix 3.

1.10 Tables

Table 1-1 Recommendations on BP lowering after TIA/stroke in major international clinical guidelines

Guideline	Timing of commencement of antihypertensive treatment after TIA/stroke	Long-term treatment target	Treatment regimen
Hypertension guidelines with specific guidance on secondary prevention of stroke			
European Society of Cardiology (ESC)/European Society of Hypertension (ESH): Guidelines for the management of arterial hypertension (2018)[59]	TIA - immediately; ischaemic stroke - after several days (routine BP lowering within 24 hours is not recommended unless patients are eligible for IV thrombolysis, in that case, target BP is <180/105 mmHg); ICH - immediately for patients with SBP ≥220 mmHg, otherwise no immediate BP lowering	TIA or ischaemic stroke - SBP target 120-130 mmHg; ICH - immediate IV therapy to target SBP <180 mmHg for patients with SBP ≥220 mmHg	RAS antagonist + CCB or thiazide-like diuretic
ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)[95]	Ischaemic stroke or TIA - start (or re-start, if previously treated) antihypertensive treatment for those with an established BP of ≥140/90 a few days after the event; acute ischaemic stroke - treat BP if >185/110 mmHg in patients eligible for thrombolysis to <185/110 mmHg, consider treating BP if >220/120 mmHg in patients not eligible for thrombolysis/thrombectomy, with a reduction of 15% during the first 24 hours; ICH - immediate treatment with IV infusion if SBP > 220 mmHg, but acute SBP lowering to <140 mmHg should be avoided in spontaneous ICH presenting within 6 hours of the acute event and SBP 150-220 mmHg	TIA or ischaemic stroke - BP target <130/80 mmHg; lacunar stroke - a target SBP <130 mmHg may be reasonable	ACEi, ARB, thiazide diuretic, or combination treatment consisting of a thiazide diuretic plus ACEi
International Society of Hypertension (ISH): Global hypertension practice guidelines (2020)[200]	TIA - no recommendation; ischaemic stroke - lowering over one hour if BP ≥220/120 mmHg (≥185/110 mmHg if thrombolysis is indicated) to mean arterial pressure -15%; ICH - immediate lowering for patients with SBP ≥180 mmHg	Ischaemic stroke - BP should be lowered if ≥140/90 mmHg and treated to a target of <130/80 mmHg (<140/80 in elderly patients); ICH - immediate IV therapy to target SBP 130-180 mmHg for patients with SBP ≥180 mmHg	RAS antagonists, CCBs, and diuretics are first-line drugs

Hypertension Canada: Guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children (2018)[186]	Acute ischaemic stroke - treat BP if >185/110 mmHg in patients eligible for thrombolysis to <180/105 mmHg; Ischaemic stroke or TIA - treatment of hypertension should not be routinely undertaken acutely unless extreme BP elevation (≥220/120 mmHg, lower by 15-25%), treatment should be strongly considered after the acute phase; ICH - acute SBP lowering to <140 mmHg should be avoided	Ischaemic stroke - after the acute phase, target BP is <140/90 mmHg	ACEi + thiazide/thiazide-like diuretic
The Japanese Society of Hypertension Guidelines for the Management of Hypertension (2019)[202]	Acute ischaemic stroke - treat BP if >185/110 mmHg in patients eligible for thrombolysis to <185/105 mmHg, or 85-90% of the pre-treatment value, consider treating BP if >220/120 mmHg in patients not eligible for thrombolysis/thrombectomy, to 85% of the pre-treatment value; acute ICH - treat if BP >140 mmHg to reduce BP to <140 mmHg as soon as possible (with caution in increased intracranial pressure); acute SAH - treat if BP >160 mmHg to 80% of the pre-treatment value (with caution in increased intracranial pressure)	Ischaemic stroke (post-acute) - treat all with SBP>130 mmHg (one month or more after onset) to <130/80 mmHg (<140/90 mmHg in patients with marked stenosis of the bilateral carotid arteries or occlusion of a main trunk of the cerebral arteries, or unevaluated patients)	CCB, ACEi, ARB, or diuretic
Stroke-specific guidelines			
American Heart Association (AHA)/American Stroke Association (ASA): Guideline for the prevention of stroke in patients with stroke and transient ischemic attack (2021)[32]	No specific additional recommendations	TIA or ischaemic stroke in patients with hypertension - BP target <130/80 mmHg; TIA or ischaemic stroke in patients with no history of hypertension and who have an average office BP of ≥130/80 mmHg - consider antihypertensive treatment	ACEi, ARB, thiazide diuretic, or combination treatment consisting of a thiazide diuretic + ACEi
American Heart Association (AHA)/American Stroke Association (ASA): Guidelines for the management of spontaneous intracerebral hemorrhage (2015)[269]	ICH – measures to control BP should begin immediately; treatment with IV infusion if SBP > 220 mmHg; if SBP is 150-220 mmHg, acute SBP lowering to 140 mmHg is recommended	ICH – BP target <130/80 mmHg	NA

Canadian stroke best practice recommendations on secondary prevention of stroke (2020)[233]	No specific additional recommendations	Ischaemic stroke - after the acute phase, target BP is <140/90 mmHg; lacunar stroke - aggressive BP lowering to achieve a consistent SBP target of <130 mmHg; ICH - BP should be aggressively monitored, treated, and controlled to sustain a consistent BP target of <130/80 mmHg; in symptomatic flow-restricting vascular stenosis, it is reasonable to aim for higher than usual BP targets; encourage regular home BP monitoring to assess control	ACEi + thiazide/thiazide-like diuretic
UK Royal College of Physicians (RCP): National clinical guideline for stroke, 5th edition (2016)[60]	Stroke or TIA - initiate treatment before hospital discharge or at two weeks, whichever is the soonest, or at the first clinic visit for people not admitted to hospital; ICH – urgent treatment to lower SBP to 140 mmHg for at least 7 days in those who present within 6 hours of acute ICH with SBP > 150 mmHg (unless the Glasgow Coma Scale score is <6, the haematoma is very large and death is expected, a structural cause is identified, or neurosurgical evacuation is pending)	Stroke or TIA - target clinic SBP <130 mmHg (140-150 mmHg in patients with severe bilateral carotid artery stenosis), it is appropriate to lower BP in patients who previously would have been considered normotensive	CCB or thiazide-like diuretic in people aged 55 or over, or of African or Caribbean origin at any age, + ACEi/ARB if target BP is not achieved; ACEi or ARB in people aged 54 or younger, not of African or Caribbean origin

UK National Institute of Clinical Excellence (NICE), Stroke and transient ischaemic attack in over 16s (2019)[270]	Acute ischaemic stroke – antihypertensive therapy is only recommended if there is a hypertensive emergency (e.g. hypertension in the presence of encephalopathy, nephropathy, heart failure, aortic dissection, pre-eclampsia), and treatment should be considered to achieve a target BP of 185/110 mmHg in candidates for IV thrombolysis; ICH – rapidly lower SBP to a target of 130-140 mmHg within one hour of starting treatment and for at least 7 days in those who present within 6 hours of acute ICH with SBP 150-220 mmHg (unless the Glasgow Coma Scale score is <6, the haematoma is very large and death is expected, a structural cause is identified, or neurosurgical evacuation is pending)	NA	NA
UK National Institute of Clinical Excellence (NICE) Clinical Knowledge Summaries, Stroke and TIA (2020)[235]	Stroke or TIA - treatment should be initiated by secondary care following diagnosis	Stroke or TIA - target clinic SBP <130 mmHg (140-150 mmHg in patients with severe bilateral carotid artery stenosis)	May include a thiazide-like diuretic, long-acting CCB, or ACEi
Transient ischaemic attack (TIA); intracerebral haemorrhage (ICH); blood pressure (BP); systolic blood pressure (SBP); renin-angiotensin-system (RAS); calcium channel blocker (CCB); angiotensin-converting enzyme inhibitor (ACEi); angiotensin II receptor blocker (ARB); subarachnoid haemorrhage (SAH)			

Table 1-2 Main randomised controlled trials of BP lowering and secondary stroke prevention

Study	Year	Country	n	Sex, male (%)	Mean age, y	Stroke type	Mean baseline BP, mmHg	Intervention	Primary outcome	Mean follow-up, y	Mean BP difference at follow-up, mmHg	RR for recurrent cerebro-vascular events
HSCSG[271]	1974	USA	452	59	60	Ischaemic stroke/TIA: 96%, unknown (4%)	167/100	Deserpidine vs placebo	Any stroke	2.3	25/12	RR 0.80 (0.49-1.29)
Dutch TIA Trial[128]	1993	Netherlands	1473	64	NA, 52% >65y	Ischaemic stroke: 66% (non-disabling), TIA: 34%	157/91	Atenolol vs placebo	Vascular death, non-fatal stroke, or non-fatal myocardial infarction	2.6	6/5	HR 0.82 (0.57–1.19)
TEST[126]	1995	Sweden	720	70	71	Ischaemic stroke: 86%, TIA: 8%, ICH: 6%	NA	Atenolol vs placebo	Death, stroke and myocardial infarction	2.3	NA	HR 1.00 (0.75–1.35)
PATS[127]	1995	China	5665	72	60	Ischaemic stroke/TIA: 84%, ICH: 16%	154/93	Indapamide vs placebo	Fatal and non-fatal stroke	2	5/2	HR 0.73 (0.60–0.89)
HOPE*[272]	2000	International	1013	NA	NA	Ischaemic stroke/TIA: 100%	151/79	Ramipril vs placebo	Recurrent stroke (sub-study)	5	3/2	RR 0.58 (0.30-1.13)
PROGRESS[71]	2001	International	6105	70	64	Ischaemic stroke: 71%, TIA/amaurosis fugax: 23%, ICH: 11%, Unknown 5%	147/86	Perindopril ± indapamide vs placebo	Fatal or non-fatal stroke (ischaemic stroke + ICH)	3.9	9/4	HR 0.73 (0.64–0.84)
Liu et al.[273]	2005	China	1520	71	64	Ischaemic stroke/TIA: 82%, ICH: 18%	145/87	Perindopril + indapamide vs placebo	Fatal or non-fatal stroke (ischaemic stroke + ICH)	4	14/6	HR 0.45 (0.35–0.59)

MOSES[131]	2005	Germany/ Austria	1352	54	68	Ischaemic stroke: 61%, TIA: 33%, ICH: 6%	151/87	Eprosartan vs nitrendipine	Composite of total mortality and all vascular events	2.5	-1.5/-0.6	IDR 0.75 (0.55-0.97) in favour of eprosartan
PRoFESS[64]	2008	International	20,332	71	66	Ischaemic stroke/TIA: 100%	144/84	Telmisartan vs placebo	Fatal or non-fatal stroke (ischaemic stroke + ICH)	2.5	4/2	HR 0.95 (0.86–1.04)
SPS3[29]	2013	International	3020	63	63	Lacunar ischaemic strokes, MRI confirmed: 100%	144/79	Lower target (< 130) SBP vs standard target (130-149 mmHg)	Fatal or non-fatal stroke (ischaemic stroke + ICH)	3.7	11 (SBP)	HR 0.81 (0.64–1.03)
PAST-BP[30]	2015	UK	379	59	72	Stroke (undifferentiated): 48%, TIA: 52%	143/79	Lower target (< 130) SBP vs standard target (<140 mmHg)	Change in clinic SBP between baseline and 12 months	1	14/6	N/A
PODCAST[31]	2017	UK	83	64	74	Ischaemic stroke: 93%, ICH: 7%	147/82	Lower target (< 125) SBP vs standard target (<140 mmHg)	Addenbrooke's Cognitive Eamination Revised (ACE-R)	2	11/6	N/A
RESPECT[28]	2019	Japan	1280	70	67	Ischaemic stroke: 85%, ICH: 15%	145/84	Lower target (< 120/80) BP vs standard target (<140/90 mmHg)	Fatal or non-fatal stroke (ischaemic stroke + ICH)	3.9	7/3	HR 0.73 (0.49-1.11)

***Subgroup of the main trial. Transient ischaemic attack (TIA); intracerebral haemorrhage (ICH); blood pressure (BP); systolic blood pressure (SBP); relative risk (RR); hazard ratio (HR); incidence density ratio (IDR), not available (NA)**

Table 1-3 Use of various blood pressure measurement modalities in primary prevention hypertension guidelines

Guideline	Diagnostic threshold	Modality for hypertension diagnosis	Use of out-of-office measures	Management
European Society of Cardiology (ESC)/European Society of Hypertension (ESH): Guidelines for the management of arterial hypertension (2018) [59]	Hypertension is defined as mean clinic BP ≥140/90 mmHg OR ABPM daytime mean ≥135/85 mmHg / ABPM 24h mean ≥130/80 mmHg / ABPM night-time mean ≥120/70 mmHg / 3-7 day HBPM mean ≥135/85 mmHg	Single office BP measurement if BP is ≥180/110 mmHg, otherwise repeated office BP measurements on multiple visits or ABPM/HBPM	Specific indications for ABPM/HBPM: suspicion of masked and white-coat hypertension, evaluation of resistant hypertension	ABPM/HBPM for quantifying the effects of treatment and identifying possible causes of side effects (e.g. symptomatic hypotension)
National Institute for Health and Care Excellence (NICE): Clinical guideline on hypertension in adults – Diagnosis and management (2019) [1 99]	Hypertension is defined as mean clinic BP ≥140/90 mmHg AND 24-hour ABPM daytime (or 4-7 day HBPM) mean ≥135/85 mmHg	Measure office BP in both arms, using the arm with the higher reading thereafter if there is a difference of >15 mmHg. If BP is ≥140/90 mmHg then take a second measure during the consultation, and a third if the second is 'substantially different'.	Record the lower of the last two measurements. If clinic BP is ≥140/90 mmHg, ABPM is required to confirm the diagnosis, unless BP is ≥180/120 mmHg (immediate treatment if target organ damage is identified, repeat clinic BP within one week if not). HBPM can be offered only if ABPM is unsuitable or not tolerated by the patient.	Use office BP to monitor the response to treatment. If patients choose to self-monitor, advise that they use HBPM.
International Society of Hypertension (ISH): Global hypertension practice guidelines (2020) [200]	Hypertension is defined as mean clinic BP ≥140/90 mmHg over 2-3 office visits at 1-4 week intervals, or ≥180/110 mmHg over a single visit, OR ABPM daytime mean ≥135/85 mmHg / ABPM 24h mean ≥130/80 mmHg / ABPM night-time mean ≥120/70 mmHg / 3-7 day HBPM mean ≥135/85 mmHg	Office/clinic BP, measured three times with one minute between readings, with the mean of the last two readings used. If the first reading is <130/85 mmHg, no further measurement is required.	If office BP is between 130/85 and 160/100 mmHg, HBPM or ABPM is required for confirmation.	Consider HBPM to improve medication adherence

Hypertension Canada: Guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children (2018)[186]	Hypertension is defined as office BP ≥180/110 mmHg over a single visit, or mean office BP ≥140/90 mmHg AND ABPM daytime mean ≥135/85 mmHg / ABPM 24h mean ≥130/80 mmHg / 7-day HBPM mean ≥135/85 mmHg	Office/clinic BP, measured three times with the mean of the last two readings used. Single office/automated office BP measurement if BP is ≥180/110 mmHg	If office BP is ≥140/90 or automated office BP is ≥135/85, ABPM (preferred), HBPM (if ABPM is not tolerated or available), or serial office measurements over 3-5 visits (if ABPM/HBPM not available) is required for confirmation	Office BP, assessed monthly or every two months, is used to assess treatment response until readings on two consecutive visits are below target
US Preventive Services Task Force (USPSTF): Final recommendation statement on screening for hypertension in adults (2021)[201]	No guidance on thresholds for diagnosis	Office BP is indicated for initial screening but must be confirmed outside of the clinical setting with either 12-24 hour ABPM or HBPM	ABPM was used as the reference standard for office BP and HBPM in the review	No guidance
ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)[95]	Hypertension is defined as mean office BP ≥130/80 mmHg over two visits OR ABPM daytime mean ≥130/80 mmHg / ABPM 24h mean ≥125/75 mmHg / ABPM night-time mean ≥110/65 mmHg / HBPM (based on readings on ≥2 occasions) mean ≥130/80 mmHg	Office/clinic BP recorded initially in both arms, and subsequently in the arm with the higher reading, with an average of ≥2 readings obtained on ≥2 occasions	ABPM/HBPM is recommended for screening for white-coat hypertension before diagnosing hypertension, in untreated adults with BP 130/80 - 160/100 mmHg, and for screening for masked hypertension in untreated adults with BP 120/75 - 129/79 mmHg	ABPM/HBPM is recommended for titration of BP-lowering medication, in conjunction with telehealth counselling or clinical interventions
Joint National Committee VIII, Evidence-Based Guideline for the Management of High Blood Pressure in Adults (2014)[274]	Hypertension is defined as office BP ≥140/90 mmHg	Office BP	No specific recommendations for ABPM/HBPM	No specific guidance, office BP implied

The Japanese Society of Hypertension Guidelines for the Management of Hypertension (2019)[202]	Hypertension is defined as office BP ≥140/90 mmHg, AND HBPM BP ≥135/85 mmHg	Office BP (mean of at least two measures with stable values at intervals of 1-2 minutes, on at least two different occasions) AND 5-7 day HBPM	ABPM is indicated when HBPM fluctuates around 135/85 mmHg or office BP fluctuates around 140/90 mmHg, when a definite diagnosis of masked or white-coat hypertension is not diagnosed on HBPM, or when home and office levels markedly differ	Antihypertensive treatment should be based and titrated using HBPM rather than office BP
Korean Society of Hypertension Guidelines for the management of hypertension: part II-diagnosis and treatment of hypertension (2018)[205]	Hypertension is defined as office BP ≥140/90 mmHg, AND HBPM BP ≥135/85 mmHg or 24-hour ABPM daytime mean ≥135/85 mmHg/24-hour mean ≥130/80 mmHg or AOBP mean ≥135/85 mmHg	Office BP (mean of at least two measures with stable values at intervals of 1-2 minutes, on a single occasion) AND 7-day HBPM	HBPM is recommended to diagnose sustained HTN, white coat HTN, and masked HTN and to estimate prognosis (i.e. all cases). ABPM can be used for identifying white coat and masked HTN and estimating prognosis. AOBP can be used if HBPM/ABPM is not available	Antihypertensive treatment should be based and titrated using HBPM or ABPM
Chinese Guidelines for Prevention and Treatment of Hypertension—A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension (2018)[203]	Hypertension is defined as office BP ≥140/90 mmHg	Office BP (two BP measurements should be taken 1–2 min apart and averaged for records. An additional measurement is required if the first two readings differ by > 5 mmHg, and the mean value of the three readings should be recorded)	If possible, out-of-office BP measurement should be performed to diagnose white-coat hypertension and masked hypertension, evaluate the efficacy of antihypertensive therapy, and assist the diagnosis and treatment of resistant hypertension	Home BP monitoring may assist in adjusting treatment regimens. Remote real-time BP monitoring is a new possibility. Patients with high psychological anxiety are not recommended to have their BP checked frequently.
Blood pressure (BP); ambulatory BP monitoring (ABPM); home BP monitoring (HBPM)				

Table 1-4 Studies of ambulatory blood pressure monitoring in secondary stroke prevention

Author	Year	Study type	n	Mean age (SD)	Sex (male %)	Events	Timing of ABPM	Main findings	Predictive analyses, follow-up
Castilla-Guerra et al.[275]	2009	Prospective cohort study	101	71 (11)	61%	Ischaemic stroke (85%); ICH (15%)	On admission (within 24 hours of stroke onset); 6-month follow-up; 12-month follow-up	Chronic disruption of circadian rhythm of BP up to one-year post-stroke	None
Castilla-Guerra et al.[276]	2011	Prospective cohort study	50	68 (11)	62%	Ischaemic stroke (100%)	Within 6 months after stroke, post-discharge	Nocturnal hypotension present in 42%	None
Cugini et al.[277]	1997	Retrospective cohort study	51	58 (14)	51%	TIA (100%)	Chronic (after 'recent' TIA)	Inadequate BP management (based on clinic BP) in 90% when assessed on ABPM	None
Davison et al.[278]	2019	Randomised controlled trial - post-hoc analysis	80	74 (10)	66%	Minor ischaemic stroke (34%); TIA (66%)	Baseline (3 days - 12 weeks after stroke/TIA); 6-month follow-up	Daytime and 24-hour ABPM BP was significantly lower than clinic BP, suggesting a marked white-coat effect, but was also lower than HBPM BP	None
Harbison et al.[279]	2008	Cross-sectional study	100	69 (11)	49%	Stroke (69%, no information on ischaemic vs haemorrhagic); TIA (31%)	1-6 months after stroke	Hypertension and hypotension on ABPM was associated with post-stroke fatigue	None
Nakamura et al.[280]	1995	Prospective cohort study	76	63 (6)	80%	Ischaemic stroke	More than one month after stroke	Nocturnal dipping (vs non-dipping) on ABPM was associated	Yes, mean 2.3 years of follow-up, no survival analysis

						(84%); TIA (16%)		with recurrent stroke, but only among treated participants	
Phillips et al.[281]	2000	Case-control study	166	70 (11)	49%	Ischaemic stroke (88%); ICH (12%)	1 week - 4 years after stroke	The prevalence of non-dipping on ABPM was higher in patients with stroke than in matched controls	None
Sasaki et al.[282]	2011	Prospective cohort study	48	82 (8)	25%	Ischaemic stroke (90%); ICH (10%)	1-3 months after stroke	Nocturnal BP fall was blunted in the majority (~90%), and overall, nocturnal BP was higher than diurnal BP (population = elderly bedridden stroke survivors)	None
Staals et al.[283]	2009	Cross-sectional study	123	65 (23)	61%	Lacunar stroke (100%)	1-6 months after stroke	High BP on ABPM was associated with concurrent cerebral microbleeds	None
Tao et al.[284]	2017	Prospective cohort study	1764	63 (11)	68%	Ischaemic stroke (90%); TIA (10%)	ABPM during hospitalisation (within 7 days of onset)	There was no association between blood pressure variability on ABPM measurement and stroke recurrence	Yes, recurrent non-fatal stroke during one-year follow-up. 24-hour ABPM top versus bottom quartile of mean SBP adjusted HR for recurrent stroke = 1.9 (95%CI 1.1-3.4)
Webb et al.[173]	2018	Prospective cohort study	472	66 (13)	58%	TIA and minor stroke (proportions not documented)	1 month post-event	BP variability (CV) on awake ABPM was not associated with risk of recurrent stroke, death, or vascular events	Yes, recurrent stroke, vascular events, and all-cause mortality during 2-5 years follow-up. Awake ABPM BP variability HR (per SD, adjusted for mean BP) for vascular events/vascular death = 1.08 (95% CI 0.77–1.52)
Xu et al.[285]	2021	Prospective cohort study	1996	63 (11)	67%	Ischaemic stroke	During hospitalisation	Nocturnal SBP, non-dipping and reverse dipping did not significantly predict the risk of	Yes, recurrent non-fatal stroke during three months of follow-up.

						(88%); TIA (12%)	(within 7 days of onset)	stroke recurrence, but ABPM profile (normal, morning surge profile, or high nocturnal BP profile) did	24-hour ABPM mean SBP (per mmHg) adjusted HR for recurrent stroke = 1.01 (95%CI 0.99-1.02)
Yamamoto et al.[286]	1998	Prospective cohort study	105	68 (8)	69%	Lacunar stroke (100%)	More than one-month post-discharge, once BP control was achieved based on clinic BP	High BP on ABPM, especially nocturnal hypertension and blunting of nocturnal fall in BP were associated with the development of recurrent stroke and silent ischaemic lesions on MRI	Yes, mean 3.2 years of follow-up, no survival analysis
Yamamoto et al.[287]	2002	Prospective cohort study	177	69 (9)	63%	Lacunar stroke (100%)	14-30 days after stroke	High BP on ABPM was independently associated with recurrent vascular events, and associations were stronger than for clinic BP, but not for dementia. Non-dipping status was independently associated with the development of dementia	Yes, mean 8.9 years of follow-up. 24-hour ABPM high SBP (>145 vs <130 mmHg) adjusted HR for recurrent vascular events = 10.3 (95%CI 1.3-81.3)
Yamamoto et al.[288]	2011	Prospective cohort study	224	70 (9)	60%	Lacunar stroke (100%)	2-4 weeks after stroke, without antihypertensive treatment	Non-dipping and riser status on 24-hour ABPM was associated with cognitive impairment, but high SBP (>145 mmHg) was not	None
Zakopoulos et al.[17]	2006	Prospective cohort study	187	65 (9)	70%	Ischaemic stroke (79%); ICH (21%)	120 (+/- 30) days after stroke	ABPM is significantly more sensitive than clinic BP measurement. Masked hypertension was found in 16% overall, white-coat hypertension in 4.8%. Reverse dipping has a higher prevalence among those with masked hypertension	None

Transient ischaemic attack (TIA); intracerebral haemorrhage (ICH); blood pressure (BP); systolic blood pressure (SBP); ambulatory BP monitoring (ABPM)

Table 1-5 Studies of home blood pressure monitoring in secondary stroke prevention

Author	Year	Study type	n	Mean age (SD)	Sex (male %)	Events	Timing of HBPM	Main findings	Predictive analyses, follow-up
Davison et al.[241]	2018	Randomised controlled trial	171	73 (10)	65%	Minor ischaemic stroke (34%); TIA (66%)	6 weeks after stroke/TIA; 3-5 month follow-up	HBPM (+/- telemonitoring and guided therapy) did not result in lower 6-month ABPM BP compared with usual care, despite good adherence.	None
Tao et al.[284]	2017	Prospective cohort study	1764	63 (11)	68%	Ischaemic stroke (90%); TIA (10%)	From discharge to 90-days post event, twice daily	Long-term BP variability on HBPM was a better predictor for stroke recurrence than short-term variability on ABPM	Yes, recurrent non-fatal stroke during one-year follow-up. HBPM top versus bottom quartile of mean SBP adjusted HR for recurrent stroke = 1.3 (95% CI 0.7–2.1). Indices of long-term BPV on HBPM were significantly associated with stroke recurrence (SD: adjusted HR: 1.939, 95% CI: 1.122–3.351; CV: adjusted HR 1.955, 95% CI: 1.174–3.255), independent of mean SBP
Dai et al.[289]	2020	Prospective cohort study	2325	63 (11)	67%	Ischaemic stroke (89%); TIA (11%)	Within 3 months post-event	Systolic and diastolic BP variability on HBPM were associated with stroke recurrence	Yes, recurrent stroke and cardiovascular events during three months of follow-up. Adjusted OR per quartile systolic BP SD 1.72 (95% CI 1.09-2.71), CV: 1.86, (95% CI 1.19-2.92)

Hanley et al.[290]	2015	Randomised controlled trial (pilot)	55	71 (12)	60%	Ischaemic stroke (49%); TIA (51%)	More than 3 months post-event	10.1 (HBPM) vs 3.8 (control) mean reduction in 6-month follow-up ABPM	None
Kerry et al.[239]	2013	Randomised controlled trial (pilot)	381	72 (12)	58%	Ischaemic stroke (32%); TIA (61%); ICH (5%); Unknown (2%)	Within 9 months post-event	HBPM did not improve blood pressure control in patients with hypertension and a history of stroke	None
Webb et al.[173]	2018	Prospective cohort study	472	66 (13)	58%	TIA and minor stroke (proportions not documented)	1 week of HBPM just before 1-month post-event	BP variability (CV) on HBPM was not associated with stroke risk but was associated with all-cause mortality and a composite of death and cardiovascular events	Yes, recurrent stroke, vascular events, and all-cause mortality during 2-5 years follow-up. HBPM BP variability HR (per SD, adjusted for mean BP) for vascular events/vascular death = 1.41 (95% CI 1.09–1.83)

Transient ischaemic attack (TIA); intracerebral haemorrhage (ICH); blood pressure (BP); systolic blood pressure (SBP); home BP monitoring (HBPM)

1.11 Figures

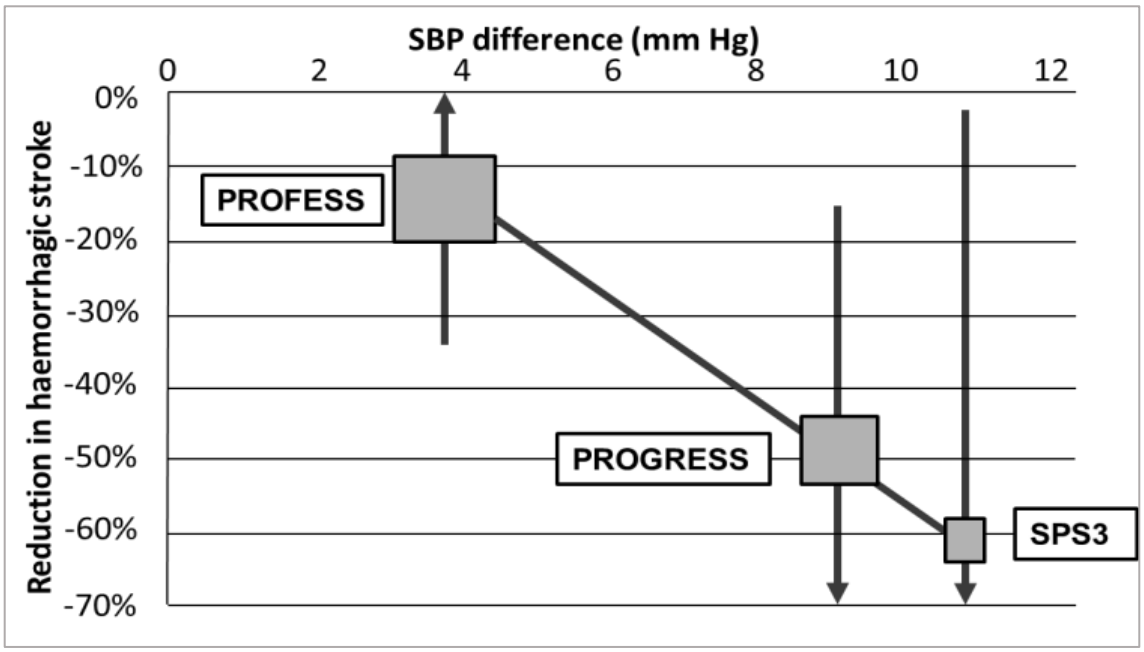


Figure 1-1 Reduction in haemorrhagic stroke in clinical trials (from the UK TRIDENT HBPM sub-study protocol (see Appendix 3.1), courtesy of the TRIDENT investigators)

Systolic blood pressure (SBP)

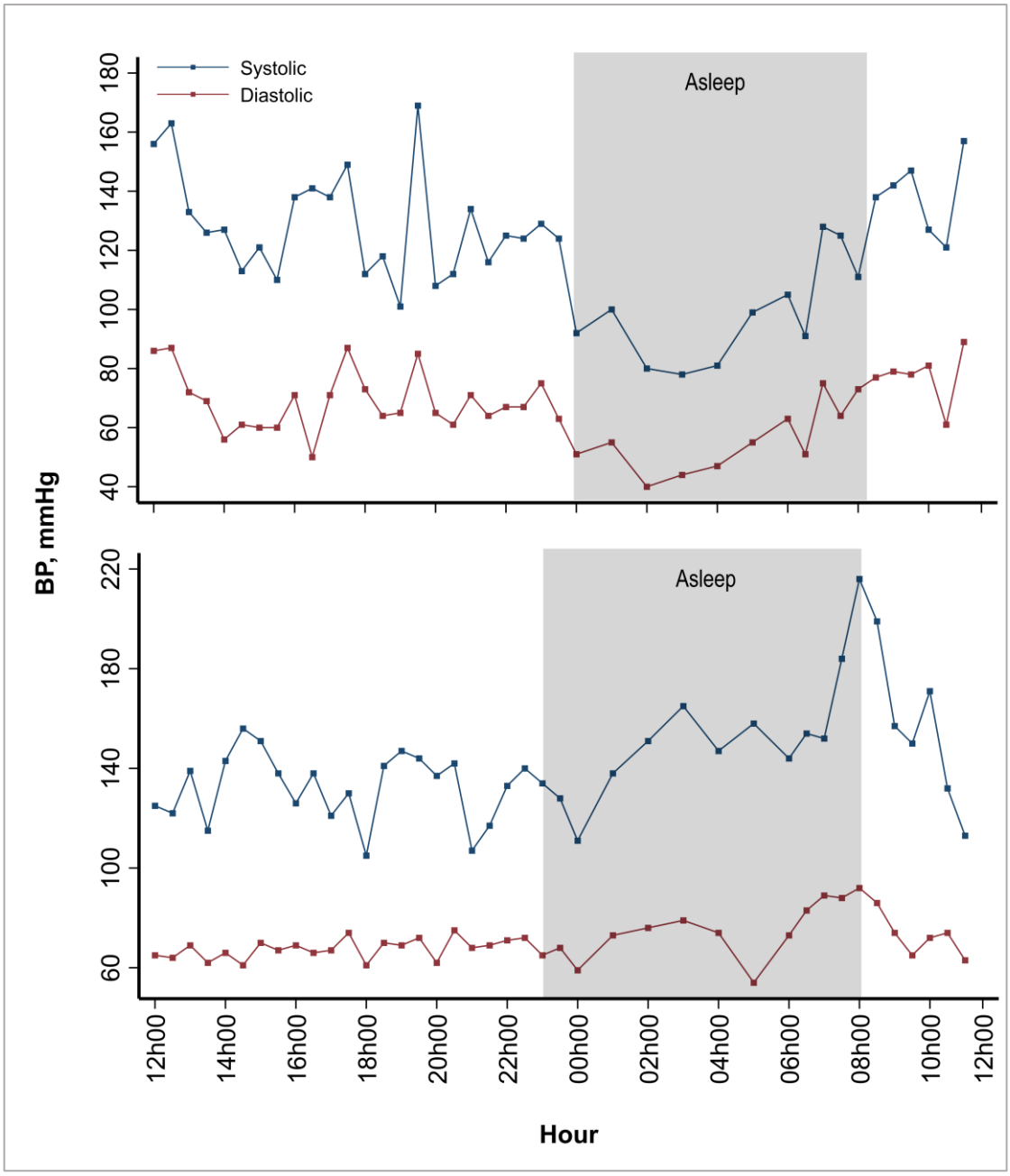


Figure 1-2 Normal 'dipping' profile (top) and abnormal 'non-dipping' profile (bottom) on 24-hour ambulatory BP monitoring after stroke

24-hour ambulatory blood pressure (BP) monitoring traces of two participants in the COMMIT study, performed one month after minor ischaemic stroke. Monitoring was performed at home with an A&D TM-2430 monitor in the non-dominant arm. BP was measured at 30-minute intervals during the day (06:00 to 00:00) and 60-minute intervals at night, and the shaded area corresponds to time asleep, as documented in a patient diary.

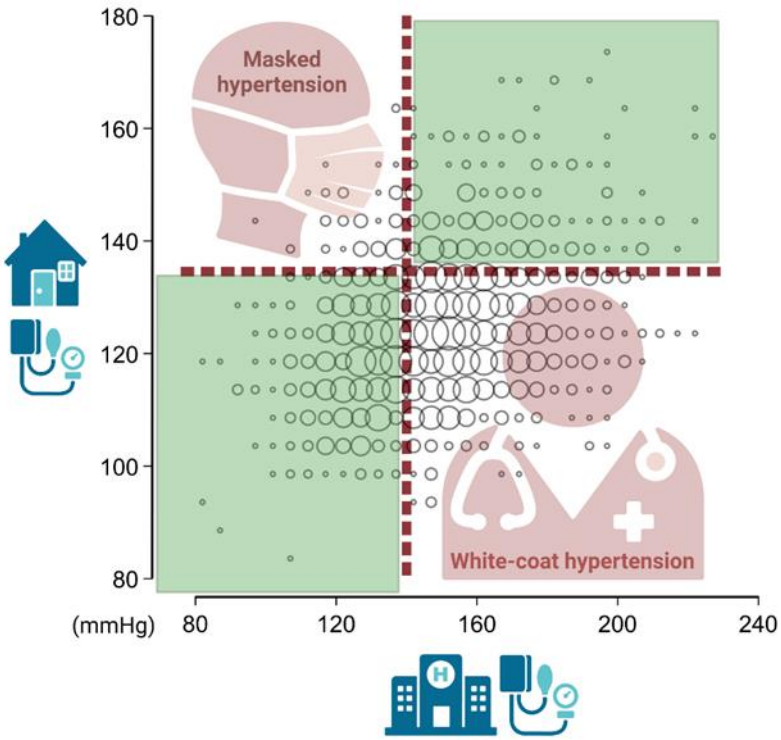


Figure 1-3 Masked and white-coat hypertension in the COMMIT population, as defined by disagreement between home BP monitoring and clinic BP

Mean systolic blood pressure (BP) on 7-day home BP monitoring (y-axis) versus clinic BP recordings (x-axis, mean of two seated readings) in 1656 participants in the COMMIT study, performed on clinic attendance for acute TIA/minor stroke. Home BP monitoring was performed three times daily with a telemetric device. The green shaded area corresponds to the agreement between the two modalities (true hypertension/normotension). The size of the markers in the scatter plot are weighted by the number of cases in each 5 mmHg bin of systolic BP on each modality. Masked hypertension was defined as clinic systolic BP <140 and mean 7-day home systolic BP ≥135 mmHg. White-coat hypertension was defined as clinic systolic BP ≥140 and mean 7-day home systolic BP <135 mmHg.

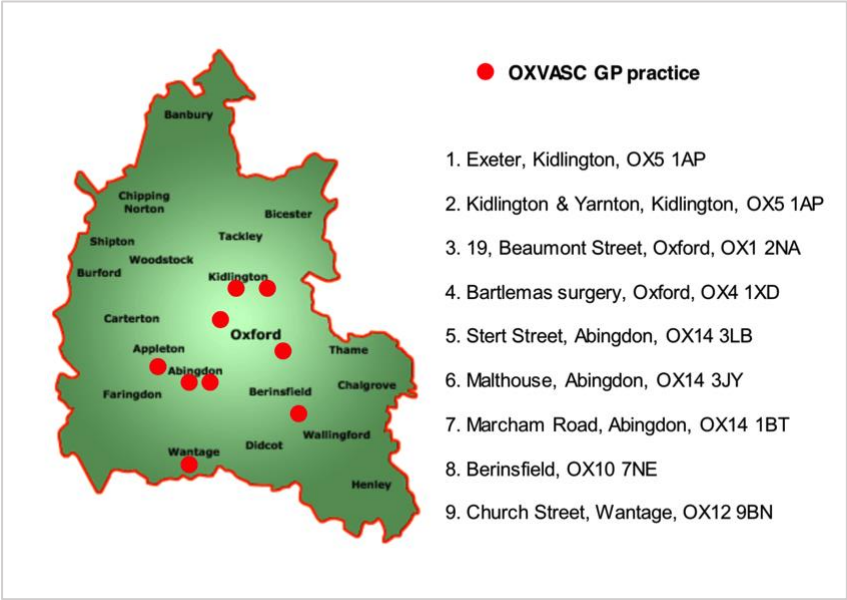


Figure 1-4 Oxford Vascular Study primary care practices

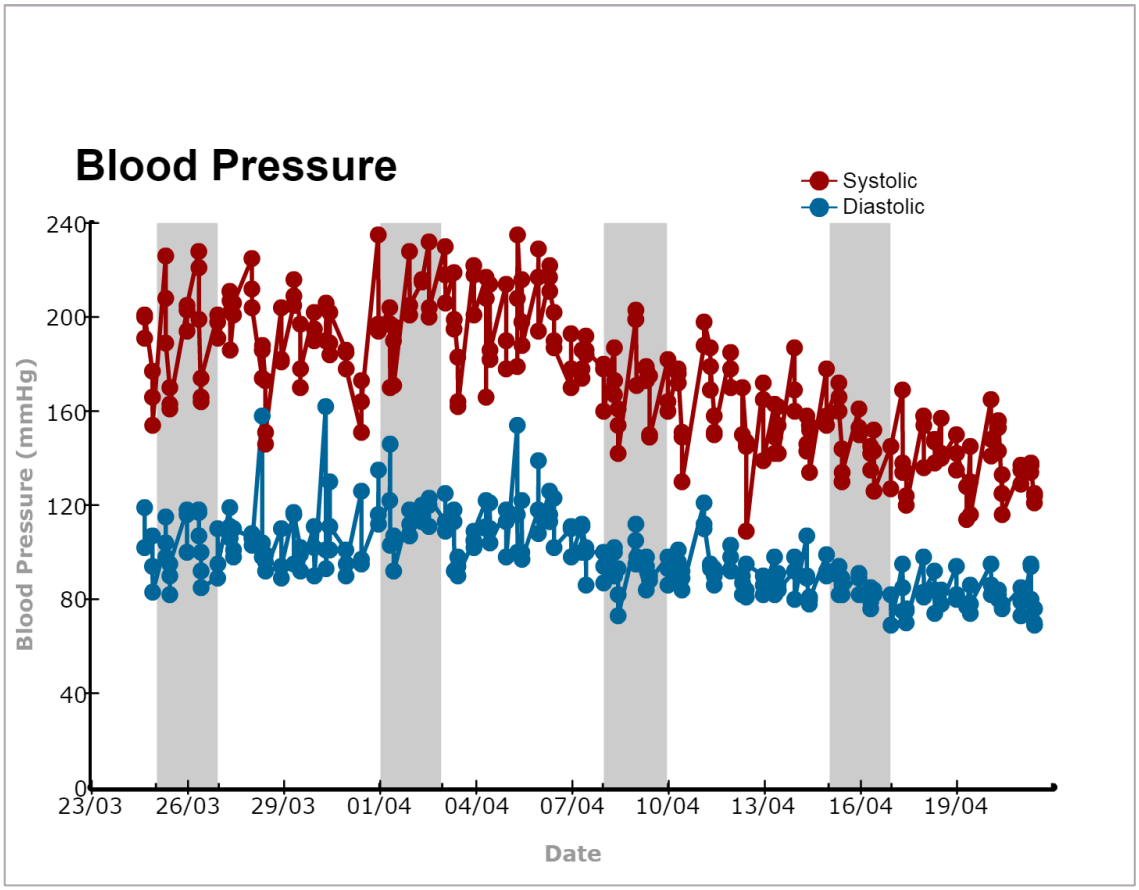


Figure 1-5 A sample real-time blood pressure tracing from the secure server used for the COMMIT and PROHIBIT-ICH studies

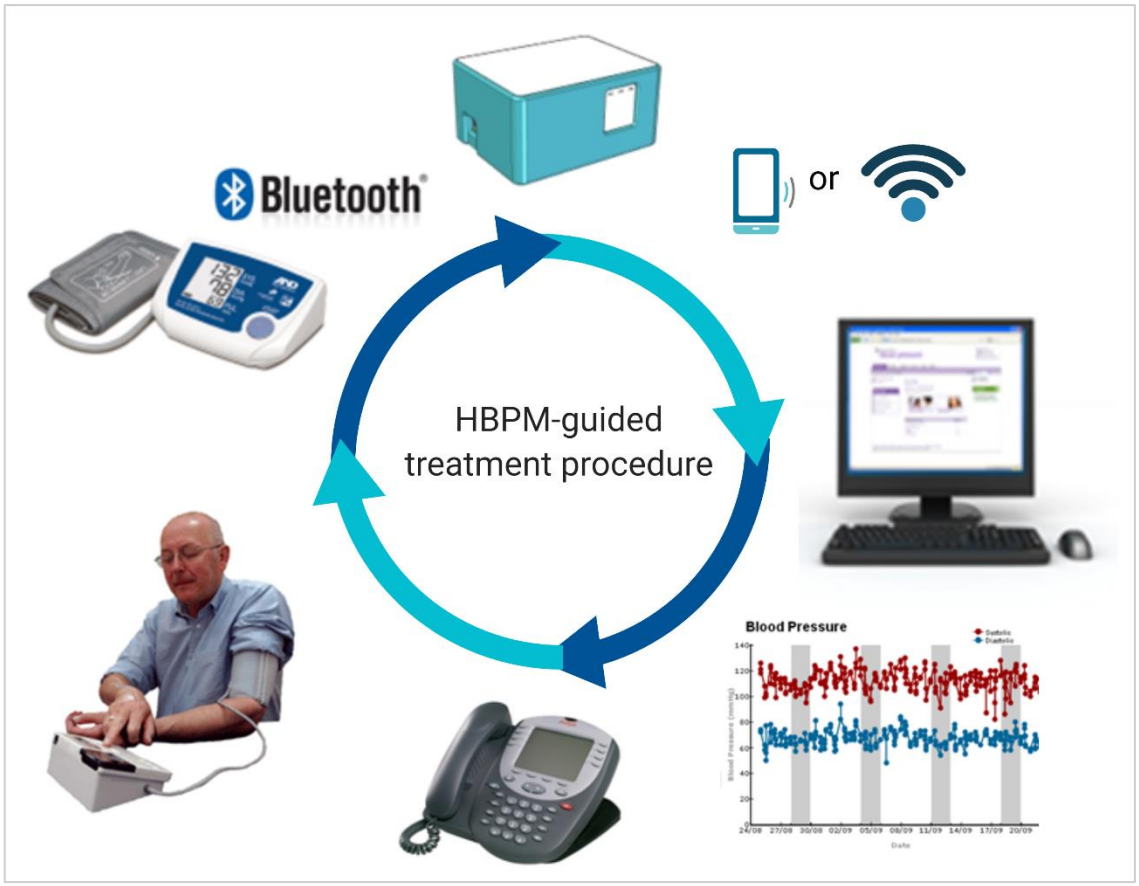


Figure 1-6 Home blood pressure monitoring-guided blood pressure management programme schema

Home blood pressure monitoring (HBPM). The patient records their blood pressure at home, readings are transferred automatically by Bluetooth to a Raspberry Pi microcomputer hub, which, in turn, transmits data by cellular network or Wi-Fi to a secure service that I accessed, analysed, and called the patient by telephone to advise medication changes and post prescriptions (for the COMMIT study) / advise the patient's GP to prescribe new medications (for the PROHIBIT-ICH trial)

Chapter 2: Early assessment of blood pressure after TIA and minor stroke (Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study)

2.1 Abstract 61
2.2 Introduction 63
2.3 Methods 65
2.3.1 Study design and participants 65
2.3.2 Procedures 65
2.3.3 Statistical analysis **67**
2.4 Results 69
2.5 Discussion 73
2.6 Tables 77
2.7 Figures 90

2.1 Abstract

Background: Clinical guidelines recommend treatment of hypertension after acute transient ischaemic attack (TIA) and minor stroke based on clinic blood pressure measurement despite its well-recognised limitations in other settings. A transient rise in blood pressure in the acute stages after TIA/stroke ('post-stroke hypertension') coupled with high background blood pressure variability might further undermine the utility of early clinic blood pressure to guide treatment decisions. Home blood pressure monitoring (HBPM) improves diagnosis of hypertension and better predicts vascular events in primary prevention, but it has not been investigated in secondary prevention. In this chapter, I aimed to establish the extent of misdiagnosis of hypertension by clinic blood pressure versus telemetrically-verified HBPM early after TIA or minor stroke and to assess prognostic values.

Methods: After initial clinic blood pressure assessment, consecutive eligible patients with an acute TIA or minor stroke in a population-based study (Oxford Vascular Study) measured their blood pressure three times daily at home with a telemetric device. Misclassification of hypertension on clinic blood pressure versus mean blood pressure on the first three days of HBPM (masked hypertension - clinic blood pressure <140/90 and home blood pressure ≥135/85; transient post-event hypertension - clinic blood pressure ≥140/90 and home blood pressure <135/85 mmHg) was related to the risk of recurrent major vascular events (MVE) on ten-year follow-up.

Results: Of 1650 patients who underwent HBPM (mean/SD age=69.7/13.1), 1217 (73.8%) were hypertensive in clinic, of whom 452 (37.1%) had only transient post-event hypertension based on three-day HBPM. Of the 433 who were normotensive on clinic blood pressure, 112 (25.9%) had masked hypertension based on HBPM. Mean systolic blood pressure on three-day HBPM predicted MVE (n=222) more strongly (p_{diff}=0.004) (HR 1.38 per 20 mmHg, 95%CI 1.18-1.62, p<0.0001) than did baseline clinic blood pressure (1.05, 0.94-1.16, p=0.59), with clinic blood pressure undermined both by a

good prognosis in patients with transient post-event hypertension (ten-year MVE risk: HR=0.99, 0.80-1.24, p=0.96 versus correctly-classified normotension) and a poor prognosis in those with masked hypertension (HR=1.82, 1.05-3.12, p=0.032 versus correctly-classified normotension). Indeed, the relative risk of MVE in patients with transient post-event hypertension versus masked hypertension (HR=0.54, 0.32-0.91, p=0.021) was inversely related to their mean baseline clinic blood pressure (154/87 vs 128/76 mmHg, p<0.0001) but consistent with mean blood pressure on three-day HBPM (124/74 vs 140/82 mmHg, p<0.0001).

Conclusion: Diagnosis of hypertension based on conventional measurement of blood pressure early after TIA and minor stroke results in high rates of both overdiagnosis related to transient post-event hypertension and underdiagnosis due to masked hypertension. The use of three-day HBPM immediately after initial assessment allows better prognostication and is likely to improve secondary prevention.

2.2 Introduction

Guidelines recommend early antihypertensive treatment after transient ischaemic attack (TIA) and minor stroke to a systolic blood pressure target of 120-130 mmHg, in contrast to major ischaemic stroke where a delay of at least several days is advised.[59] Moreover, whereas blood pressure can be monitored carefully in hospital after major stroke, diagnosis of hypertension after TIA/minor stroke is often based on one-off assessment in the clinic or emergency department,[59, 60, 95, 291] despite well-recognised limitations of clinic blood pressure in diagnosis in primary prevention,[181, 198, 292-295] where 'white-coat hypertension' (isolated clinic hypertension)[292] and 'masked hypertension' (normal clinic but elevated home blood pressure)[295] are common in untreated[181, 294] and treated[293, 294] individuals. Indeed, these limitations might particularly undermine the utility of early clinic blood pressure assessment after TIA and minor stroke. First, people with TIA/stroke have increased background visit-to-visit variability in clinic blood pressure,[162, 232] and hence chance 'low' or 'high' readings.[161] Second, transiently elevated blood pressure ('post-stroke hypertension') is common in patients hospitalised after major stroke, possibly representing either a physiological response to brain injury or elevated anxiety levels,[296, 297] but there are few data in patients with TIA and minor stroke.

In primary prevention settings, home blood pressure monitoring (HBPM) improves diagnosis of hypertension by identifying masked and white-coat hypertension and better predicting vascular events[213, 215] and is preferred by patients to ambulatory blood pressure monitoring (ABPM),[211] but it has not been investigated in secondary prevention. HBPM is prone to imprecise recordings because of patient misreporting[220, 222] but this can be avoided with the use of telemetric systems that automatically report all measurements taken.[224] In view of the increased variability in clinic blood pressure in TIA and minor stroke,[162, 232] and the possibility that blood pressure might also be transiently elevated after these more minor events, I hypothesised that use of early clinic or emergency department blood pressure would lead to inadequate diagnosis of ongoing

hypertension and that a short period of HBPM immediately after the acute assessment would therefore have better prognostic value. In the absence of any previous comparisons of the prognostic value of clinic blood pressure versus HBPM in secondary prevention, and of the prognostic value of telemetric HBPM in any setting,[215] I designed a prospective telemetric HBPM study in a population-based cohort of patients assessed early after TIA and minor stroke to compare the predictive value of clinic blood pressure with HBPM for recurrent vascular events over long-term follow-up.

2.3 Methods

2.3.1 Study design and participants

The COMMIT study was nested within the Oxford Vascular Study (OXVASC), a population-based cohort study of the incidence and outcome of all acute vascular events in a defined population of 92,728 individuals, registered with around 100 general practitioners (GPs) in nine primary care practices in Oxfordshire, UK.[264, 298] OXVASC was approved by the Oxfordshire research ethics committee, including the HBPM substudy (OREC A: 05/Q1604/70). Written, informed consent was obtained for study interview and follow-up, including ongoing review of medical records and death certificates.

Consecutive OXVASC patients with TIA or minor stroke were prospectively recruited to this blood pressure monitoring study between April 1st 2008 and March 31st 2019. Case ascertainment was done using multiple overlapping methods and is near-complete for events reaching medical attention.[265, 299] These methods included a rapid access daily clinic to which GPs and the local emergency department refer individuals with suspected cerebrovascular events, daily searches of emergency departments, relevant hospital wards, eye hospital attendances, radiographic or vascular surgical investigations or procedures, and searches of GP practice diagnostic codes and referrals to acute and community hospitals.

2.3.2 Procedures

All consenting patients underwent a standardised medical history and examination, ECG, blood tests, a stroke protocol MRI brain scan and contrast-enhanced MRA (or CT brain scan and either a carotid Doppler ultrasound or CT-angiogram when MR imaging was contraindicated), an echocardiogram, and 5-days of ambulatory cardiac monitoring. All patients were assessed by a study physician and reviewed by the senior study neurologist (Professor Peter Rothwell). The aetiology of ischaemic events was classified

according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[267] Patients were followed up face-to-face at one, three, six, 12, 60, and 120 months. Recurrent vascular events were identified at each follow-up and by ongoing re-ascertainment.[265, 299] Post-event, pre-hospital acute blood pressure from paramedic/emergency department/GP records were also collected, and all premorbid blood pressure readings (both paper and electronic) were extracted from lifelong patient records held in primary care during the 15 years preceding ascertainment.

Clinic blood pressure was measured in the non-dominant arm by trained personnel, with two measurements made five minutes apart in the sitting position, after five minutes of rest. Patients were provided with a Bluetooth-enabled, regularly-calibrated, telemetric blood pressure monitor, either an A&D UA-767 BT or an IEM Stabil-o-Graph, on the day of the baseline clinic assessment. After appropriate training on the day, they were asked to perform three home blood pressure readings over ten minutes, three times daily (after waking, midday, and evening). Measurements were automatically transmitted by Bluetooth to a Raspberry Pi microcomputer hub, for secure transmission via a cellular network to a server hosting a password-protected website for review and download (OBS Medical, Abingdon, UK).

Patients continued monitoring for at least one month. Treatment of hypertension (commencement or intensification of medication) was recommended according to current guidelines,[59, 60, 95] based on clinic readings and HBPM, aiming for a target blood pressure <130/80 mmHg. Treatment was organised via outpatient prescription of medication unless there were contraindications or patients refused. Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a morning dose of perindopril arginine 5mg plus indapamide 1.25mg, or amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion. Patients were advised to obtain and take prescribed medication on the day of assessment if clinic systolic blood pressure ≥180 mmHg.

2.3.3 Statistical analysis

Clinic blood pressure was calculated as the mean of the two baseline clinic measurements. HBPM measurements were manually assessed to remove those with erroneous recordings due to incorrect date/time stamps (n=87,<0.1%). Recordings with systolic blood pressure<50 mmHg (n=3), diastolic blood pressure >140 mmHg if pulse pressure<40 mmHg (n=5), and any pulse pressure<10 mmHg (n=6) were excluded. The first three days of HBPM were used to compare HBPM to baseline clinic blood pressure. If the first reading coincided with the date and time of the baseline clinic reading, this was excluded, as some patients were instructed to take a test reading. If the first day only included evening readings taken on the day of clinic assessment, then the next full day of readings was incorporated as 'day one' for the calculation of blood pressure parameters. Missing data are reported, and were not imputed.

Prior hypertension was defined as a diagnosis reported by the patient or in primary care records or by antihypertensive treatment. Current hypertension was defined as mean clinic blood pressure ≥140/90 or ≥130/80, and HBPM blood pressure ≥135/85 or ≥130/80 mmHg, according to diagnostic thresholds from European and US guidelines, respectively.[59, 95, 199] Masked hypertension was defined as clinic blood pressure <140/90 and mean HBPM blood pressure ≥135/85 mmHg.[59] Transient post-event hypertension was defined as clinic blood pressure ≥140/90 mmHg and mean HBPM blood pressure<135/85 mmHg, using the guideline definition of white-coat hypertension.[59] Sensitivity analyses were performed restricting to untreated patients at baseline, to those in whom antihypertensive treatment was not intensified, and to those with clinic systolic blood pressure within the range of 120-179 mmHg. This range was selected as Professor Rothwell's group has shown previously that clinic blood pressure<120 mmHg is unlikely to be associated with a usual systolic blood pressure ≥140 mmHg in TIA/stroke,[161] and clinic systolic blood pressure ≥180 mmHg is treated even in major ischaemic stroke during/after reperfusion therapy.[300]

Means, medians, and proportions of baseline characteristics were stratified according to antihypertensive treatment at baseline, and compared using t-tests, Wilcoxon rank-sum tests, and chi-square tests, respectively. Logistic regression was performed to investigate the associations of masked and transient post-event hypertension, adjusted for age, sex, and antihypertensive treatment. The risk of major vascular events (MVE: cardiovascular death, stroke, myocardial infarction, acute peripheral vascular events), stroke, and coronary events was determined by Cox regression for hypertension on clinic blood pressure and HBPM, and by fitting blood pressure as a continuous variable to determine the hazard ratios per 20 and 10 mmHg higher mean systolic and diastolic blood pressure, respectively. Models were not adjusted, since comparisons of each measurement modality were made within the same population. The time at risk commenced from the first day after the patient completed the number of blood pressure monitoring days in question. Hazard ratios for different measurement modalities were compared using Z-tests, and likelihood ratio tests were used to assess model fit after the introduction of HBPM to models of clinic systolic blood pressure. All analyses were performed using Stata version 16.1.

2.4 Results

Of 1833 consecutive eligible patients with TIA or minor stroke, 51 (2.8%) declined to take part in the blood pressure-monitoring study, and 126 (6.9%) were excluded due to early death, acute intercurrent illness, severe dementia, excessive physical disability, or residence outside of the study area (Figure 2-1). The remaining 1656 (90.3%) consented to HBPM, of whom 1650 (99.6%) had a sufficient number of readings to be included in predictive analyses (three did not tolerate frequent blood pressure readings, one withdrew, one nursing home resident was unable to comply, and one developed acute illness).

Median time from referral to clinic assessment was one (IQR 0-3) day. In total, 43,191 HBPM readings were transmitted in the first three days after clinic (mean per patient=26; SD=9.1). Median follow-up was 5.4 years (IQR 2.9-7.9), with 9116 total person-years. 13 (0.8%) patients were lost to follow-up, having withdrawn from OXVASC (n=9) or moved residence outside the study area and refused telephone follow-up (n=4), but mortality data were complete for all participants. Mean age at baseline clinic assessment was 69.7 (SD 13) years, and 51.4% of participants were men (Table 2-1). 1042 (62.9%) had prior hypertension.

There was only moderate correlation between systolic blood pressure in clinic and mean systolic blood pressure on three-day HBPM (r^2=0.31, p<0.0001, Figure 2-2), and there was weak agreement for the diagnosis of current hypertension (kappa=0.29, 95%CI 0.25-0.34). Compared with three-day HBPM, hypertension was misdiagnosed (masked or transient post-event hypertension) based on clinic blood pressure in 564 (34%) patients. Hypertension was found in 73.9% of patients based on clinic blood pressure ≥140/90 mmHg versus 53.2% based on three-day HBPM ≥135/85 mmHg (p<0.0001), but masked hypertension was also common on clinic blood pressure (of 433 patients with clinic blood pressure<140/90 mmHg, 25.9% had three-day HBPM ≥135/85 mmHg; Table 2-2).

Masked hypertension was associated with older age (>70 years, OR=2.21, 95%CI=1.52-3.43, p<0.0001), higher (130-139/85-89) clinic blood pressure (2.33, 1.45-3.71, p<0.0001), and hyperlipidaemia (1.69, 1.05-2.71, p=0.030) after adjusting for age, sex, and antihypertensive treatment. The proportion with masked hypertension also increased with atherosclerotic risk factors (adjusted OR=1.23 per additional risk factor, 1.04-1.45, p=0.013), reaching 36.4% in patients with more than three (Figure 2-3).

Of 973 patients with clinic-systolic blood pressure 140-180 mmHg, 389 (40.0%) had transient post-event hypertension based on three-day HBPM (Table 2-2), irrespective of antihypertensive prescription at baseline clinic (Table 2-3), whereas 152/174 patients with clinic systolic blood pressure ≥180 mmHg had hypertension persisting on three-day HBPM. Transient post-event hypertension was not positively associated with atherosclerotic risk factors (adjusted OR 0.78 per risk factor, 0.71-0.86, p<0.001, Figure 2-3, Figure 2-4) and was unrelated to the aetiology of TIA/stroke (Figure 2-5**,** Table 2-4). blood pressure stabilised by day 2 and the rapid initial fall in blood pressure on HBPM was seen irrespective of antihypertensive prescription at baseline clinic (Figure 2-6**,** Figure 2-7**,** Figure 2-8), and normotension was maintained during subsequent monitoring (Figure 2-6**,** Figure 2-9).

In patients with transient post-event hypertension who had a pre-hospital, acute, post-event blood pressure reading (within 24 hours) prior to clinic, mean prior blood pressure was similar to the clinic reading (156.1/84.3, SD 26.3/14.5 vs 153.2/86.2, SD 15.4/10.9, p=0.23/0.07, Table 2-5). Indeed, when using pre-hospital blood pressure in lieu of clinic blood pressure, similar rates of transient post-event hypertension were found (Table 2-6). However, in this group, and in the transient post-event hypertension group overall, premorbid blood pressure measured in primary care prior to the event was much lower (most recent pre-morbid reading 134.4/76.4, SD 14.7/9.6; five-year average 135.9/77.7, SD 11.4/7.5, p<0.0001 for all comparisons with clinic blood pressure; Table 2-7).

The predictive value of mean systolic blood pressure for the risk of recurrent MVE was greater on three-day HBPM than clinic blood pressure (two-tailed p_{diff}=0.004, Figure 2-10). The addition of one-day or three-day mean systolic blood pressure on HBPM to models containing clinic blood pressure resulted in significant improvements to predictive value (one-day HBPM p=0.001, three-day HBPM p<0.0001). Hypertension (BP≥130/80 mmHg) on three-day HBPM was associated with a 44% (95%CI 6-96, p=0.021) higher risk of recurrent MVE. A 20 mmHg increment in systolic blood pressure on three-day HBPM was associated with a 38% (18-62, p<0.0001) higher risk of recurrent MVE (Table 2-8), a 32% (9-59, p=0.004) higher risk of recurrent stroke, and a 74% (26-238, p=0.004) higher risk of recurrent myocardial infarction (MI) or cardiac death (Table 2-9). The predictive value of HBPM was greatest in those with clinic systolic blood pressure 120-180 mmHg (Table 2-8). In contrast, no significant predictive value for MVE was found for hypertension on clinic blood pressure (HR 0.90, 0.61-1.33, p=0.61) or for a 20 mmHg increment in clinic-systolic blood pressure (HR 1.05, 0.94-1.18, p=0.37). Results were similar using different thresholds for the diagnosis of hypertension (Table 2-10) and when stratified by delay to assessment (Table 2-11). Clinic blood pressure was only predictive of MVE in patients in whom the clinic diagnosis was confirmed on three-day HBPM (HR 1.58, 1.08-2.32, p=0.019 for correctly-classified hypertension versus correctly-classified normotension).

In patients with transient post-event hypertension (i.e. where clinic diagnosis was not confirmed on three-day HBPM), the risk of MVE was lower than with masked hypertension (HR=0.54, 0.32-0.91, p=0.021) despite their substantially higher clinic blood pressure (154/87 mmHg versus 128/76 mmHg, p<0.0001/p<0.0001), and was similar to the risk in patients with correctly-classified normotension (HR=0.99, 0.79-1.24, p=0.965; clinic blood pressure = 124/74 mmHg; Figure 2-11). In contrast, risk in patients with masked hypertension was higher than the risk in patients with correctly-classified normotension (HR=1.82, 1.05-3.12, p=0.032), being equivalent to that in patients with

correctly-classified hypertension (164/90 mmHg, HR=1.07, 0.85-1.36, p=0.55). Similar results were found when transient post-event hypertension was calculated using one-day HBPM, when restricting to those with clinic systolic blood pressure 120-180 mmHg, when using different blood pressure thresholds, when stratifying by aetiology, and when restricting based on prior antihypertensive treatment and treatment intensification during the first month (Figure 2-12**,** Figure 2-13**,** Figure 2-14)

2.5 Discussion

Previous studies in primary prevention showed that HBPM is superior to clinic measurement in the prediction of target organ damage[212] and vascular events,[213, 215] but mine is the first study to my knowledge comparing clinic blood pressure with HBPM for the diagnosis of hypertension and prediction of vascular events in a high-risk secondary prevention cohort. In addition, mine is the first study to utilise telemonitoring in the assessment of the prognostic value of HBPM in any setting. I found high rates of misdiagnosis of hypertension using clinic blood pressure early after TIA and minor stroke, and similarly high rates when using pre-hospital acute blood pressure. I also found that the predictive value of mean systolic blood pressure for the risk of recurrent vascular events was greater on three-day HBPM than on clinic blood pressure.

In contrast to the low-risk primary prevention settings of previous comparative studies, mechanisms specific to TIA/stroke might have especially undermined the utility of early clinic blood pressure in this setting, leading to high rates of under and overdiagnosed hypertension. The prevalence of masked hypertension in my cohort was 26%, higher than the 15% reported in primary prevention settings,[59] consistent with the highly variable background visit-to-visit blood pressure after TIA/stroke.[161, 162, 232] Pre-hospital or emergency department post-event blood pressure was often high in patients with masked hypertension, suggesting that the 'normal' clinic reading was a chance 'low' due to increased variability.[161]

Transient post-event hypertension is well recognised after major stroke[296, 297] but there are few data in TIA and minor stroke.[301] The same phenomenon was highly prevalent (37%) in my cohort, possibly related to anxiety at the acute assessment,[302] and was unlikely to be simply a chance 'high' reading as blood pressure was similar in the emergency department, ambulance, or primary care among patients with an earlier post-event acute blood pressure measurement. The subsequent rapid fall in blood pressure on HBPM appeared to be spontaneous and not attributable to blood pressure-lowering

treatment, approximating to that in patients with correctly-classified normotension after just one day, even in patients who were not treated at the baseline clinic. There was also little evidence of uncontrolled hypertension preceding TIA/stroke in the transient post-event hypertension group, with both the most recent and long-term average premorbid blood pressure readings being substantially lower than the acute clinic reading. Moreover, the risk of recurrent vascular events was no higher in patients with transient post-event hypertension versus correctly-classified normotension, irrespective of antihypertensive treatment.

My findings have some important clinical implications. Although clinic blood pressure was based on the mean of two seated measures, taken five minutes apart and after five minutes of rest, which is arguably a better measure than is often obtained in usual care, clinic readings early after TIA/minor stroke were unreliable for diagnosing hypertension and lacked prognostic value, such that even a short period of HBPM immediately after initial assessment was more clinically useful. The use of three-day HBPM to correctly diagnose any continuing hypertension would not excessively delay commencement of treatment and is consistent with primary prevention guidelines.[59, 303] Use of HBPM would identify treatable masked hypertension, which I showed has a similar prognosis to correctly-classified hypertension, and would also avoid overtreatment of transient post-event hypertension. Given the low stroke risk in patients with transient post-event hypertension, immediate treatment based on clinic blood pressure alone should be considered with caution, in keeping with primary prevention guidelines for white-coat hypertension.[59, 95] Overtreatment may be a problem where TIA/minor stroke is assessed acutely in the emergency department or out-patient settings,[270] with guidelines currently recommending immediate treatment based on conventional blood pressure measurement alone.[59] Although there is wide variation in prescribing practice,[247] high rates of antihypertensive discontinuation in the first year after TIA/stroke are almost universal,[14, 244] and might partly reflect initial over-treatment.

The main strengths of my study include the large number of outcome events compared to previous studies in lower-risk primary prevention settings,[215] the use of telemonitoring to optimise HBPM,[220-222] and the collection of pre-hospital and premorbid blood pressure, which allowed us to validate my findings. However, my study had some potential shortcomings. First, since blood pressure treatment was initiated/ intensified in many patients, I might have reduced the predictive value of early blood pressure measures for recurrent vascular events, but this will have applied to both clinic and three-day HBPM readings. Second, risk associations for conventional blood pressure measurement are subject to regression dilution bias, which will also reduce predictive value, but such measurement is currently the norm in clinical practice. Third, I used telemetric HBPM to ensure the reliability of readings for comparisons with clinic blood pressure, but non-telemetric patient-recorded HBPM would likely be sufficient for normal clinical practice over short periods, as endorsed by clinical guidelines in primary prevention.[303] Fourth, ABPM was not done at baseline in this study, and might well be an alternative to three-day HBPM in this setting given the roughly equivalent predictive values in primary prevention.[228] Fifth, based on findings from the PROGRESS trial,[61] some have advocated for antihypertensive treatment after TIA/stroke irrespective of blood pressure. However, the definition of 'non-hypertensive' used in PROGRESS was clinic blood pressure<160/90 mmHg,[61] with less evidence of benefit at systolic blood pressure<140 mmHg,[63] and the trial was deliberately designed to exclude the early post-event phase, with randomised treatment delayed by at least six weeks (only after a period of 'clinical stability' of at least two weeks plus a four-week run-in period[61]) and patients were eligible for inclusion up to five years after TIA/stroke.

In conclusion, guideline-endorsed use of conventional blood pressure measurement early after TIA and minor stroke results in significant misdiagnosis of hypertension, with high rates of both masked hypertension and overdiagnosis related to transient post-

event hypertension. Use of as few as three days of HBPM immediately after initial assessment allows better prognostication and is likely to improve secondary prevention.

2.6 Tables

Table 2-1 Characteristics of participants according to antihypertensive treatment status at baseline

Patient characteristics	Whole cohort	Antihypertensive treatment¶ at assessment	No antihypertensive treatment at assessment	p-value
n (% whole cohort)	1656 (100%)	853 (51.5%)	803 (48.4%)	
Male sex, n (%)	851 (51.4%)	442 (51.8%)	409 (50.9%)	0.719
Age, mean (SD)	69.7 (13.1)	73.3 (11.1)	65.9 (14.1)	**<0.0001**
Event type, n (%)				
Stroke	652 (39.4%)	350 (41.0%)	301 (37.5%)	0.140
TIA	1004 (60.6%)	503 (59.0%)	502 (62.5%)	
Medical history prior to event, n (%)				
Hypertension (prior history/treatment)	1042 (62.9%)	853 (100%)	185 (23.0%)	**<0.0001**
Angina	191 (11.5%)	147 (17.2%)	44 (5.5%)	**<0.0001**
Diabetes mellitus	218 (13.2%)	168 (19.7%)	50 (6.2%)	**<0.0001**
Hyperlipidaemia	524 (31.7%)	350 (41.0%)	174 (21.7%)	**<0.0001**
Myocardial infarction	51 (3.1%)	44 (5.2%)	7 (0.9%)	**<0.0001**
Atrial fibrillation	193 (11.7%)	137 (16.1%)	56 (7.0%)	**<0.0001**
Heart failure	69 (4.2%)	64 (7.5%)	5 (0.6%)	**<0.0001**
Peripheral vascular disease	53 (3.2%)	43 (5.0%)	10 (1.3%)	**<0.0001**
Prior stroke	94 (5.7%)	74 (8.7%)	20 (2.5%)	**<0.0001**
Prior TIA	240 (14.5%)	125 (14.7%)	115 (14.3%)	0.848
Lifestyle factors (self-reported)				
Current smoker, n (%)	251 (15.2%)	104 (12.2%)	147 (18.3%)	**<0.0001**
Ever-smoker, n (%)	887 (53.6%)	470 (55.1%)	417 (51.9%)	0.196
Alcohol intake u/week, median (IQR) ǂ	2 (10)	2 (10)	2 (11)	0.081
Blood pressure, mmHg, mean (SD)				
Clinic, systolic	151.4 (22.9)	153.6 (23.3)	149.0 (22.3)	**<0.0001**
Clinic, diastolic	85.1 (13.3)	83.7 (13.5)	86.6 (13.0)	**<0.0001**

Hypertension (BP ≥130/80 mmHg), n (%)	1468 (88.7%)	762 (89.3%)	706 (87.9%)	0.366
HBPM first day of monitoring, systolic*	138.1 (17.4)	141.1 (17.6)	135.1 (16.5)	**<0.0001**
HBPM first day of monitoring, diastolic*	80.6 (11.1)	80.9 (11.4)	81.3 (10.6)	**0.013**
Hypertension (BP ≥130/80 mmHg), n (%)*	1222 (74.1%)	661 (77.9%)	561 (70.0%)	**<0.0001**
HBPM first 3 days of monitoring, systolic*	135.5 (16.2)	138.7 (16.4)	132.1 (15.2)	**<0.0001**
HBPM first 3 days of monitoring, diastolic*	79.0 (10.3)	78.5 (10.8)	79.5 (9.8)	0.063
Hypertension (BP ≥130/80 mmHg), n (%)*	1123 (68.1%)	618 (72.8%)	505 (63.1%)	**<0.0001**

Standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP). ¶ Antihypertensive treatment was defined as any medication specifically prescribed for reducing blood pressure. ǂ Data missing for 87 participants. * Complete HBPM n=1650

Table 2-2 Prevalence of masked and transient post-event hypertension using the first one and three days of telemetric HBPM

	One day	Three days
Mean BP, mmHg (SD)	138.1/80.6 (17.4/11.1)	135.5/79.0 (16.2/10.3)
Masked hypertension, n/total normotensive at baseline clinic (%)	136/433 (31.4%)	112/433 (25.9%)
Masked undiagnosed hypertension, n/total normotensive, untreated, and no prior diagnosis of hypertension at baseline clinic (%)	65/220 (29.6%)	48/220 (21.8%)
Masked uncontrolled hypertension, n/total normotensive and treated at baseline clinic (%)	61/187 (32.6%)	55/187 (29.4%)
Masked hypertension, n/total hypertensive on HBPM (%)	136/858 (13.7%)	112/877 (12.8%)
Masked hypertension overall*, n/total (%)	136/1650 (8.2%)	112/1650 (6.8%)
Transient post-event hypertension, n/total hypertensive at baseline clinic (%)	359/1217 (29.5%)	452/1217 (37.1%)
Transient post-event hypertension, n/total hypertensive and untreated at baseline clinic (%)	187/552 (33.9%)	244/552 (44.2%)
Transient post-event hypertension, n/total normotensive on HBPM (%)	359/656 (54.7%)	452/773 (58.5%)
Transient post-event hypertension overall*, n/total (%)	359/1650 (21.8%)	452/1650 (27.4%)

Home blood pressure monitoring (HBPM); blood pressure (BP); standard deviation (SD). Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. *Expressed as a proportion of all participants with at least 3 full days of HBPM after baseline clinic.

Table 2-3 Prevalence of transient post-event hypertension on 3-day HBPM by clinic systolic blood pressure, according to treatment status at baseline clinic (i.e. before HBPM readings were available)

	All participants		No treatment prior to baseline clinic		Treatment prior to baseline clinic		No treatment increase at baseline clinic*		Treatment increase at baseline clinic*		Never treated (prior to baseline, up to one month)	
Clinic systolic BP, mmHg	**n/total**	**Proportion**	**n/total**	**Proportion**	**n/total**	**Proportion**	**n/total**	**Proportion**	**n/total**	**Proportion**	**n/total**	**Proportion**
140 to <150	143/299	47.8%	78/140	55.7%	65/159	40.9%	45/111	40.5%	39/82	47.6%	29/42	69.1%
150 to <160	132/278	47.5%	67/125	53.6%	65/153	42.5%	35/84	41.7%	39/84	46.4%	27/35	77.1%
160 to <170	69/232	29.7%	36/100	36.0%	33/132	25.0%	15/63	23.8%	27/83	32.5%	9/19	47.4%
170 to <180	45/164	27.4%	23/76	30.3%	22/88	25.0%	3/26	11.5%	17/64	26.6%	2/8	25.0%
180 to <190	10/70	14.3%	5/25	20.0%	5/45	11.1%	1/11	9.1%	6/38	15.8%	1/1	100.0%
190 to <200	12/104	15.4%	3/18	16.7%	5/34	14.7%	3/12	25.0%	2/24	8.3%	2/2	100.0%
200 to <210	3/35	8.6%	2/16	12.5%	1/19	5.3%	0/4	0.0%	2/21	4.8%	0/2	0.0%
≥ 210	0/17	0.0%	0/7	0.0%	0/10	0.0%	0/3	0.0%	0/10	0.0%	0/0	-

Home blood pressure monitoring (HBPM); blood pressure (BP). Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg. *Data available for 1114/1650 (67.5%) participants

Table 2-4 Diagnostic classification on HBPM by aetiology of TIA/stroke

Diagnostic classification based on HBPM	TOAST category, n(%)				
	Total	**Cardioembolic**	**Large artery disease**	**Small vessel disease**	**Undetermined**
True hypertension	590 (48.4%)	112 (47.1%)	103 (58.2%)	93 (56.7%)	282 (44.0%)
True normotension	224 (18.4%)	42 (17.7%)	19 (10.7%)	21 (12.8%)	142 (22.2%)
Masked hypertension	82 (6.7%)	16 (6.7%)	15 (8.5%)	11 (6.7%)	40 (6.2%)
Transient post-event hypertension	324 (26.6%)	68 (28.6%)	40 (22.6%)	39 (23.8%)	177 (27.6%)
Total	1,220	238	177	164	641

Trial of Org 10172 in Acute Stroke Treatment (TOAST); Home blood pressure monitoring (HBPM); transient ischaemic attack (TIA). 1220 participants with events of the most common four aetiologies are included. Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg.

Table 2-5 Clinic and pre-hospital BP, by BP diagnostic classification on HBPM

Assessment	BP Class	n	Systolic BP		Diastolic BP	
			Mean	SD	Mean	SD
Clinic BP	Correctly-classified hypertension	765	164.3	19.6	89.8	13.2
	Correctly-classified normotension	321	124.1	11.3	73.9	9.5
	Masked hypertension	112	128.4	7.7	76.5	8.5
	Transient post-event hypertension	452	154.4	14.7	87.3	11.0
	Total	1650	151.3	23.0	85.1	13.3
First independent post-event BP within 90 minutes	Correctly-classified hypertension	89	169.8	29.7	91.8	17.4
	Correctly-classified normotension	32	149.8	22.0	78.4	14.0
	Masked hypertension	9	161.6	38.1	91.9	20.8
	Transient post-event hypertension	36	161.1	23.0	86.2	13.4
	Total	166	163.6	28.4	88.0	16.9
First independent post-event BP within 24-hours	Correctly-classified hypertension	295	165.2	27.3	89.5	16.8
	Correctly-classified normotension	137	139.5	22.2	78.8	13.4
	Masked hypertension	47	158.2	27.4	86.6	14.8
	Transient post-event hypertension	144	156.1	26.3	84.3	14.5
	Total	623	156.9	27.8	85.7	16.0

Blood pressure (BP); home blood pressure monitoring (HBPM); standard deviation (SD). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg. First post-event BP was sourced from emergency department medical records, GP records, and paramedic reports for a subset of the population that were assessed prior to clinic.

Table 2-6 Prevalence of masked and transient post-event hypertension, defined using pre-hospital/emergency department BP, using the first one and three days of telemetric HBPM

	One day	Three days
Mean BP, mmHg (SD)	138.1/80.6 (17.4/11.1)	135.5/79.0 (16.2/10.3)
Masked hypertension, n/total normotensive at baseline clinic (%)	57/138 (41.3%)	40/138 (29.0%)
Masked hypertension overall*, n/total (%)	57/623 (9.2%)	40/623 (6.4%)
Transient post-event hypertension, n/total hypertensive at baseline clinic (%)	151/485 (31.1%)	183/485 (37.7%)
Transient post-event hypertension overall*, n/total (%)	151/623 (24.2%)	183/623 (29.4%)

Home blood pressure monitoring (HBPM); blood pressure (BP); standard deviation (SD). Transient post-event hypertension was defined as pre-hospital BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as pre-hospital BP <140/90 and mean three-day home BP ≥135/85 mmHg. *Expressed as a proportion of all participants with at least 3 full days of HBPM after baseline clinic.

Table 2-7 Clinic and premorbid BP, by BP diagnostic classification on HBPM

Assessment	BP Class	n	Systolic BP		Diastolic BP	
			Mean	SD	Mean	SD
Clinic BP	Correctly-classified hypertension	765	164.3	19.6	89.8	13.2
	Correctly-classified normotension	321	124.1	11.3	73.9	9.5
	Masked hypertension	112	128.4	7.7	76.5	8.5
	Transient post-event hypertension	452	154.4	14.7	87.3	11.0
	Total	1650	151.3	23.0	85.1	13.3
Most recent pre-event premorbid BP	Correctly-classified hypertension	600	140.8	15.6	78.9	10.5
	Correctly-classified normotension	244	126.1	16.2	72.7	9.3
	Masked hypertension	88	132.8	10.8	76.4	9.2
	Transient post-event hypertension	351	134.4	14.7	76.5	9.6
	Total	1283	135.7	16.1	76.9	10.2
5-year average premorbid BP	Correctly-classified hypertension	578	143.7	12.2	80.1	8.5
	Correctly-classified normotension	237	128.8	14.8	74.5	7.7
	Masked hypertension	85	135.6	12.0	77.2	7.9
	Transient post-event hypertension	341	135.9	11.4	77.7	7.5
	Total	1241	138.2	13.8	78.2	8.3
10-year average premorbid BP	Correctly-classified hypertension	592	144.0	12.2	81.2	7.8
	Correctly-classified normotension	241	129.4	13.6	75.4	7.3
	Masked hypertension	88	136.6	12.0	78.5	7.1
	Transient post-event hypertension	348	136.2	11.0	78.8	6.8
	Total	1269	138.6	13.4	79.2	7.7

Blood pressure (BP); home blood pressure monitoring (HBPM); standard deviation (SD). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg.

Table 2-8 Prevalence of hypertension and risk of recurrent MVE (combined stroke, myocardial infarction, peripheral vascular events, vascular death) on clinic BP and HBPM

	All patients					Patients with baseline clinic SBP 120-180 mmHg				
	Prevalence cases/total (%)	Events n	HR MVE	(95% CI)	p-value	Prevalence cases/total (%)	Events n	HR MVE	(95% CI)	p-value
Hypertension (BP ≥130/80 mmHg)										
Clinic	1468/1656 (88.7%)	222	0.90	(0.61 - 1.33)	0.610	1271/1377 (92.3%)	182	1.09	(0.63 - 1.87)	0.769
HBPM First Day	1222/1650 (74.1%)	213	1.49	(1.06 - 2.09)	**0.021**	1028/1372 (74.9%)	175	1.70	(1.15 - 2.52)	**0.008**
HBPM First 3 Days	1123/1650 (68.1%)	212	1.44	(1.06 - 1.96)	**0.021**	934/1372 (68.1%)	174	1.67	(1.17 - 2.37)	**0.005**
SBP (per 20 mmHg)	-					-				
Clinic	-	222	1.05	(0.94 - 1.18)	0.368	-	182	1.09	(0.90 - 1.31)	0.387
HBPM First Day	-	213	1.28	(1.11 - 1.48)	**0.001**	-	175	1.50	(1.25 - 1.81)	**<0.0001**
HBPM First 3 Days	-	212	1.38	(1.18 - 1.62)	**<0.0001**	-	174	1.59	(1.31 - 1.94)	**<0.0001**

Major vascular events (MVE); blood pressure (BP); home blood pressure monitoring (HBPM); transient ischaemic attack (TIA); hazard ratio (HR); confidence interval (CI); systolic blood pressure (SBP).

Table 2-9 The risk of vascular events associated with a diagnosis of hypertension (130/80) and for a 20/10 mmHg higher SBP and DBP, respectively, on HBPM and baseline clinic BP post-TIA/stroke

	Baseline Clinic				HBPM First Day				HBPM First 3 Days			
Outcome	Events	HR	95% CI	p-value	Events	HR	95% CI	p-value	Events	HR	95% CI	p-value
Hypertension (BP ≥130/80 mmHg)												
MVE	222	0.90	(0.61 - 1.33)	0.610	213	1.49	(1.06 - 2.09)	**0.021**	212	1.44	(1.06 - 1.96)	**0.021**
Stroke	156	1.21	(0.72 - 2.02)	0.478	154	1.38	(0.94 - 2.04)	0.103	153	1.33	(0.93 - 1.91)	0.114
MI, SCD & IHD Death	49	0.70	(0.33 - 1.49)	0.355	49	1.61	(0.78 - 3.31)	0.199	49	1.68	(0.86 - 3.28)	0.131
SBP (20 mmHg higher)												
MVE	222	1.05	(0.94 - 1.18)	0.368	213	1.28	(1.11 - 1.48)	**0.001**	212	1.38	(1.18 - 1.62)	**<0.0001**
Stroke	156	1.09	(0.95 - 1.25)	0.201	154	1.24	(1.04 - 1.48)	**0.015**	153	1.32	(1.09 - 1.59)	**0.004**
MI, SCD & IHD Death	49	1.00	(0.78 - 1.28)	0.999	49	1.58	(1.18 - 2.13)	**0.002**	49	1.74	(1.26 - 2.38)	**0.001**
DBP (10 mmHg higher)												
MVE	222	0.89	(0.81 - 0.99)	**0.028**	213	0.94	(0.83 - 1.07)	0.371	212	0.96	(0.88 - 1.06)	0.428
Stroke	156	1.00	(0.89 - 1.13)	0.940	154	1.05	(0.91 - 1.21)	0.543	153	1.07	(0.92 - 1.25)	0.401
MI, SCD & IHD Death	49	0.69	(0.55 - 0.85)	**0.001**	49	0.79	(0.61 - 1.03)	0.084	49	0.78	(0.59 - 1.04)	0.087

Systolic blood pressure (SBP); diastolic blood pressure (DBP); home blood pressure monitoring (HBPM); blood pressure (BP); confidence interval (CI); hazard ratio (HR); myocardial infarction (MI); sudden cardiac death (SCD); ischaemic heart disease (IHD).

Table 2-10 The risk of recurrent MVE (combined stroke, myocardial infarction, peripheral vascular events, vascular death) associated with a diagnosis of residual hypertension on clinic BP and HBPM by different hypertension thresholds

		≥130/80 mmHg (US primary prevention hypertension guidelines)			≥135/85 mmHg			≥140/90 mmHg for clinic and ≥135/85 mmHg for HBPM (European primary prevention hypertension guidelines)		
	Events	HR	95% CI	p-value	HR	95% CI	p-value		95% CI	p-value
Clinic	222	0.90	(0.61 - 1.33)	0.610	0.96	(0.70 - 1.33)	0.822	1.13	(0.84 - 1.53)	0.418
HBPM First Day	213	1.49	(1.06 - 2.09)	**0.021**	1.38	(1.04 - 1.84)	**0.027**	1.38	(1.04 - 1.84)	**0.027**
HBPM First 3 Days	212	1.44	(1.06 - 1.96)	**0.021**	1.60	(1.21 - 2.12)	**0.001**	1.60	(1.21 - 2.12)	**0.001**

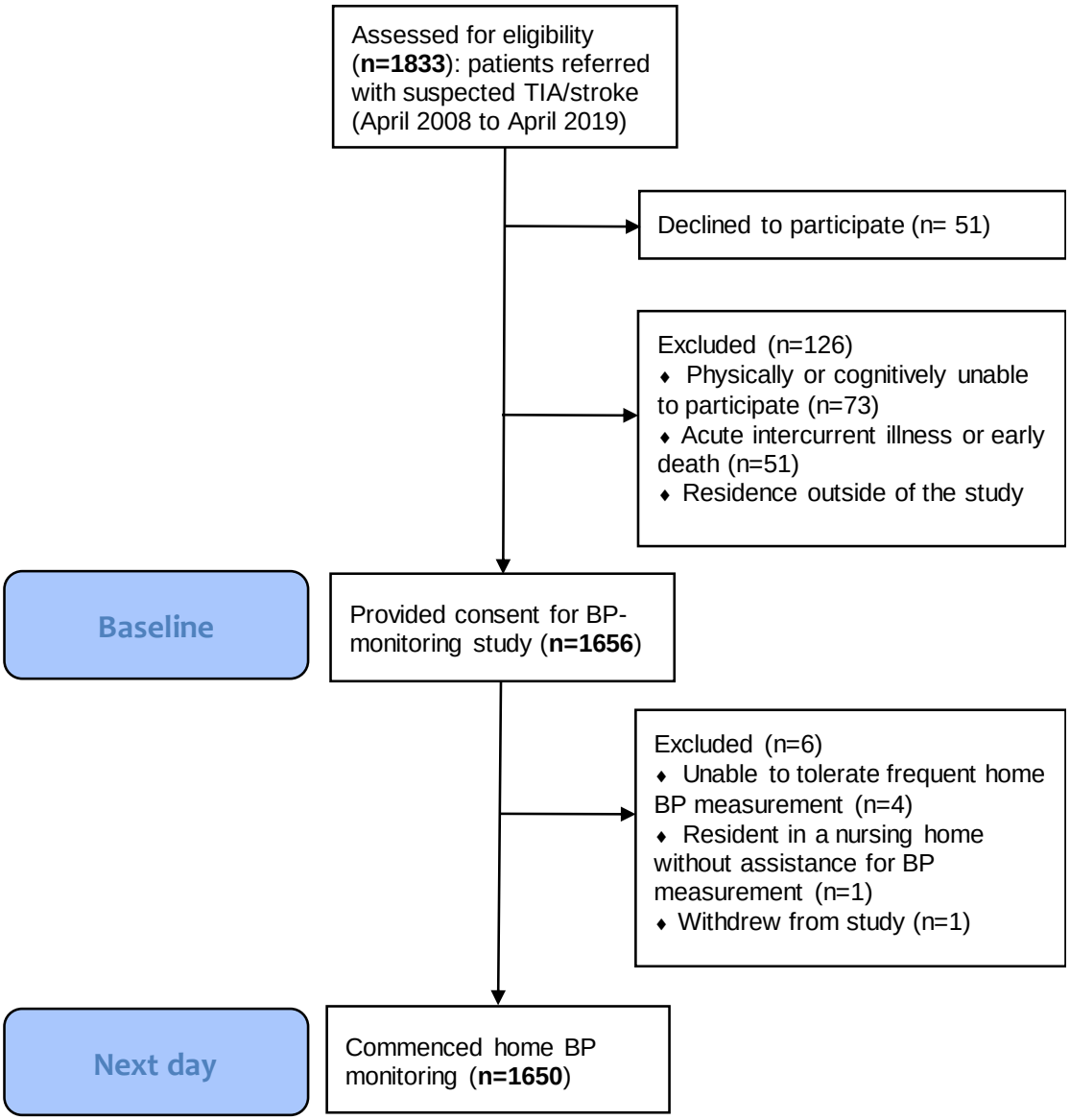
MVE (major vascular events); Blood pressure (BP); home blood pressure monitoring (HBPM); confidence interval (CI); hazard ratio (HR)

Table 2-11 Risk of recurrent MVE (combined stroke, myocardial infarction, peripheral vascular events, vascular death) on clinic and HBPM SBP, by time to assessment

	All patients				Patients assessed within the first 3 days after TIA/stroke				Patients assessed more than 3 days after TIA/stroke			
	Events n	HR MVE	(95% CI)	p-value	Events n	HR MVE	(95% CI)	p-value	Events n	HR MVE	(95% CI)	p-value
SBP (per 20 mmHg)												
Clinic	222	1.05	(0.94 - 1.18)	0.368	68	1.01	(0.83 - 1.23)	0.947	154	1.08	(0.94 - 1.24)	0.289
1-day HBPM	213	1.28	(1.11 - 1.48)	**0.001**	65	1.34	(1.03 - 1.75)	**0.027**	148	1.26	(1.05 - 1.50)	**0.012**
3-day HBPM	212	1.38	(1.18 - 1.62)	**<0.0001**	65	1.54	(1.16 - 2.04)	**0.002**	147	1.31	(1.08 - 1.59)	**0.005**

MVE (major vascular events); BP (blood pressure); home blood pressure monitoring (HBPM); TIA (transient ischaemic attack); hazard ratio (HR); confidence interval (CI); systolic blood pressure (SBP).

2.7 Figures



Transient ischaemic attack (TIA); blood pressure (BP)

Figure 2-1 Flowchart of study inclusion and exclusion

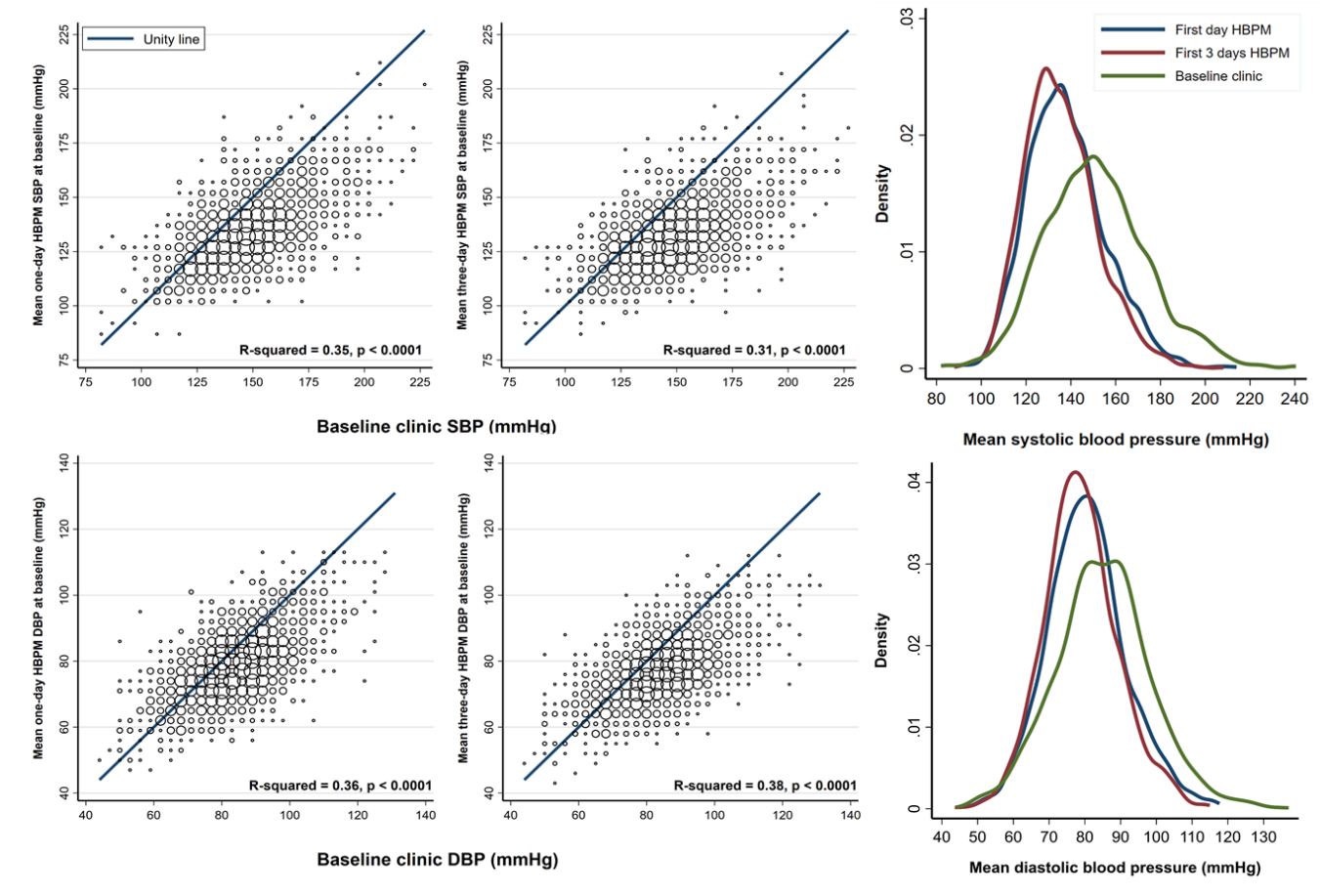


Figure 2-2 Distribution and scatter plots of mean blood pressure on home monitoring with baseline clinic BP

Blood pressure (BP); home BP monitoring (HBPM); systolic BP (SBP); diastolic BP (DBP). The size of the markers in the scatter plots are weighted by the number of cases in each 5 mmHg bin of systolic BP and each 3 mmHg bin of diastolic BP on HBPM and baseline clinic BP. Frequencies in the kernel plots are given per 3 mmHg bands of systolic BP and per 2 mmHg bands of diastolic BP.

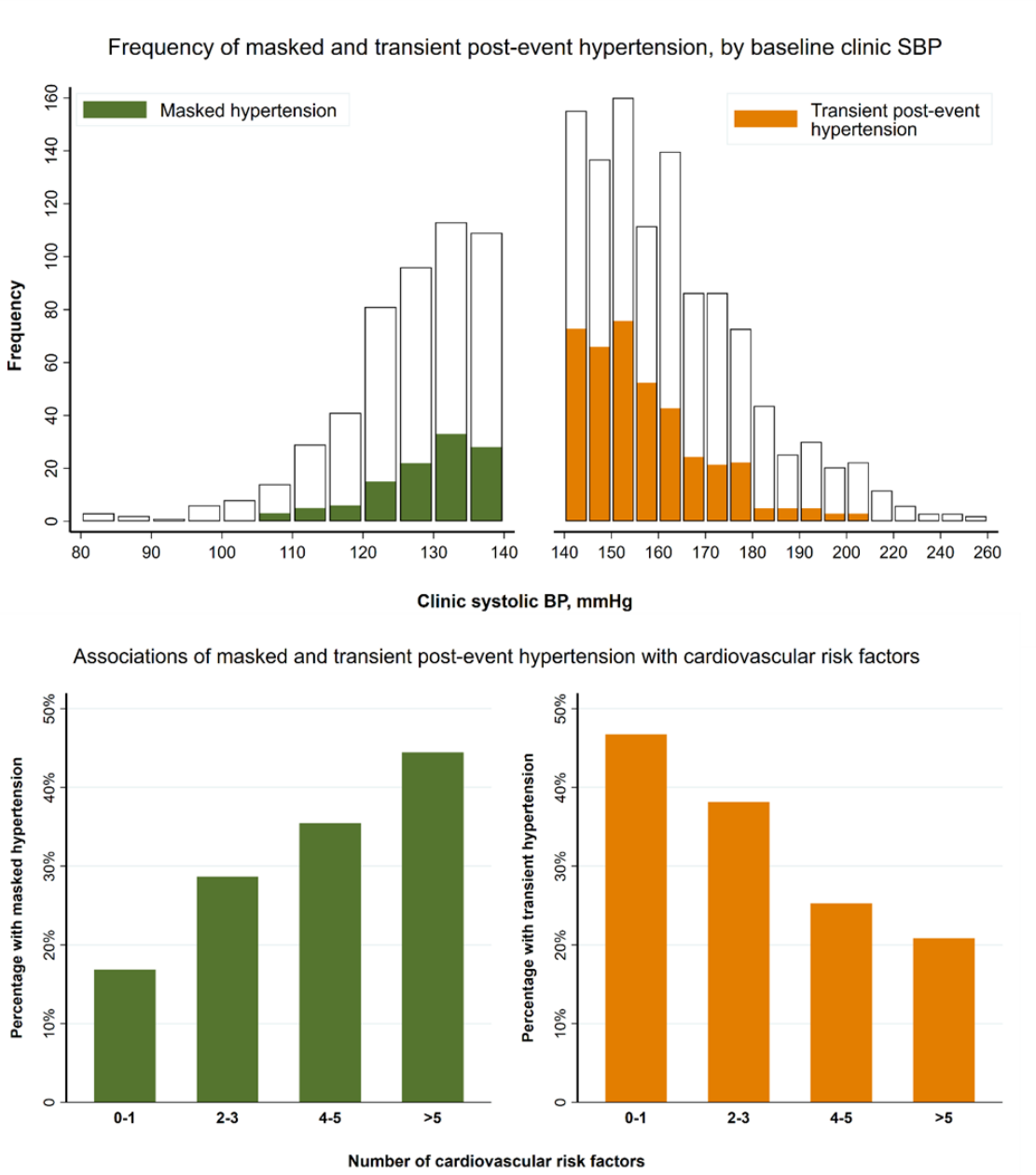


Figure 2-3 Masked hypertension and transient post-event hypertension by clinic systolic blood pressure (top), and by number of cardiovascular risk factors at baseline (bottom)

Cardiovascular risk factors: coronary heart disease (myocardial infarction or unstable angina), diabetes mellitus, smoking (current or historic), peripheral vascular disease, hyperlipidaemia, family history of stroke/myocardial infarction. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg, and expressed as a percentage of those who were found to be normotensive on baseline clinic BP assessment. Transient post-event hypertension was defined as clinic BP ≥140/90 mm Hg and mean three-day home BP <135/85 mmHg and expressed as a percentage of those who were found to be hypertensive on baseline clinic BP assessment.

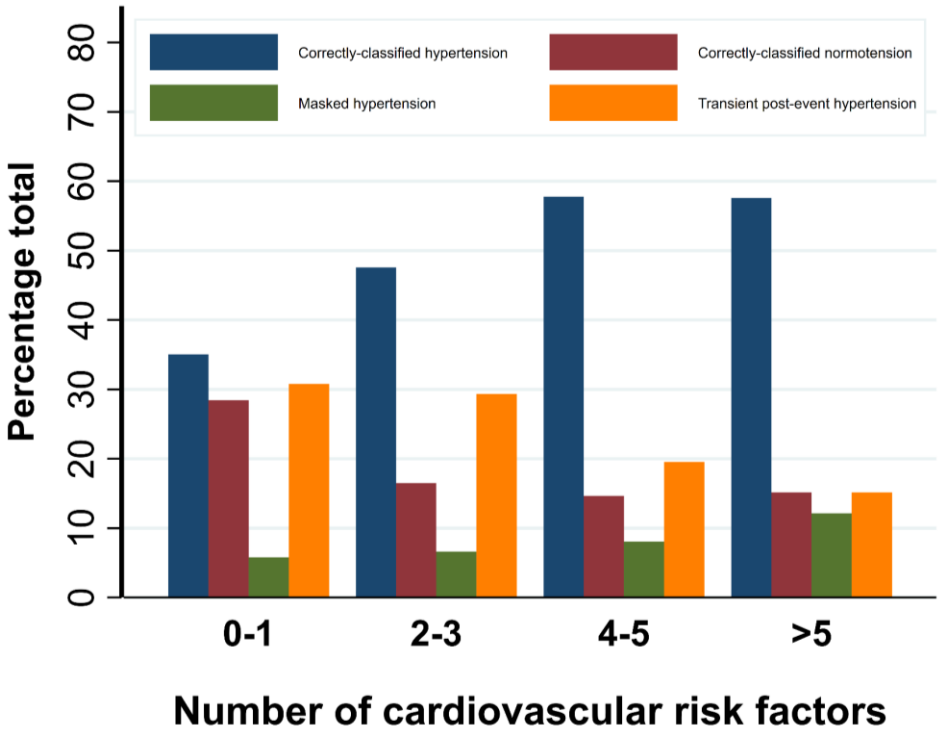


Figure 2-4 Blood pressure diagnostic categorisation by vascular risk factors

Blood pressure (BP). Cardiovascular risk factors: coronary heart disease (myocardial infarction or unstable angina), diabetes mellitus, smoking (current or historic), peripheral vascular disease, hyperlipidaemia, family history of stroke/myocardial infarction. Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg.

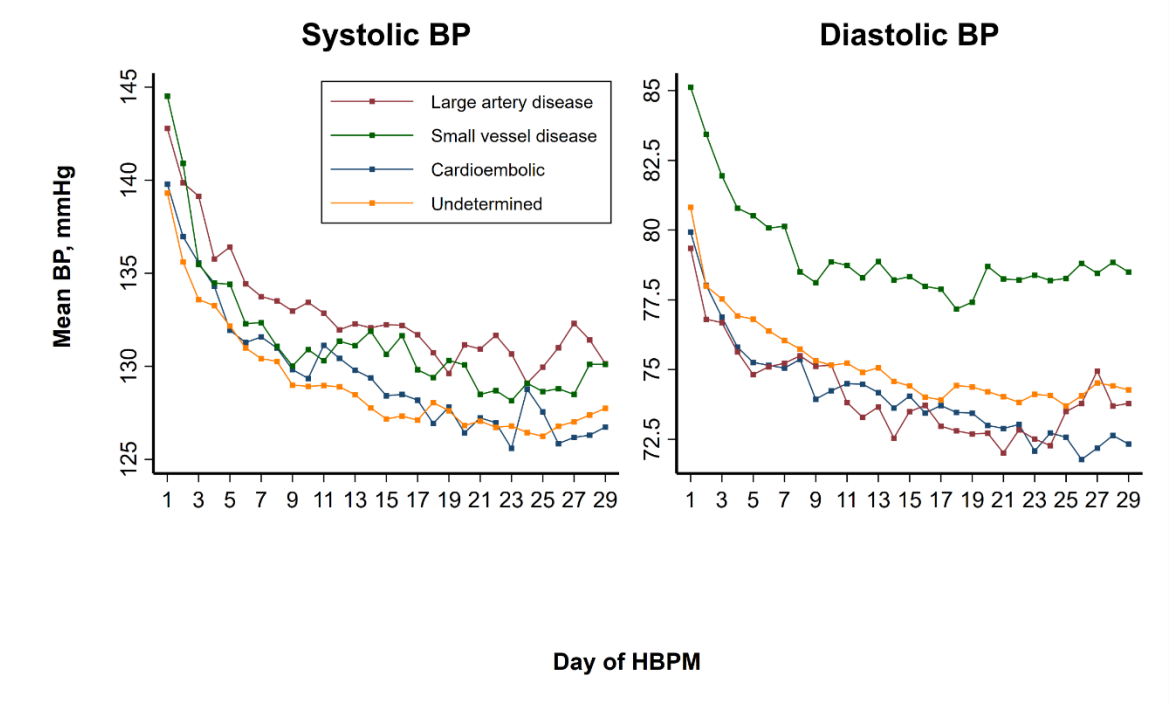


Figure 2-5 Home blood pressure over one month of monitoring, by TOAST classification

Trial of Org 10172 in Acute Stroke Treatment (TOAST); Home blood pressure monitoring (HBPM); blood pressure (BP). 1220 participants with events of the most common four aetiologies are included.

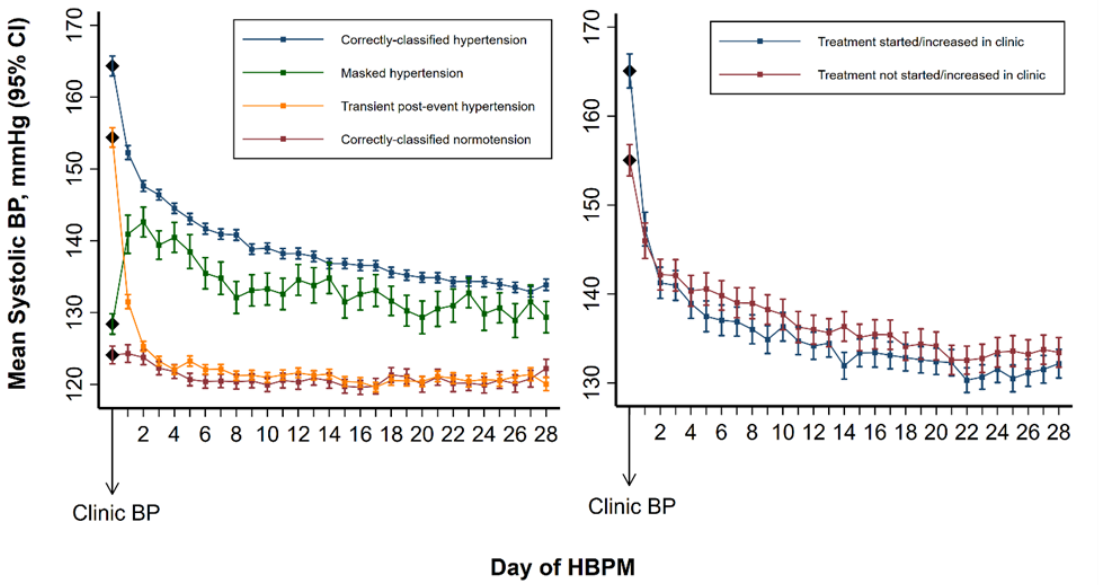


Figure 2-6 Clinic (day 0) and home (day 1-28) systolic BP, by categorisation of BP on baseline clinic and three-day HBPM, and by the commencement of treatment among hypertensive participants at baseline clinic

Home blood pressure monitoring (HBPM); blood pressure (BP); confidence interval (CI). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg. Data on baseline antihypertensive treatment were available for 1114/1650 (67.5%) participants. Treatment initiation/dose increases are those performed in clinic only (i.e. prior to the commencement of HBPM).

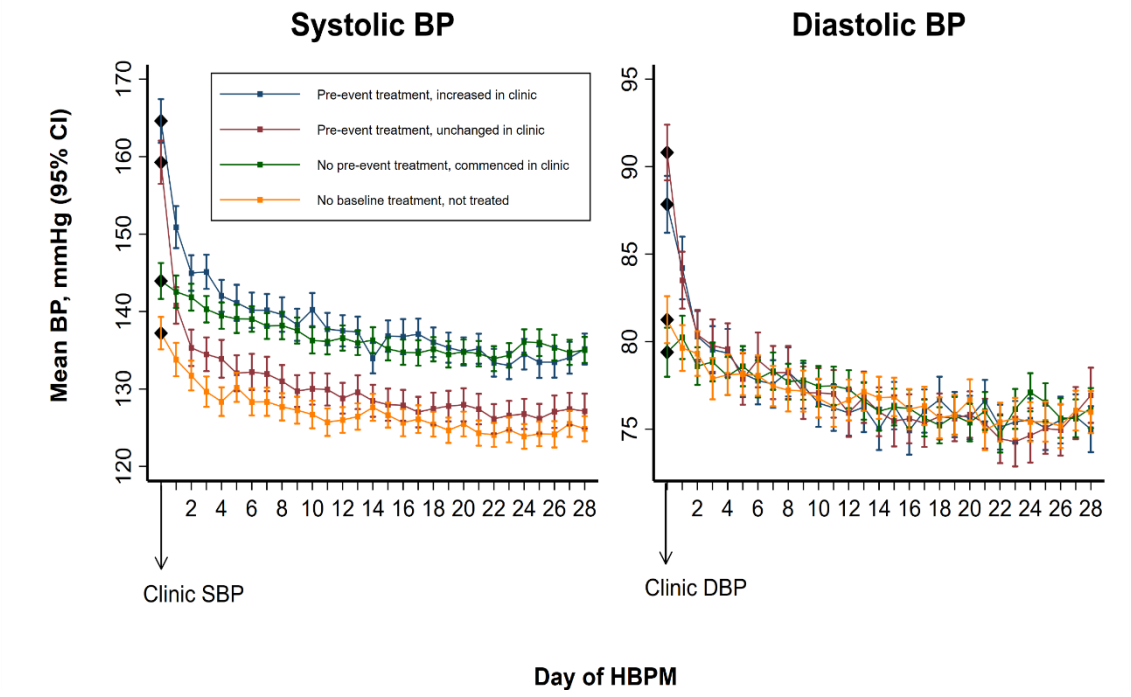


Figure 2-7 Clinic (day 0) and home (day 1-28) blood pressure, by categorisation of blood pressure on baseline clinic and three-day HBPM

Home blood pressure monitoring (HBPM); blood pressure (BP); confidence interval (CI); systolic blood pressure (SBP); diastolic blood pressure (DBP). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg.

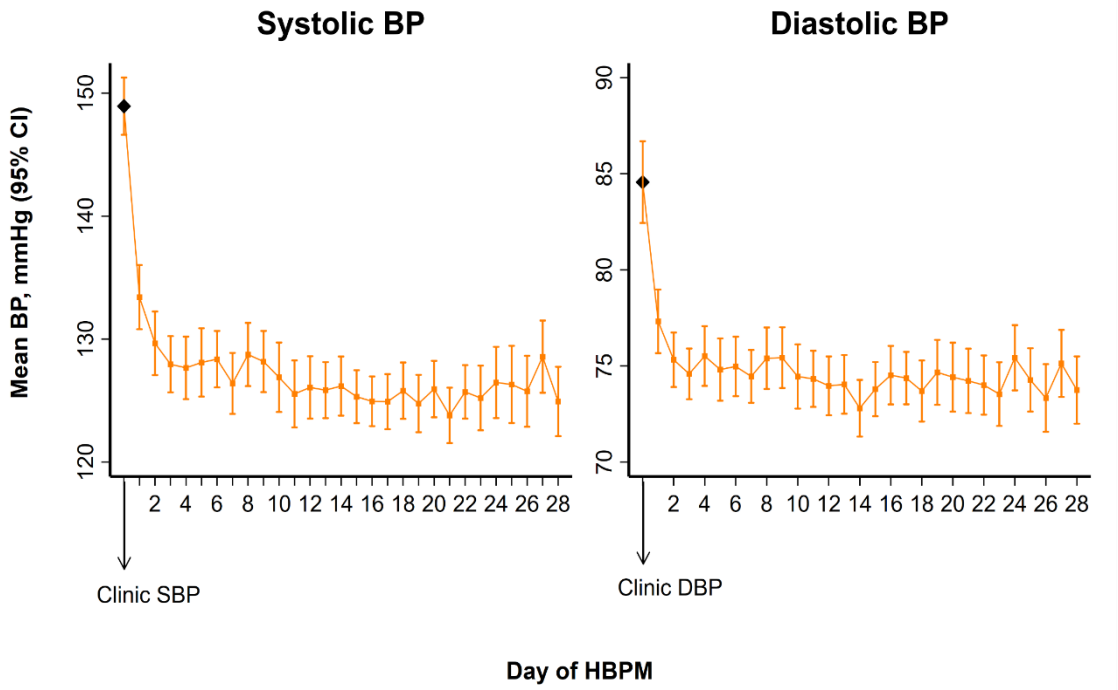


Figure 2-8 Clinic (day 0) and home (day 1-28) blood pressure in patients with transient post-event hypertension who were not prescribed antihypertensive treatment at baseline clinic

Home blood pressure monitoring (HBPM); blood pressure (BP); confidence interval (CI); systolic blood pressure (SBP); diastolic blood pressure (DBP). Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg. Data on baseline antihypertensive treatment were available for 1114/1650 (67.5%) participants.

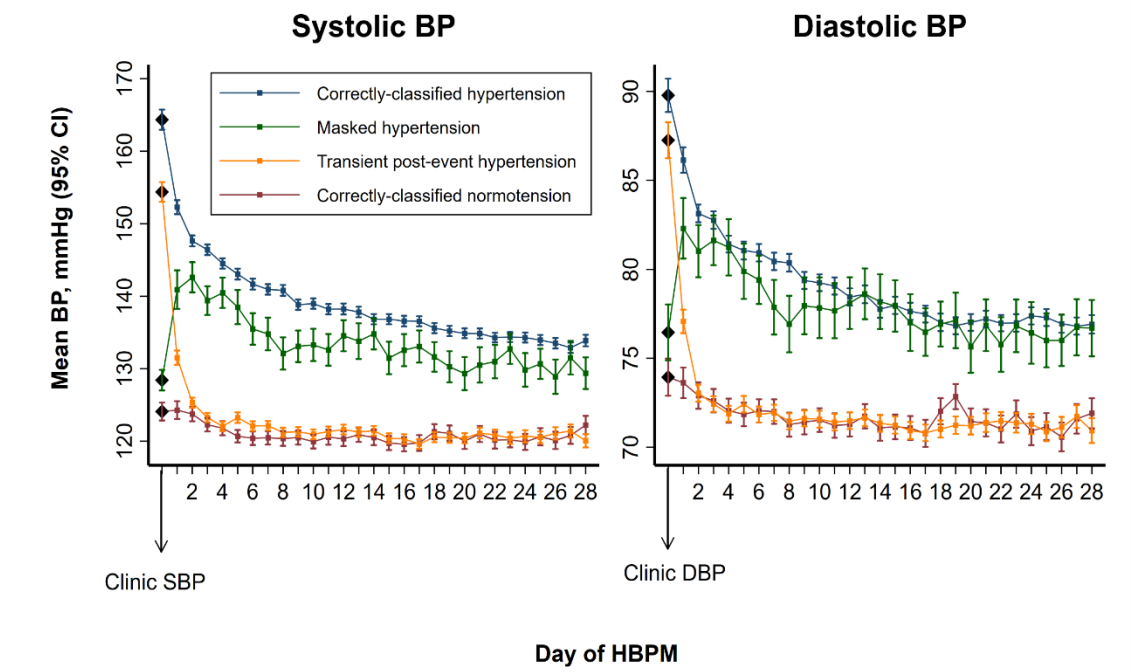


Figure 2-9 Clinic (day 0) and home (day 1-28) blood pressure, by categorisation of blood pressure on baseline clinic and three-day HBPM

Home blood pressure monitoring (HBPM); blood pressure (BP); confidence interval (CI); systolic blood pressure (SBP); diastolic blood pressure (DBP). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg.

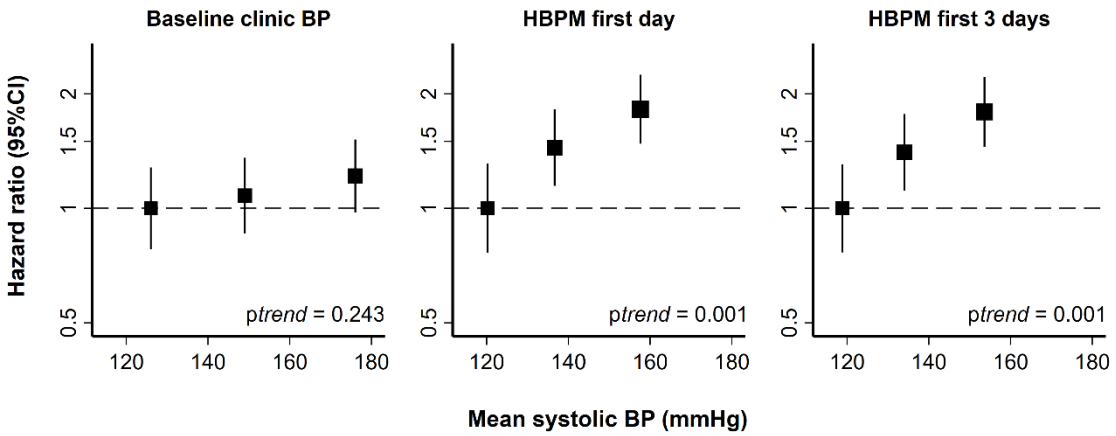


Figure 2-10 Hazard ratios (95% CI) for major vascular events, by tertiles of systolic blood pressure on clinic and home measurement, plotted against the mean systolic BP in each tertile.

Confidence interval (CI); home blood pressure monitoring (HBPM); blood pressure (BP). The area of each square is inversely proportional to the variance of the tertile-specific log risk.

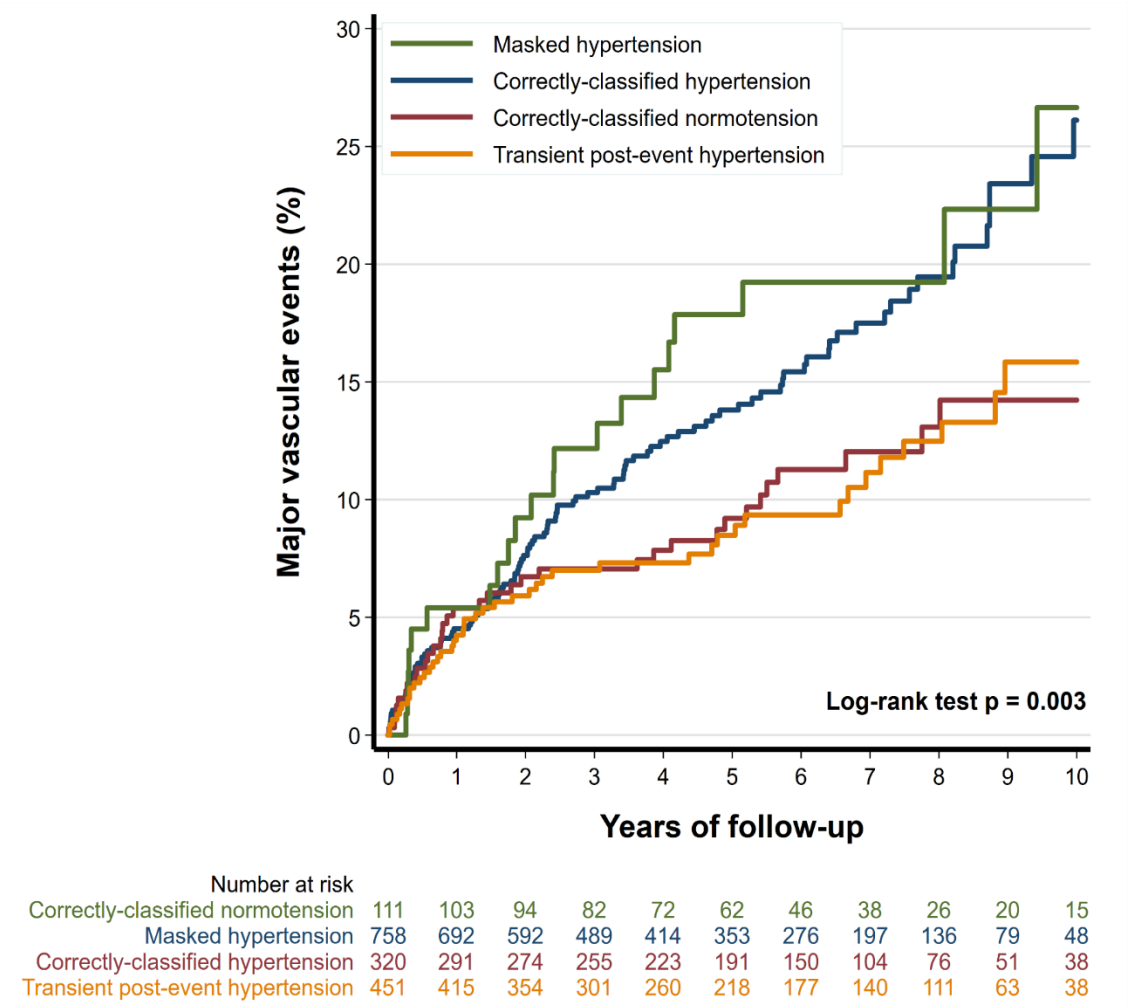


Figure 2-11 Cumulative incidence of major vascular events by diagnostic category of hypertension based on 3-day HBPM

Home blood pressure monitoring (HBPM). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg.

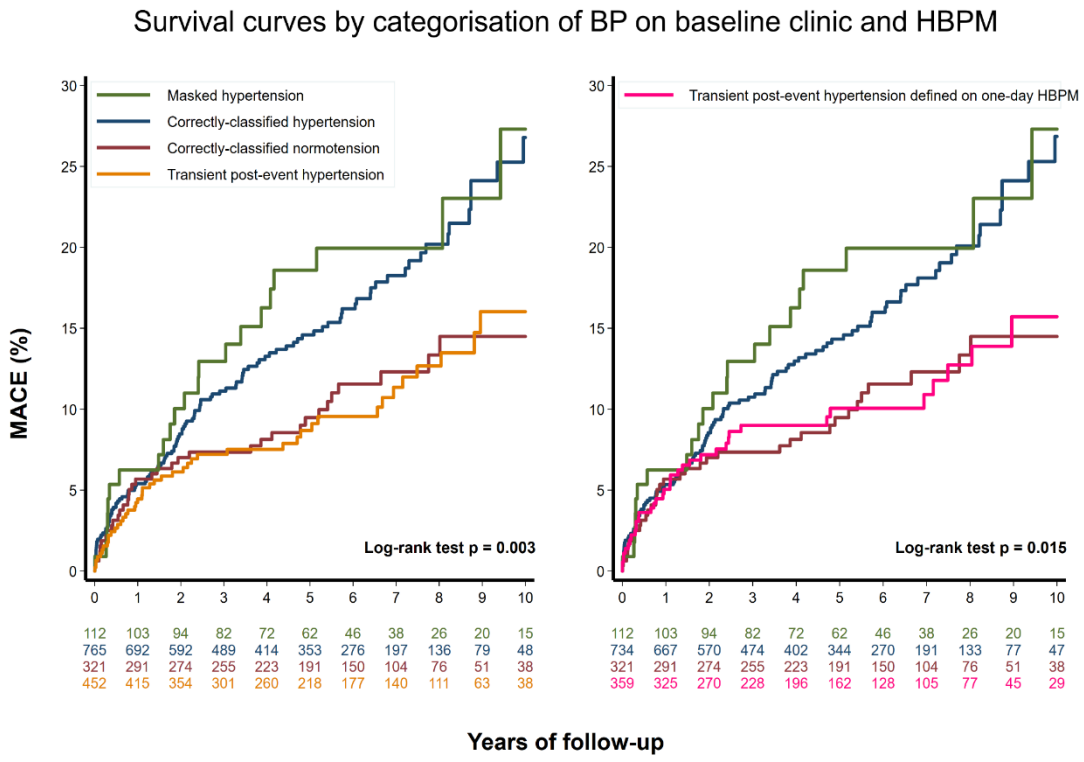


Figure 2-12 Survival curves and numbers at risk, by categorisation of blood pressure on baseline clinic and three-day HBPM

Home blood pressure monitoring (HBPM); blood pressure (BP); standard deviation (SD). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg (left), and mean one-day home BP <135/85 mmHg (right).

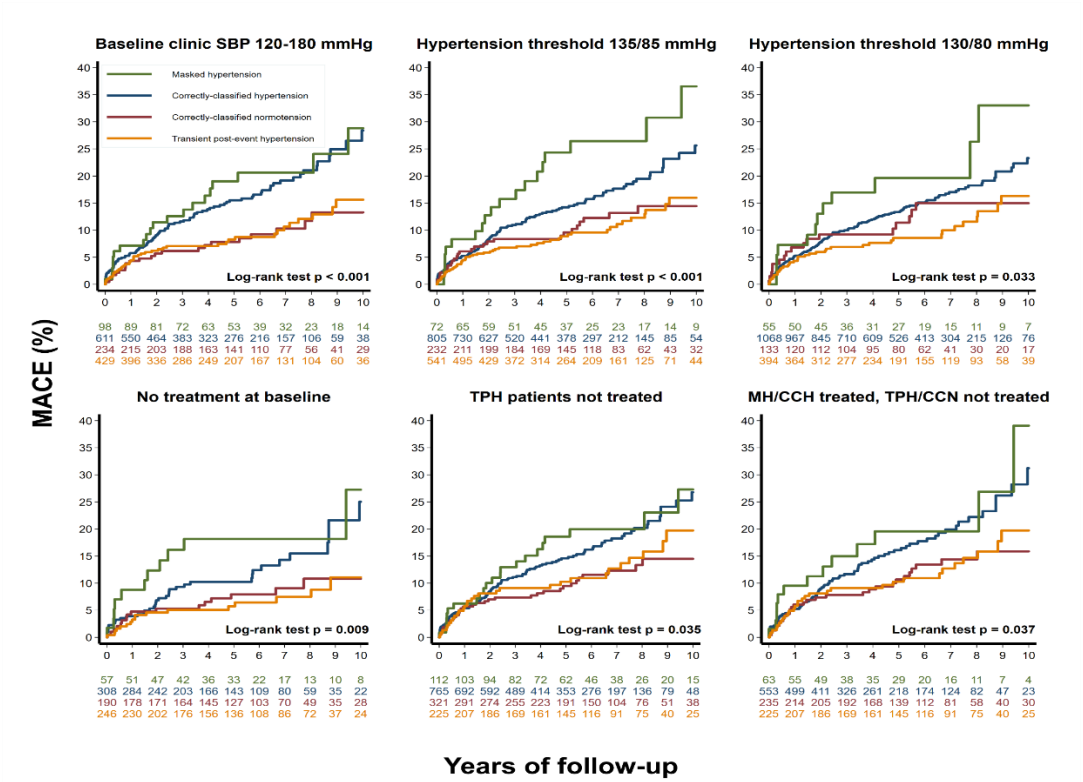


Figure 2-13 Survival curves and numbers at risk, by categorisation of blood pressure on baseline clinic and three-day HBPM, using different BP thresholds and by treatment status

Home blood pressure monitoring (HBPM); systolic blood pressure (SBP); transient post-event hypertension (TPH); masked hypertension (MH); correctly-classified hypertension (TH); correctly-classified normotension (TN); major adverse cardiovascular events (MACE). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg unless the threshold is specified. Sustained normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg unless the threshold is specified. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg unless the threshold is specified. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg unless the threshold is specified. Where the threshold is specified in the plot title, that threshold is used for each definition. Treatment at baseline refers to any medications prescribed specifically for blood pressure lowering, at the time of the baseline treatment. 'Treated' or 'not treated' in the fifth and sixth plots refer to the presence or absence of any net increase in the number of agents or dose of antihypertensive medications between baseline and one month of HBPM.

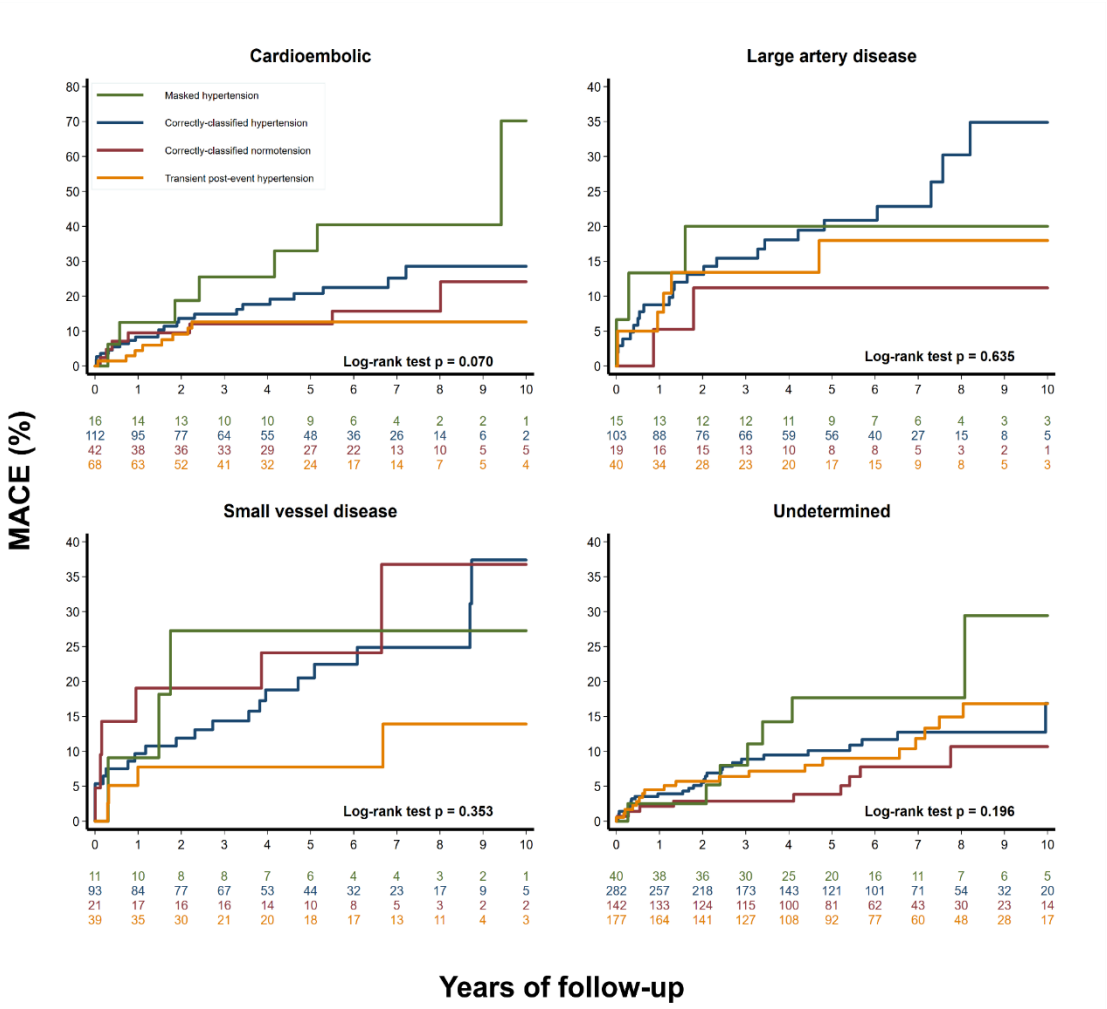


Figure 2-14 Survival curves and numbers at risk, by categorisation of blood pressure on baseline clinic and three-day HBPM, based on TOAST classification

Trial of Org 10172 in Acute Stroke Treatment (TOAST); home blood pressure monitoring (HBPM); major adverse cardiovascular events (MACE). Correctly classified hypertension was defined as clinic BP ≥140/90 and mean three-day home BP ≥135/85 mmHg. Correctly classified normotension was defined as clinic BP <140/90 and mean three-day home BP <135/85 mmHg. Masked hypertension was defined as clinic BP <140/90 and mean three-day home BP ≥135/85 mmHg. Transient post-event hypertension was defined as clinic BP ≥140/90 mmHg and mean three-day home BP <135/85 mmHg.

Chapter 3: Office, ambulatory, and telemetric home blood pressure monitoring: comparative predictive value for vascular events in a high-risk, treated population (Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study)

3.1 Abstract 105
3.2 Introduction 107
3.3 Methods 109
3.3.1 Study design and participants 109
3.3.2 Procedures 109
3.3.3 Statistical analysis 110
3.4 Results 114
3.5 Discussion 119
3.6 Tables 123
3.7 Figures 139

3.1 Abstract

Background: Accurate and reliable measurement of blood pressure is necessary for diagnosis and treatment of hypertension, but current guidelines provide contradictory recommendations on the use of office, ambulatory (ABPM), and home blood pressure monitoring (HBPM), and it remains unclear which modality is superior. Prediction of vascular events is arguably the best comparative measure, but few studies have compared these modalities in the same population and are limited by a low number of vascular events during follow-up. Therefore, I aimed to assess the relative prognostic value of mean blood pressure on contemporaneous office, 24-hour ABPM, and telemetrically verified HBPM in a secondary prevention cohort with a high rate of vascular events.

Methods: Consecutive eligible patients with TIA/minor stroke in a population-based study (Oxford Vascular Study) measured their blood pressure three times daily at home with a telemetric device, with antihypertensive treatment prescribed as necessary. Office blood pressure was assessed at a one-month follow-up clinic visit, and patients underwent 24-hour ABPM immediately prior to the visit. Mean blood pressure and hypertension (above guidelines thresholds) on office blood pressure, ABPM, and HBPM during the seven days prior to the visit were related to the risk of recurrent vascular events on ten-year follow-up.

Results: Among 1376 patients (mean/SD age=69.6/12.8), of whom 1125 (82%) were on antihypertensive treatment at the time of blood pressure assessment, the proportion with hypertension (blood pressure ≥130/80 mmHg) on seven-day HBPM (n=672, 48.8%) was lower than that on office blood pressure (821, 59.7%, p<0.0001) or 24-hour ABPM (blood pressure ≥125/75 mmHg, 773, 56.2%, p=0.006). Despite this, mean systolic blood pressure on HBPM was the strongest predictor of recurrent major vascular events (MVE, HR per SD 1.30, 95%CI 1.13-1.51, p<0.0001) during 7793 person-years of follow-up, while office systolic blood pressure had little predictive value (HR per SD 1.14, 0.98-

1.33, p=0.10). There was poor correlation between mean systolic blood pressure on HBPM and awake ABPM (r^2=0.28, p<0.0001), and among 274 (19.9%) participants with hypertension on ABPM but normotension on HBPM, there was a lower risk of MVE (HR 0.58, 95%CI 0.36-0.95, p=0.032) compared to the rest of the study population, driven by a particularly low risk in those aged <75 years (HR 0.29, 0.12-0.72, p=0.0008). Mean systolic blood pressure on HBPM was independently predictive of MVE after adjustment for awake ABPM systolic blood pressure (HR per SD 1.27, 1.07-1.51, p=0.006), but asleep ABPM systolic blood pressure added some prognostic value to a combination of office and HBPM systolic blood pressure (HR per SD residual asleep ABPM 1.18, 1.02-1.38, p=0.029).

Conclusion: The use of awake ABPM led to overdiagnosis of hypertension in younger subjects, while mean systolic blood pressure on seven-day HBPM was the strongest predictor for recurrent vascular events, with some additional prognostic value provided by asleep ABPM. Reliance on office blood pressure to diagnose hypertension and guide treatment decisions should be discouraged, and seven-day HBPM combined with some overnight readings appears to be the optimal strategy for accurate and clinically relevant characterisation of blood pressure.

3.2 Introduction

Elevated blood pressure is the strongest modifiable risk factor for vascular disease; over half of the global burden of ischaemic heart disease and stroke is attributable to high systolic blood pressure.[3] The diagnosis and management of hypertension depend upon the accurate measurement of blood pressure,[187] but there remains uncertainty about which measurement modality is best. Office blood pressure is the method of measurement most often used in clinical practice, but its limitations for the diagnosis of hypertension are well recognised.[177] Substantial misclassification occurs, with both 'masked hypertension' (normal office but elevated out-of-office blood pressure)[295] and 'white-coat hypertension' (isolated office hypertension)[292] being common in untreated[181, 294] and treated[293, 294] individuals.

Ambulatory blood pressure monitoring (ABPM) is more accurate and better predicts vascular events than office blood pressure,[191, 193, 194, 198, 304, 305] and is regarded as the gold standard by some guidelines.[198, 199, 204] Home blood pressure monitoring (HBPM) is cheaper, also permits the diagnosis of white-coat and masked hypertension, and is preferred by patients to ABPM.[211] It produces more reproducible blood pressure data and is a better predictor of vascular events and mortality than office blood pressure.[213-215] However, HBPM devices do not usually record blood pressure at night, and this may represent an important disadvantage in light of evidence that nocturnal hypertension measured by ABPM may be independently associated with vascular events.[140, 192, 306-308] Moreover, HBPM can be prone to incomplete and imprecise recordings because of patient misreporting[220-223] but these can be avoided with the use of telemetric systems to verify measurements.[221, 224-227]

Hypertension guidelines now acknowledge that diagnosis and management of hypertension is sub-optimal when based only on office blood pressure, and most require diagnostic confirmation by out-of-office measures.[59, 95, 186, 187, 198-205] However, they provide contradictory recommendations on the choice of modality, with some favouring

HBPM first-line,[202, 205] and others recommending HBPM only if ABPM is not tolerated.[199] Prediction of vascular events is arguably the most clinically relevant comparative measure, but few studies have compared office blood pressure, ABPM, and HBPM in the same sample and are limited by a low number of vascular events.[193, 308-311] In this chapter, I aimed to provide a general assessment of the relative prognostic value of mean blood pressure on contemporaneous office, ABPM, and telemetrically verified HBPM, in a high-risk, secondary prevention cohort with a high rate of vascular events.

3.3 Methods

3.3.1 Study design and participants

The Oxford Vascular Study (OXVASC) is a longitudinal, population-based cohort study of the incidence and outcome of all acute vascular events in a defined population of 92,728 individuals, registered with around 100 general practitioners in nine primary care practices in Oxfordshire, UK.[264, 298] OXVASC was approved by the Oxfordshire research ethics committee, including the HBPM substudy (OREC A: 05/Q1604/70). Written, informed consent or assent from relatives was obtained for all participants for study interview and follow-up, including ongoing review of primary care and hospital records and death certificate data.

3.3.2 Procedures

Consecutive patients with TIA or non-disabling stroke were prospectively recruited to this blood pressure-monitoring study between April 1st 2008 and March 31st 2019 from OXVASC. Case ascertainment of TIA/stroke was done using multiple overlapping methods and is near-complete for events reaching medical attention.[265, 299] These methods included a rapid access daily clinic to which general practitioners and the local emergency department referred individuals with suspected cerebrovascular events, daily searches of emergency departments, relevant hospital wards, eye hospital attendances, radiographic or vascular surgical investigations or procedures, and monthly searches of primary care practice diagnostic codes and referrals to acute and community hospitals. All consenting patients underwent a standardised medical history and examination, ECG, and blood tests. Patients underwent a stroke protocol MRI brain scan and contrast-enhanced MRA (or CT brain scan and either a carotid Doppler ultrasound or CT-angiogram when MR imaging was contraindicated), an echocardiogram, and five days of ambulatory cardiac monitoring. All patients were assessed by a study physician and reviewed by the senior study neurologist (Professor Peter Rothwell). Patients were followed up face-to-face at one, three, six, 12, 60, and

120 months. Recurrent cardiovascular events were ascertained at each follow-up and by multiple methods of ascertainment.[265, 299]

Office blood pressure was measured in the non-dominant arm by trained personnel, with two measurements made five minutes apart in the sitting position, after five minutes of rest. Patients were provided with a Bluetooth-enabled, regularly-calibrated, telemetric blood pressure monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT, on the day of the baseline clinic assessment. After appropriate training on the day, they were asked to perform three home blood pressure readings over ten minutes, three times daily (after waking, midday, and evening). Measurements were automatically transmitted by Bluetooth to a Raspberry Pi microcomputer hub, for secure transmission via a cellular network to a server hosting a password-protected website for review and download (OBS Medical, Abingdon, UK). Patients continued monitoring for at least one month. The day before the one-month follow-up visit, ABPM was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by trained study personnel. Blood pressure was measured at 30-minute intervals during the day (07:00 to 23:00) and 60-minute intervals at night. Patients were asked to refrain from excessive activity during recordings and were asked to keep a diary of their day. Hypertension was treated according to current guidelines,[95] initially based on baseline office readings and then according to HBPM, aiming for a target blood pressure<130/80 mmHg. Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a combination of perindopril arginine 5mg and indapamide 1.25mg, or amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion. Patients were generally advised to take their antihypertensive medication in the morning.

3.3.3 Statistical analysis

Office blood pressure at one-month follow-up was calculated as the mean of the two sitting measurements during the assessment. HBPM readings for each participant were downloaded from the encrypted website and manually assessed to remove those with

erroneous measures or incorrect date/time stamps (n=87, <0.1%). Recordings with systolic blood pressure <50 mmHg (n=3), diastolic blood pressure >140 mmHg if pulse pressure<40 mmHg (n=5), and any pulse pressure<10 mmHg (n=6) were excluded. Seven days of HBPM prior to ABPM were used to compare the three modalities, according to guidelines on HBPM.[59, 303] Mean blood pressure on ABPM was derived after exclusion of artefactual measurements according to predefined criteria,[312] analogous to those used for HBPM. Sleep and wake times for ABPM were determined by individual users' diary cards, and among 11 (0.8%) patients with night-time readings who did not return the diary card and were unavailable to confirm sleep/wake times over the phone, fixed narrow time intervals were applied (0900-2100h for awake, 0100-0600h for asleep) as per guideline recommendations.[210] Nocturnal blood pressure dipping status was defined as a nocturnal systolic blood pressure reduction of ≥10% of awake systolic blood pressure. Prior hypertension was defined as a diagnosis reported by the patient, prior antihypertensive treatment, or hypertension listed on the primary care list of diagnoses. Hypertension was defined at each time-point as mean blood pressure ≥130/80 mmHg for office blood pressure, HBPM, and awake ABPM, with lower thresholds for 24-hour ABPM (≥125/75 mmHg) and asleep ABPM (≥110/65 mmHg), according to guidelines.[95] Masked hypertension was defined as office blood pressure<130/80 and mean HBPM/awake ABPM blood pressure ≥130/80 mmHg, and white-coat hypertension was defined as office blood pressure ≥130/80 mmHg and mean HBPM/awake ABPM blood pressure<130/80 mmHg, also using guideline definitions.[95] For extra analyses in patients who refused ABPM, the HBPM period was taken as the seven days prior to the one-month follow-up assessment, or days 23-29 in those who did not attend. Day-to-day blood pressure variability was quantified using seven-day HBPM by calculating the standard deviation (SD), coefficient of variation (CV-100 x SD/mean), average real variability ($\frac{\mathbf{1}}{\boldsymbol{n-1}}\sum_{\boldsymbol{i=1}}^{\boldsymbol{n-1}}|\boldsymbol{BP_{i+1}} - \boldsymbol{BP_i}|$, where BP_i represents the ith blood pressure measurement for i=1, 2… n),[162, 313] and root mean square error (blood

pressure variability around the fitted linear regression line of blood pressure and day of HBPM). Missing data are reported, and were not imputed.

Means, medians, and proportions of baseline characteristics were stratified according to diagnostic agreement of HBPM and ABPM at one month and to 24-hour ABPM dipping status, and compared using t-tests, Wilcoxon rank-sum tests, and chi-square tests, respectively. The prevalence of hypertension and dipping status were compared across modalities using McNemar's tests. Logistic regression was performed to investigate the associations of masked and white-coat hypertension, calculated using both HBPM and awake ABPM, adjusted for age, sex, and antihypertensive treatment.

The risk of major vascular events (MVE: cardiovascular death, stroke, myocardial infarction, acute peripheral vascular events), stroke, and all-cause mortality were determined by Cox regression for hypertension on office blood pressure, HBPM, and ABPM, and by fitting blood pressure as a continuous variable to determine the hazard ratios per standard deviation increment in systolic blood pressure and diastolic blood pressure to standardise differences between modalities in terms of blood pressure distribution. The time at risk commenced from the day of the one-month follow-up assessment, or day 30 in patients who did not attend. Models were not adjusted for participant characteristics or vascular risk factors, since comparisons of each measurement modality were made within the same population. However, mean blood pressure measured by each method was examined by age, categorised into the following groups: <50, 50 to <60, 60 to <70, 70 to <80, and ≥80 years, and sensitivity analyses were performed with adjustment for or stratification by age because of previously described differences in the relationship between systolic blood pressure and age across different measurement modalities.[314]

Participants aged <75 years were chosen as an additional subgroup within which to examine risk prediction, as associations of systolic blood pressure with cardiovascular events and death have been observed in people aged >75 years,[315] despite a large

beneficial effect of antihypertensive treatment in trials of the very elderly in primary prevention,[316] but strong associations in observational studies at younger ages.[176]

Combination models were used to evaluate for any additional value of one modality over another, with likelihood ratio tests performed to assess model fit after the sequential introduction of a second modality. To account for the possibility of inaccurate results in combined models due to multicollinearity of blood pressure derived from different measurements,[311] sensitivity analyses with combined models containing only residual out-of-office blood pressure (the residuals from linear regression with office blood pressure, i.e., the contribution of out-of-office blood pressure not explained by office blood pressure) were completed. All analyses were performed using Stata version 16.1.

3.4 Results

Of 1833 patients with TIA or minor stroke in the OXVASC clinic during the study period, 51 (2.8%) declined to take part in the blood pressure-monitoring study, and 126 (6.9%) were excluded due to early death, acute intercurrent illness, severe dementia, excessive physical disability, or residence outside of the study area (Figure 3-1). 1656 (90.3%) consented to the blood pressure monitoring study, of whom 1626 (98.2%) continued HBPM until their one-month follow-up clinic assessment, 13 withdrew, three died, four developed serious intercurrent illness, and ten were unable to tolerate HBPM for one month. 1609 (97.2%) attended their scheduled one-month follow-up assessment, of whom 1382 (85.9%) agreed to be fitted for 24-hour ABPM and tolerated monitoring, 118 (8.5%) refused, and 109 (7.9%) didn't tolerate the machine for a sufficient number of readings to be used for the calculation of awake mean blood pressure. 22 (1.6%) patients removed the ABPM device during or before night-time readings so that only daytime blood pressure data were available. Overall, 1376 (83.1%) patients had ABPM, HBPM, and office blood pressure data at one-month follow-up to be included in comparative analyses. Median follow-up was 5.6 years (IQR 3.0-8.0), with 7793 total patient-years.

The mean age of consenting participants at baseline clinic was 69.6 (SD 12.8) years, and 52.7% were men (Table 3-1). 700 (50.9%) patients were currently prescribed at least one antihypertensive drug at the time of their TIA/stroke, increasing to 1125 (81.8%) at the time of one-month follow-up. Overall, 956 (69.5%) patients had their antihypertensive medications changed (i.e. either started, new agents prescribed, dosage alterations, or stopped) between their initial clinic assessment and one-month follow-up, of which 907 (94.9%) was a net dosage increase (Figure 3-2).

Mean office blood pressure was 4.3/1.0 mmHg higher than on HBPM, 1.6/0.9 mmHg higher than on awake ABPM, 5.9/3.7 mmHg higher than on 24-hour ABPM, and 14.4/9.6 mmHg higher than on asleep ABPM (all comparisons $p<0.001/p<0.001$, Figure 3-3).

Mean systolic blood pressure was lower on seven-day HBPM than awake ABPM (-2.7 mmHg, 95%CI -2.1 to -3.4, p<0.0001), the 95% limits of agreement were -26.8 to 21.4 mmHg, and there was relatively poor correlation between the two modalities (r^2=0.28, p<0.0001, Figure 3-4). Mean systolic blood pressure increased significantly from the youngest (<50 years) to the oldest (>80 years) age category when measured in clinic (124.8 to 136.1 mmHg, p<0.0001), and on seven-day HBPM (123.3 to 132.8 mmHg, p<0.0001), but not on awake ABPM (129.1 to 131.7 mmHg, p=0.062), while trends in diastolic blood pressure were similar for all modalities with increasing age (Figure 3-5). Mean office systolic blood pressure was higher than that on HBPM across all age groups; however, for awake ABPM, the difference varied by age, with higher office systolic blood pressure among patients aged ≥70 (mean [SE] difference 3.5 [0.6] mmHg, p<0.0001) and lower office systolic blood pressure among those aged <50 years (-4.4 [1.1] mmHg, p=0.0002, Figure 3-6).

There was also weak agreement for the diagnosis of hypertension (office blood pressure vs HBPM k=0.22, 0.17-0.27; office blood pressure vs awake ABPM k=0.32, 0.27-0.37; HBPM vs awake ABPM kappa=0.30, 95%CI 0.25-0.35; HBPM vs 24-hour ABPM [threshold 125/75 mmHg] k=0.32, 0.27-0.37, Figure 3-7**,** Figure 3-8**,** Figure 3-9). HBPM had a sensitivity of 69.3% (95%CI 65.7-72.8) and a specificity of 61.1% (57.4-64.7, AUC 0.65 [0.63-0.68]) for the diagnosis of hypertension when awake ABPM was used as the reference standard. Among 480 (34.9%) participants in whom there was diagnostic disagreement between ABPM and HBPM, those with hypertension on HBPM but normotension on ABPM were older (mean [SD] age 73[12] vs 69[13], p<0.0001), were more likely to have a history of hypertension (142/68.9% vs 139/50.7%, age-adjusted p=0.002), and were more likely to be taking antihypertensive treatment (182/88.4% vs 204/74.5%, age-adjusted p=0.003, Table 3-2). The proportion of patients with hypertension (blood pressure ≥130/80 mmHg) on office blood pressure was 59.7% (n=821) and was lower when defined by seven-day HBPM (n=672, 48.8%, p<0.0001,

Table 3-3). Hypertension was also more prevalent when defined by 24-hour ABPM (blood pressure ≥125/75 mmHg, n=773, 56.2%) than on HBPM (p=0.006), driven by high rates of nocturnal hypertension (asleep ABPM [blood pressure ≥110/65 mmHg], n=969/1368, 70.8%). Nocturnal hypertension often coincided with daytime hypertension, with a high prevalence among those with hypertension on awake ABPM compared to those with normotension (637/734, 86.8% versus 332/634, 52.4%; OR=5.97, 95%CI: 4.59-7.78, p<0.0001), and among those with hypertension versus normotension on HBPM (553/667, 82.9% versus 419/701, 59.3%; OR=3.21, 95%CI: 2.38-4.33, p<0.0001). As expected, nocturnal hypertension was more prevalent in patients with a non-dipping versus a dipping pattern on 24-hour ABPM (578/88.9% vs 391/54.5%, p<0.0001). Compared to those with a dipping pattern, patients with a non-dipping pattern were older (mean [SD] age 73[11] vs 66[13], p<0.0001), and were more likely to have cardiovascular risk factors and higher day-to-day systolic blood pressure variability on HBPM, even after adjustment for age (Table 3-4).

The detection of white-coat hypertension (office blood pressure ≥130/80, out-of-office blood pressure<130/80 mmHg) was greater when defined according to HBPM (n=344, 25.0%) than awake ABPM (n=272, 19.8%, p<0.0001), and the discrepancy was even larger when restricting to patients not taking antihypertensive therapy (28.7% vs 17.9%, p<0.0001), and those aged <50 years (26.7% vs 16.7%, p<0.0001, Table 3-5). The proportion of patients with masked hypertension (office blood pressure<130/80, out-of-office blood pressure ≥130/80 mmHg), however, was similar when defined according to HBPM (n=196, 14.2%) and awake ABPM (n=191, 13.9%, p=0.83) overall, but was higher when defined according to awake ABPM than HBPM in untreated patients (14.3% vs 6.8%, p=0.002) and those ages <50 years (15.8% vs 11.7%, p=0.017). Increasing age was associated with a higher prevalence of masked hypertension defined by HBPM (OR for each 10-year increment 1.16, 95% CI 1.02-1.31, p=0.022) but not awake ABPM (0.95, 0.85-1.07, p=0.43, Figure 3-10). Masked hypertension was positively associated

with several vascular risk factors, while an inverse relationship was frequently observed for white-coat hypertension, defined by either modality (Table 3-6).

The predictive value of mean systolic blood pressure for the risk of recurrent major vascular events (MVE), stroke, and mortality was greatest on HBPM and asleep ABPM (Table 3-7**,** Table 3-8). Each standard deviation increment in systolic blood pressure on seven-day HBPM was associated with a 30% (95% CI 13-51, p<0.0001) higher risk of recurrent MVE, while asleep and awake ABPM were associated with a 29% (11-49, p=0.001) and a 20% (3-39, p=0.02) higher risk per standard deviation, respectively. The associations of HBPM systolic blood pressure with MVE were particularly strong in participants aged <75 years (Table 3-7**,** Figure 3-11).

Measures of day-to-day systolic blood pressure variability on HBPM also had significant prognostic value, including after adjustment for mean systolic blood pressure in individuals aged <75 years (Table 3-7). In contrast, no significant predictive value for recurrent MVE was found for office hypertension (HR 0.86, 0.63-1.16, p=0.316) or office systolic blood pressure (HR 1.14 per SD, 95%CI 0.98-1.33, p=0.096).

Systolic blood pressure on HBPM was also highly predictive of MVE and mortality in an additional group of patients who refused or could not tolerate ABPM (HR 1.64 per SD, 1.22-2.22, p=0.001, Table 3-9). A non-dipping pattern on 24-hour ABPM was associated with a 59% (15-216, p=0.003) increased hazard of MVE, but this association was largely accounted for by the older age of individuals with this blood pressure pattern (Table 3-7**,** Table 3-10**,** Figure 3-12**,** Figure 3-13).

Absolute and relative risks of recurrent MVE according to the agreement between awake ABPM and HBPM for the diagnosis of hypertension, stratified by age, are shown in Figure 3-14. For those with a diagnosis of hypertension on ABPM but normotension on HBPM (n=274, 19.9%), there was a 42% lower risk of MVE (HR 0.58, 95%CI 0.36-0.95, p=0.032) relative to the rest of the study population, despite a substantial difference in

mean blood pressure on awake ABPM (136.3/77.5 [7.7/6.3] vs 129.0/73.8 [13.5/8.2], p<0.0001/p<0.0001). This was driven by a low risk in those aged <75 years (HR 0.29, 0.12-0.72, p=0.0008), which was maintained after adjustment for age within this age stratum (HR 0.31, 0.12-0.77, p=0.011).

In models combining methods of monitoring, mean systolic blood pressure on HBPM was independently predictive of MACE after adjustment for office systolic blood pressure (HR 1.29 per SD, 1.10-1.51, p=0.001) or awake ABPM systolic blood pressure (HR 1.27, 1.07-1.51, p=0.006, Table 3-11). In contrast, awake ABPM had no significant independent predictive value after adjustment either for HBPM systolic blood pressure (HR 1.05, 0.88-1.25, p=0.589) or for office systolic blood pressure (HR 1.16, 0.98-1.38, p=0.085). Systolic blood pressure on asleep ABPM had independent predictive value after adjustment for awake ABPM (HR 1.26, 1.04-1.53, p=0.016), and residual asleep ABPM systolic blood pressure added some prognostic value to a combination of office and residual HBPM systolic blood pressure (HR per SD residual asleep ABPM 1.18, 1.02-1.38, p=0.029, Table 3-12).

In a meta-analysis combining the present results with those from all identified studies reporting risk of vascular events by continuous systolic blood pressure recorded on contemporaneous office blood pressure, HBPM, and ABPM,[193, 309, 310] HBPM (fixed-effect HR per SD of systolic blood pressure 1.47, 95%CI 0.33-1.61) and asleep ABPM (HR 1.48, 1.35-1.61) emerged as the strongest predictors, but there was substantial heterogeneity (Figure 3-15).

3.5 Discussion

Hypertension guidelines provide contradictory recommendations on how to diagnose hypertension, with some explicitly favouring ABPM over HBPM for hypertension diagnosis,[199, 204] and others recommending HBPM first-line,[202, 205] because of a scarcity of studies with an adequate number of vascular outcomes to compare the relative prognostic value of the two modalities.[228] This is the first study to my knowledge comparing office blood pressure, ABPM, and HBPM for the diagnosis of hypertension and prediction of vascular events in a high-risk cohort with a large burden of recurrent vascular events. I found that office blood pressure, even when using multiple resting measures, had little prognostic value, while mean systolic blood pressure on seven-day HBPM and asleep ABPM were the strongest predictors for recurrent vascular events, with some additional prognostic value provided by their combined use. Importantly, the use of awake ABPM alone lead to overdiagnosis of hypertension in younger subjects, and those with hypertension on ABPM but normotension on HBPM had a low risk of vascular events.

My findings have some clinical implications. First, despite awake ABPM being recommended first-line to confirm a diagnosis of hypertension in the UK National Institute of Clinical Excellence guidelines for anyone with office blood pressure between 140/90 and 180/120 mmHg,[199] I have shown that it might be inaccurate for the diagnosis of hypertension in high-risk, non-elderly individuals. The guidelines are based on cost-effectiveness studies that favoured daytime ABPM over HBPM, but these analyses assumed that ABPM had 100% sensitivity and specificity for the identification of clinically relevant hypertension due to a lack of comparative prognostic studies of clinical outcomes.[229-231] Indeed, HBPM had only modest sensitivity and specificity for the diagnosis of hypertension in my study when awake ABPM was used as the gold standard, despite it having the strongest prognostic value. The reduced predictive value of awake ABPM in my study can be explained by higher systolic blood pressure

measurements on awake ABPM than on office blood pressure or HBPM in younger individuals (a phenomenon that has been established in previous studies)[314, 317] but which did not predict a higher risk of vascular events. In fact, the pattern of the difference between systolic blood pressure on awake ABPM and office blood pressure or HBPM in my cohort exactly mirrors that reported in the largest meta-analysis on the subject, with a similar age threshold of 50 years for the reversal of the relationship of systolic blood pressure on awake blood pressure with office blood pressure.[318] The findings might be accounted for by the properties of the measurement; since patients were advised to relax in a chair before office blood pressure and HBPM measurements, these were effectively a measure of resting blood pressure, while ABPM, as a measure of active blood pressure, may have been affected by higher physical activity levels in younger individuals. This has relevance for the detection of masked hypertension in non-elderly subjects; as expected from these differences, the prevalence of masked hypertension was higher when defined according to awake ABPM than HBPM in younger participants. However, this was not prognostically informative, since younger participants with hypertension on awake ABPM but normotension on HBPM had a substantially lower vascular risk than the rest of the study population. Second, mean systolic blood pressure on HBPM was a strong predictor of vascular events, day-to-day blood pressure variability on seven-day HBPM had prognostic value independent of mean blood pressure in younger individuals, and HBPM was highly predictive among patients who refused or did not tolerate ABPM. Specifically, awake ABPM had no additional prognostic value over HBPM. This has clinical significance, as HBPM is less expensive, more widely available, and better tolerated by patients than ABPM,[211, 303] and can additionally be used to guide treatment and improve long-term blood pressure control in primary prevention when combined with co-interventions such as systematic antihypertensive medication titration or patient education. [227, 237, 238] Third, asleep ABPM blood pressure strongly predicted recurrent vascular events overall, independently of awake ABPM, and added some prognostic information to models including office blood

pressure and HBPM. A 24-hour ABPM non-dipping pattern was strongly associated with pre-existing vascular disease and antihypertensive treatment but had limited predictive value after accounting for the older age of participants with a non-dipping profile. This is consistent with previous findings that suggest that non-dipping might just be a marker of pre-existing disease or daytime administration of antihypertensive agents rather than having independent prognostic value for vascular events.[140] Taken together, my observations suggest that although asleep blood pressure readings have predictive utility, they need not be performed in the context of 24-hour ABPM to determine 24-hour blood pressure dipping patterns. This is important given the recent advent of night-time HBPM, which is comparable to nocturnal blood pressure measured by ABPM,[217] appears to predict independently of office blood pressure and daytime HBPM,[218, 219] and is gaining popularity due to the development of silent wrist-based monitors that are purported to not interrupt sleep.[216]

The main strengths of my study include the large number of patients and outcome events compared to previous studies in lower-risk primary prevention settings.[193, 215, 228, 308-311] the contemporaneous comparison of all three blood pressure measurement modalities, and the use of home blood pressure telemonitoring. The system was no more complicated for patients to use than a conventional blood pressure monitor and provided valid and reliable blood pressure data without compromising acceptability. This overcomes the problems of incomplete, imprecise, or optimistic patient recordings in conventional HBPM.[220-222] However, my analyses had some potential shortcomings. First, HBPM was performed for the full duration of the first month after TIA/stroke, while ABPM was performed for the first time at one-month follow-up. An acclimatisation effect may thus have contributed to the lower systolic blood pressure recorded on HBPM versus awake ABPM, which contrasts with the pattern seen in some, but not all, previous studies performed in primary prevention.[229, 309, 319] However, the same pattern of blood pressure differences between awake ABPM and HBPM across age categories was

observed for awake ABM and office blood pressure, as described above, thus it is more likely to be accounted for by another mechanism. Second, since blood pressure treatment was subsequently altered based on office, HBPM, and ABPM measurements at one month, I will have reduced the predictive value for recurrent vascular events for each modality. Third, risk associations for office blood pressure are subject to regression dilution bias. However, I aimed to compare the prognostic value of HBPM and ABPM to the modality of blood pressure assessment (office measurements recorded on a single visit) used in current clinical practice. Fourth, the high cost of blood pressure telemonitoring technologies[221] pose barriers to the application of the strategy used in this study to current practice. For the purpose of this research, I needed to ensure the absolute reliability of HBPM for comparisons with ABPM and clinic blood pressure. However, non-telemetric patient-recorded HBPM is likely to be sufficient for normal clinical practice over short periods, is endorsed by clinical guidelines in primary prevention,[303] and is the modality of choice in NHS England's primary care HBPM protocol currently being implemented.[320] Additionally, night-time HBPM telemonitoring is expected to be introduced into clinical practice in the near future.[217]

In conclusion, mean systolic blood pressure on seven-day HBPM and asleep ABPM was the strongest predictor of vascular events in this high-risk population, but awake ABPM overdiagnosed hypertension. Primary prevention guidelines recommending ABPM above HBPM may require further validation, especially in younger individuals. HBPM combined with some overnight recording appears to be the optimal strategy for diagnosis of hypertension and accurate prognostication.

3.6 Tables

Table 3-1 Participant characteristics

n	1376
Male sex, n (%)	725 (52.7%)
Age, mean (SD)	69.6 (12.8)
Event type, n (%)	
Stroke	531 (38.6%)
TIA	845 (61.4%)
Medical history prior to event, n (%)	
Hypertension (prior history/treatment)	854 (62.1%)
Angina	156 (11.3%)
Diabetes mellitus	166 (12.1%)
Hyperlipidaemia	439 (31.9%)
Myocardial infarction	38 (2.8%)
Atrial fibrillation	158 (11.5%)
Heart failure	57 (4.1%)
Peripheral vascular disease	48 (3.5%)
Prior stroke	78 (5.7%)
Prior TIA	206 (15.0%)
Lifestyle factors (self-reported)	
Current smoker, n (%)	206 (15.0%)
Ever-smoker, n (%)	734 (53.3%)
Alcohol intake u/week, median (IQR)ǂ	2 (11)
Antihypertensive use, n (%)	
Baseline	700 (50.9%)
One-month follow-up	1125 (81.8%)
Baseline BP mmHg, mean (SD)	
Clinic, systolic	152.0 (22.9)
Clinic, diastolic	85.3 (13.2)
HBPM first day of monitoring, systolic	138.2 (17.3)
HBPM first day of monitoring, diastolic	80.7 (11.0)
HBPM first 3 days of monitoring, systolic	135.4 (16.0)
HBPM first 3 days of monitoring, diastolic	78.9 (10.2)
One-month follow-up BP mmHg, mean (SD)	
Clinic, systolic	132.5 (21.5)
Clinic, diastolic	75.3 (10.9)
HBPM 3 days prior to one-month clinic, systolic	127.2 (12.4)
HBPM 3 days prior to one-month clinic, diastolic	74.2 (9.1)
HBPM 7 days prior to one-month clinic, systolic	127.8 (12.5)
HBPM 7 days prior to one-month clinic, diastolic	74.5 (9.1)
ABPM awake, systolic	130.5 (12.9)
ABPM awake, diastolic	74.6 (8.0)
ABPM asleep, systolic¶	117.6 (15.5)
ABPM asleep, diastolic	65.8 (8.5)
ABPM 24-hour, systolic	126.2 (12.4)
ABPM 24-hour, diastolic	71.7 (7.6)

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP)). ǂ Alcohol intake data missing for 87 participants ¶ Asleep ABPM data missing for 8 participants.

Table 3-2 Characteristics of participants for whom there was disagreement between HBPM and awake ABPM in the diagnosis of hypertension

	Agreement	ABPM hypertension, HBPM normotension	HBPM hypertension, ABPM normotension	ABPM vs HBPM disagreement, p-value	ABPM vs HBPM disagreement, age-adjusted p-value
n (% whole cohort)	896 (65.1%)	274 (19.9%)	206 (15.0%)	-	-
Age, mean (SD)	69.2 (12.8)	68.6 (13.0)	72.6 (12.1)	**0.0006**	-
Male sex, n (%)	472 (52.7%)	150 (54.7%)	103 (50%)	0.588	0.417
Event type, n (%)					
Stroke	354 (39.5%)	94 (34.3%)	83 (40.3%)	0.260	0.144
TIA	542 (60.5%)	180 (65.7%)	123 (59.7%)		
Medical history prior to event, n (%)					
Hypertension (prior history/treatment)	573 (64.0%)	139 (50.7%)	142 (68.9%)	**<0.0001**	**0.002**
Angina	110 (12.3%)	19 (6.9%)	27 (13.1)	**0.035**	0.069
Diabetes mellitus	112 (12.5%)	20 (7.3%)	34 (16.5%)	**0.007**	**0.006**
Hyperlipidaemia	289 (32.3%)	78 (28.5%)	72 (35.0%)	0.298	0.235
Myocardial infarction	24 (2.7%)	8 (2.9%)	6 (2.9%)	0.968	0.875
Atrial fibrillation	95 (10.6%)	32 911.7%)	31 915.1%)	0.195	0.612
Heart failure	43 (4.8%)	6 (2.2%)	8 (3.9%)	0.162	0.445
Peripheral vascular disease	35 (3.9%)	6 92.2%)	7 (3.4%)	0.398	0.593
Prior stroke	48 (5.4%)	18 (6.6%)	12 (5.8%)	0.745	0.696
Prior TIA	126 (14.1%)	45 (16.4%)	35 (17.0%)	0.429	0.729
Ever-smoker, n (%)	476 (53.1%)	129 (47.1%)	129 (62.6%)	**0.001**	**<0.0001**
Antihypertensive use, n (%)					
One-month follow-up	739 (82.5%)	204 (74.5%)	182 (88.4%)	**<0.0001**	**0.003**
One-month follow-up BP mmHg, mean (SD)					
Clinic, systolic	132.8 (18.9)	133.9 (16.8)	126.8 (14.7)	**<0.0001**	**<0.0001**

Clinic, diastolic	76.0 (11.1)	75.3 (10.2)	73.4 (10.8)	0.052	0.403
HBPM 7 days prior to one-month clinic, systolic	128.4 (13.9)	121.2 (6.0)	133.8 (7.7)	**<0.0001**	**<0.0001**
HBPM 7 days prior to one-month clinic, diastolic	74.9 (9.6)	70.3 (6.8)	78.4 (7.6)	**<0.0001**	**<0.0001**
ABPM awake, systolic	130.7 (14.2)	136.3 (7.7)	121.9 (5.8)	**<0.0001**	**<0.0001**
ABPM awake, diastolic	74.7 (8.4)	77.5 (6.3)	70.2 (6.3)	**<0.0001**	**<0.0001**
ABPM asleep, systolic	118.2 (16.3)	119.2 (14.1)	112.9 (12.4)	**<0.0001**	**<0.0001**
ABPM asleep, diastolic	66.2 (8.8)	66.3 (8.1)	63.6 (7.0)	**0.0001**	**0.0008**
ABPM 24-hour, systolic	126.6 (13.8)	130.5 (7.9)	118.9 (6.4)	**<0.0001**	**<0.0001**
ABPM 24-hour, diastolic	71.9 (8.0)	73.8 (6.0)	67.9 (5.7)	**<0.0001**	**<0.0001**

Ambulatory blood pressure monitoring (ABPM); home blood pressure monitoring (HBPM); standard deviation (SD); transient ischaemic attack (TIA); blood pressure (BP)

Table 3-3 Blood pressure and hypertension on HBPM, ABPM, and clinic BP based on antihypertensive use at one-month follow-up

Blood pressure measurement ***n (% whole cohort)***	**Whole cohort** ***1376 (100%)***	**No antihypertensive use** ***251 (18.2%)***
Clinic		
BP mean (SD), mmHg	132.5/75.3 (21.5/10.9)	128.0/76.3 (15.7/10.5)
Hypertension [≥130/80 mmHg], n (%)	821 (59.7%)	132 (52.6%)
7-day HBPM		
BP mean (SD), mmHg	127.8/74.5 (12.5/9.1)	122.0/73.5 (11.1/8.3)
Hypertension [≥130/80 mmHg], n (%)	672 (48.8%)	77 (30.7%)
Awake ABPM		
BP mean (SD), mmHg	130.5/74.6 (12.9/8.0)	128.5/75.5 (12.4/6.8)
Hypertension [≥130/80 mmHg], n (%)	740 (53.8%)	123 (49.0%)
Asleep ABPM¶		
BP mean (SD), mmHg	117.6/65.8 (15.5/8.5)	112.3/64.6 (14.2/8.0)
Hypertension [≥110/65 mmHg], n (%)	969 (70.8%)	145 (58.0%)
24-hour ABPM		
BP mean (SD), mmHg	126.2/71.7 (12.4/7.6)	123.3/72.1 (11.3/6.3)
Hypertension [≥125/75 mmHg], n (%)	773 (56.2%)	128 (51.0%)

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); standard deviation (SD). ¶ Asleep ABPM data missing for 8 participants.

Table 3-4 Baseline characteristics and BP of patients based on 24-hour ABPM dipping status

Baseline characteristics	Non-dippers	Dippers	p-value	Age-adjusted p-value
n (% cohort with asleep ABPM, n=1368)	650 (47.5%)	718 (52.5%)		
Age, mean (SD)	73.1 (11.4)	66.3 (13.0)	**<0.0001**	-
Male sex, n (%)	328 (50.5%)	326 (45.4%)	0.126	0.477
Event type, n (%)				
Stroke	260 (40.0%)	265 (36.9%)	0.240	0.140
TIA	390 (60.0%)	453 (63.1%)		
Medical history prior to event, n (%)				
Hypertension (prior history/treatment)	452 (69.5%)	395 (55.0%)	**<0.0001**	**0.003**
Angina	104 (16.0%)	51 (7.1%)	**<0.0001**	**0.001**
Diabetes mellitus	99 (15.2%)	66 (9.2%)	**0.001**	**0.006**
Hyperlipidaemia	237 (36.5%)	199 (27.7%)	**0.001**	**0.012**
Myocardial infarction	22 (3.4%)	16 (2.2%)	0.194	0.437
Atrial fibrillation	79 (12.2%)	77 (10.7%)	0.406	0.428
Heart failure	45 (6.9%)	12 (1.7%)	**<0.0001**	**<0.0001**
Peripheral vascular disease	37 (5.7%)	11 (1.5%)	**<0.0001**	**0.001**
Prior stroke	40 (6.2%)	37 (5.2%)	0.423	0.710
Prior TIA	91 (14.0%)	115 (16.0%)	0.298	0.514
Lifestyle factors (self-reported)				
Ever-smoker, n (%)	351 (54.0%)	380 (52.9%)	0.691	0.318
Current smoker, n (%)	71 (10.9%)	133 (18.5%)	**<0.0001**	0.159
Antihypertensive use, n (%)				
Baseline	387 (59.5%)	307 (42.8%)	**<0.0001**	**<0.0001**
One-month follow-up	565 (86.9%)	553 (77.0%)	**<0.0001**	**0.007**
Baseline BP mmHg, mean (SD)				
Clinic, systolic	152.9 (23.2)	151.1 (22.6)	0.133	0.568
Clinic, diastolic	84.1 (13.5)	86.4 (12.8)	**0.002**	0.317
HBPM first 3 days of monitoring, systolic	137.7 (16.8)	133.2 (14.8)	**<0.0001**	**0.005**
HBPM first 3 days of monitoring, diastolic	78.3 (10.6)	79.5 (9.9)	**0.020**	0.963
One-month follow-up BP mmHg, mean (SD)				
Clinic, systolic	133.0 (19.5)	131.1 (16.6)	**0.046**	0.674
Clinic, diastolic	74.4 (11.3)	76.4 (10.2)	**0.0005**	0.763
HBPM 7 days prior to one-month clinic, systolic	129.0 (13.0)	126.5 (12.4)	**0.0001**	0.077
HBPM 7 days prior to one-month clinic, diastolic	73.9 (9.2)	75.1 (8.9)	**0.0150**	0.738
ABPM awake, systolic	128.7 (13.1)	132.0 (12.3)	**<0.0001**	**<0.0001**
ABPM awake, diastolic	72.3 (8.0)	76.5 (7.4)	**<0.0001**	**<0.0001**
ABPM asleep, systolic	126.1 (14.9)	109.9 (11.5)	**<0.0001**	**<0.0001**
ABPM asleep, diastolic	69.1 (8.7)	62.9 (7.1)	**<0.0001**	**<0.0001**

ABPM 24-hour, systolic	127.1 (13.2)	125.2 (11.4)	**0.003**	**0.047**
ABPM 24-hour, diastolic	71.0 (7.9)	72.3 (7.0)	**0.0007**	0.510
One-month follow-up HBPM BP variability, mean (SD)				
SD, systolic	10.7 (4.3)	9.8 (4.0)	**<0.0001**	**0.020**
SD, diastolic	6.3 (2.7)	6.1 (2.3)	0.141	0.059
CV, systolic	8.2 (3.1)	7.7 (2.9)	**0.0005**	**0.042**
CV, diastolic	71.0 (7.9)	72.3 (7.0)	**0.036**	0.091
ARV, systolic	11.1 (4.7)	10.2 (4.3)	**0.0002**	**0.033**
ARV, diastolic	6.6 (2.9)	6.3 (2.5)	0.053	**0.015**
RMSE, systolic	10.1 (4.0)	9.2 (3.7)	**<0.0001**	**0.011**
RMSE, diastolic	5.9 (2.5)	5.8 (2.2)	**0.218**	0.070

Ambulatory blood pressure monitoring (ABPM); home blood pressure monitoring (HBPM); standard deviation (SD); transient ischaemic attack (TIA); blood pressure (BP); coefficient of variation (CV); average real variability (ARV); root mean square error (RMSE)

Table 3-5 Hypertension diagnostic categories based on clinic BP vs HBPM or awake ABPM

	7-day HBPM, n (%)	Awake ABPM, n (%)
Whole cohort (n=1376)		
Sustained hypertension	477 (34.7%)	549 (39.9%)
Sustained normotension	360 (26.2%)	364 (26.5%)
Masked hypertension	195 (14.2%)	191 (13.9%)
White-coat hypertension	344 (25.0%)	272 (19.8%)
No antihypertensive use (n=251)		
Sustained hypertension	60 (23.9%)	87 (34.7%)
Sustained normotension	102 (40.6%)	83 (33.1%)
Masked hypertension	17 (6.8%)	36 (14.3%)
White-coat hypertension	72 (28.7%)	45 (17.9%)
Age <50 years (n=120)		
Sustained hypertension	41 (34.2%)	53 (44.2%)
Sustained normotension	33 (27.5%)	28 (23.3%)
Masked hypertension	14 (11.7%)	19 (15.8%)
White-coat hypertension	32 (26.7%)	20 (16.7%)
Age ≥80 years (n=292)		
Sustained hypertension	115 (39.4%)	114 (39.0%)
Sustained normotension	64 (21.9%)	82 (28.1%)
Masked hypertension	59 (20.2%)	41 (14.0%)
White-coat hypertension	54 (18.5%)	55 (18.8%)

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); standard deviation (SD). Sustained hypertension was defined as clinic BP ≥130/80 and mean HBPM/ABPM BP ≥130/80 mmHg. Sustained normotension was defined as clinic BP <130/80 and mean HBPM/ABPM BP <130/80 mmHg. Masked hypertension was defined as clinic BP <130/80 and mean HBPM/ABPM BP ≥130/80 mmHg. White-coat hypertension was defined as clinic BP ≥130/80 mmHg and mean HBPM/ABPM BP <130/80 mmHg.

Table 3-6 Associations of masked and white-coat hypertension, defined by awake ABPM and HBPM, with vascular risk factors

Vascular risk factors	Masked hypertension HBPM			Masked hypertension ABPM			White-coat hypertension HBPM			White-coat hypertension ABPM		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age (per 10 years)	1.15	1.02 - 1.31	**0.022**	0.95	0.85 - 1.07	0.434	0.95	0.86 - 1.03	0.246	1.04	0.94 - 1.16	0.409
Male sex (age-adjusted)	1.02	0.75 - 1.38	0.921	1.16	0.85 - 1.58	0.353	0.79	0.62 - 1.00	0.059	0.72	0.55 - 0.94	**0.016**
Event type (age- and sex-adjusted)												
Stroke versus TIA	1.32	0.97 - 1.79	0.078	1.08	0.79 - 1.48	0.622	0.81	0.63 - 1.04	0.101	0.91	0.69 - 1.20	0.523
Medical history prior to event (age- and sex-adjusted)												
Hypertension (prior history/treatment)	1.09	0.78 - 1.51	0.616	0.61	0.44 - 0.84	**0.002**	0.99	0.76 - 1.29	0.938	1.36	1.01 - 1.82	**0.042**
Angina	1.28	1.11 - 2.59	**0.015**	1.18	0.73 - 1.89	0.499	0.59	0.38 - 0.93	**0.022**	0.71	0.44 - 1.12	0.138
Diabetes mellitus	1.78	1.69 - 2.67	**0.006**	1.12	0.71 - 1.76	0.640	0.65	0.43 - 0.99	**0.044**	1.03	0.68 - 1.55	0.894
Hyperlipidaemia	1.71	1.25 - 2.33	**0.001**	1.41	1.02 - 1.93	**0.037**	0.89	0.68 - 1.16	0.386	0.96	0.72 - 1.29	0.788
Myocardial infarction	1.07	0.44 - 2.63	0.874	1.38	0.59 - 3.21	0.455	0.75	0.32 - 1.72	0.492	0.84	0.45 - 2.04	0.697
Atrial fibrillation	0.79	0.48 - 1.30	0.358	1.22	0.77 - 1.95	0.393	0.74	0.39 - 1.42	0.364	1.44	0.97 - 2.13	0.068
Heart failure	1.33	0.67 - 2.63	0.975	1.21	0.58 - 2.53	0.607	0.91	0.61 - 1.36	0.645	0.95	0.48 - 1.87	0.882
Peripheral vascular disease	2.18	1.78 - 4.24	**0.021**	1.68	0.82 - 3.45	0.160	0.74	0.38 - 1.46	0.392	0.71	0.31 - 1.61	0.416

Prior stroke	1.07	0.57 - 2.03	0.275	1.79	1.02 - 3.15	**0.042**	0.79	0.45 - 1.41	0.437	1.01	0.56 - 1.79	0.996
Prior TIA	0.79	0.50 - 1.24	0.697	1.10	0.72 - 1.67	0.653	0.89	0.64 - 1.28	0.565	1.19	0.83 - 1.72	0.331
Ever-smoker	1.22	0.89 - 1.40	0.212	0.89	0.65 - 1.22	0.479	0.72	0.56 - 0.93	**0.011**	1.17	0.89 - 1.53	0.266
Antihypertensive use (age- and sex-adjusted)	2.41	0.66 - 1.41	**0.001**	0.98	0.65 - 1.47	0.918	0.83	0.61 - 1.14	0.249	1.15	0.80 - 1.66	0.448
Blood pressure indices (age-, sex- and treatment-adjusted)												
Nocturnal hypertension (asleep ABPM mean BP ≥110/65 mmHg)	1.16	0.81 - 1.65	0.418	1.86	1.27 - 2.72	**0.002**	0.95	0.73 - 1.25	0.735	0.48	0.87 - 1.82	0.226
Non-dipping profile on ABPM	1.01	0.74 - 1.39	0.940	0.70	0.51 - 0.97	**0.031**	0.87	0.67 - 1.12	0.274	1.28	0.97 - 1.69	0.081
HBPM SBPV: SD (top vs bottom quartile)	1.14	0.73 - 1.79	0.553	0.99	0.62 - 1.57	0.968	0.61	0.42 - 0.89	**0.009**	0.61	0.41 - 0.90	**0.014**
HBPM SBPV: CV (top vs bottom quartile)	0.78	0.50 - 1.21	0.268	0.91	0.58 - 1.44	0.695	0.93	0.65 - 1.33	0.687	0.67	0.45 - 0.99	**0.042**
HBPM SBPV: ARV (top vs bottom quartile)	1.38	0.88 - 2.15	0.161	0.87	0.55 - 1.37	0.543	0.56	0.38 - 0.81	**0.002**	0.61	0.41 - 0.92	**0.017**
HBPM SBPV: RMSE (top vs bottom quartile)	1.49	0.95 - 2.34	0.082	0.99	0.64 - 1.54	0.965	0.62	0.43 - 0.90	**0.012**	0.45	0.30 - 0.68	**<0.0001**

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); odds ratio (OR); confidence interval (CI); transient ischaemic attack (TIA); standard deviation (SD); coefficient of variation (CV); average real variability (ARV); root mean square error (RMSE). Masked hypertension was defined as clinic BP <130/80 and mean HBPM/ABPM BP ≥130/80 mmHg. White-coat hypertension was defined as clinic BP ≥130/80 mmHg and mean HBPM/ABPM BP <130/80 mmHg.

Table 3-7 The risk of recurrent major vascular events in relation to clinic BP, HBPM, and ABPM one month after TIA/stroke

	All participants (169 events)			Age <75 years (77 events)		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Hypertension						
Clinic (≥130/80 mmHg)	0.86	(0.63 - 1.16)	0.316	1.16	(0.73 - 1.83)	0.538
HBPM (≥130/80 mmHg)	1.36	(1.00 - 1.84)	**0.048**	1.83	(1.16 - 2.90)	**0.010**
Awake ABPM (≥130/80 mmHg)	1.05	(0.76 - 1.42)	0.758	0.98	(0.63 - 1.53)	0.451
24-hour ABPM (≥125/75 mmHg)	1.06	(0.78 - 1.43)	0.716	0.93	(0.59 - 1.45)	0.745
Asleep ABPM (≥110/65 mmHg)	1.27	(0.90 - 1.79)	0.167	1.12	(0.70 - 1.79)	0.649
24-hour ABPM day/night pattern						
Non-dipping pattern	1.59	(1.17 - 2.16)	**0.003**	1.54	(0.99 - 2.42)	0.057
Mean SBP (per SD increase)						
Clinic	1.14	(0.98 - 1.33)	0.096	1.37	(1.08 - 1.74)	**0.010**
HBPM	1.30	(1.13 - 1.51)	**<0.0001**	1.55	(1.26 - 1.91)	**<0.0001**
Awake ABPM	1.20	(1.03 - 1.39)	**0.020**	1.37	(1.10 - 1.70)	**0.005**
24-hour ABPM	1.23	(1.06 - 1.43)	**0.006**	1.35	(1.09 - 1.68)	**0.006**
Asleep ABPM	1.29	(1.11 - 1.49)	**0.001**	1.36	(1.09 - 1.68)	**0.006**
HBPM SBP variability (per SD increase)						
SD	1.25	(1.09 - 1.44)	**0.002**	1.46	(1.20 - 1.78)	**<0.0001**
CV	1.20	(1.04 - 1.38)	**0.012**	1.37	(1.03 - 1.19)	**0.004**
ARV	1.17	(1.02 - 1.34)	**0.026**	1.38	(1.14 - 1.66)	**0.001**
RMSE	1.23	(1.08 - 1.42)	**0.003**	1.48	(1.21 - 1.80)	**<0.0001**
SD - adjusted for mean SBP	1.16	(0.99 - 1.35)	0.064	1.27	(1.02 - 1.59)	**0.036**
CV - adjusted for mean SBP	1.16	(1.00 - 1.34)	**0.047**	1.28	(1.03 - 1.59)	**0.024**
ARV - adjusted for mean SBP	1.08	(0.93 - 1.26)	0.287	1.24	(1.02 - 1.52)	**0.034**
RMSE - adjusted for mean SBP	1.14	(0.98 - 1.33)	0.078	1.30	(1.04 - 1.62)	**0.021**

Major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); systolic blood pressure (SBP); blood pressure (BP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); hazard ratio (HR); confidence interval (CI)

Table 3-8 The risk of recurrent vascular events and mortality associated with hypertension or per standard deviation higher SBP or DBP, respectively, on clinic BP, HBPM, and ABPM at one-month post-TIA/stroke

	HBPM			Awake ABPM			24-hour ABPM			Asleep ABPM			Clinic		
Outcome	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Hypertension															
MVE	1.36	(1.00 - 1.84)	**0.048**	1.05	(0.76 - 1.42)	0.758	1.06	(0.78 - 1.43)	0.716	1.27	(0.90 - 1.79)	0.167	0.86	(0.63 - 1.16)	0.316
All cause stroke	1.38	(0.97 - 1.98)	0.074	1.11	(0.78 - 1.59)	0.558	1.06	(0.75 - 1.52)	0.734	1.21	(0.82 - 1.80)	0.341	0.96	(0.67 - 1.37)	0.803
All-cause mortality	1.37	(1.05 - 1.80)	**0.022**	1.16	(0.88 - 1.52)	0.293	1.23	(0.94 - 1.62)	0.137	1.39	(1.02 - 1.90)	**0.037**	0.88	(0.67 - 1.15)	0.344
SBP (per SD higher)															
MVE	1.30	(1.13 - 1.51)	**<0.0001**	1.20	(1.03 - 1.39)	**0.020**	1.23	(1.06 - 1.43)	**0.006**	1.29	(1.11 - 1.49)	**0.001**	1.14	(0.98 - 1.33)	0.096
All cause stroke	1.24	(1.04 - 1.47)	**0.015**	1.19	(0.99 - 1.42)	0.055	1.22	(1.02 - 1.45)	**0.028**	1.23	(1.04 - 1.47)	**0.018**	1.11	(0.92 - 1.33)	0.267
All-cause mortality	1.48	(1.30 - 1.68)	**<0.0001**	1.17	(1.02 - 1.35)	**0.025**	1.30	(1.13 - 1.49)	**<0.0001**	1.53	(1.35 - 1.73)	**<0.0001**	1.12	(0.97 - 1.29)	0.110
DBP (per SD higher)															
MVE	0.85	(0.73 - 0.99)	**0.033**	0.86	(0.74 - 1.00)	0.051	0.93	(0.79 - 1.08)	0.341	1.07	(0.92 - 1.25)	0.355	0.80	(0.68 - 0.94)	**0.005**

All cause stroke	0.96	(0.80 - 1.15)	0.628	0.95	(0.79 - 1.14)	0.580	1.01	(0.84 - 1.21)	0.910	1.08	(0.90 - 1.29)	0.403	0.91	(0.75 - 1.09)	0.297
All-cause mortality	0.77	(0.67 - 0.88)	**<0.0001**	0.70	(0.60 - 0.80)	**<0.0001**	0.76	(0.66 - 0.88)	**<0.0001**	1.07	(0.93 - 1.23)	0.313	0.66	(0.57 - 0.76)	**<0.0001**

Systolic blood pressure (SBP); diastolic blood pressure (DBP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); confidence interval (CI); hazard ratio (HR); major adverse cardiovascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); myocardial infarction (MI); sudden cardiac death (SCD); ischaemic heart disease (IHD).

Table 3-9 The risk of recurrent vascular events and mortality associated with hypertension or per standard deviation higher SBP or DBP, respectively, on clinic BP and HBPM in patients who refused or did not tolerate ABPM

	HBPM (n=250)				Clinic (n=216)			
Outcome	Events	HR	95% CI	p-value	Events	HR	95% CI	p-value
Hypertension								
MVE	29	2.27	(1.03 - 4.98)	**0.042**	28	1.03	(0.48 - 2.20)	0.939
Stroke	16	1.31	(0.49 - 3.51)	0.597	16	0.85	(0.32 - 2.29)	0.748
All-cause mortality	56	2.94	(1.63 - 5.32)	**<0.0001**	48	1.01	(0.57 - 1.80)	0.973
SBP (per SD higher)								
MVE	29	1.64	(1.22 - 2.22)	**0.001**	28	1.24	(0.87 - 1.77)	0.231
Stroke	16	1.26	(0.79 - 1.99)	0.327	16	1.28	(0.81 - 2.02)	0.291
All-cause mortality	56	1.82	(1.47 - 2.27)	**<0.0001**	48	1.21	(0.92 - 1.58)	0.175
DBP (per SD higher)								
MVE	29	1.24	(0.87 - 1.76)	0.229	28	0.84	(0.56 - 1.26)	0.401
Stroke	16	1.39	(0.88 - 2.20)	0.160	16	0.94	(0.56 - 1.58)	0.803
All-cause mortality	56	1.13	(0.87 - 1.46)	0.353	48	0.82	(0.60 - 1.13)	0.227

Systolic blood pressure (SBP); diastolic blood pressure (DBP); home blood pressure monitoring (HBPM); blood pressure (BP); ambulatory blood pressure monitoring (ABPM); confidence interval (CI); hazard ratio (HR); major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death)

Table 3-10 The risk of recurrent major vascular events in relation to clinic BP, HBPM, and ABPM one month after TIA/stroke

	All participants (169 events)			Age-adjusted		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Hypertension						
Clinic (≥130/80 mmHg)	0.86	(0.63 - 1.16)	0.316	0.86	(0.64 - 1.17)	0.346
HBPM (≥130/80 mmHg)	1.36	(1.00 - 1.84)	**0.048**	1.26	(0.93 - 1.71)	0.140
Awake ABPM (≥130/80 mmHg)	1.05	(0.76 - 1.42)	0.758	1.12	(0.83 - 1.52)	0.451
24-hour ABPM (≥125/75 mmHg)	1.06	(0.78 - 1.43)	0.716	1.10	(0.81 - 1.49)	0.542
Asleep ABPM (≥110/65 mmHg)	1.27	(0.90 - 1.79)	0.167	1.08	(0.76 - 1.52)	0.673
24-hour ABPM dipping						
Non-dipping pattern	1.59	(1.17 - 2.16)	**0.003**	1.23	(0.90 - 1.69)	0.190
Mean SBP (per SD increase)						
Clinic	1.14	(0.98 - 1.33)	0.096	1.06	(0.91 - 1.23)	0.465
HBPM	1.30	(1.13 - 1.51)	**<0.0001**	1.18	(1.01 - 1.37)	**0.036**
Awake ABPM	1.20	(1.03 - 1.39)	**0.020**	1.18	(1.01 - 1.37)	**0.034**
24-hour ABPM	1.23	(1.06 - 1.43)	**0.006**	1.18	(1.02 - 1.38)	**0.031**
Asleep ABPM	1.29	(1.11 - 1.49)	**0.001**	1.45	(0.98 - 1.34)	0.091
HBPM SBP variability (per SD increase)						
SD	1.25	(1.09 - 1.44)	**0.002**	1.14	(0.99 - 1.32)	0.068
CV	1.20	(1.04 - 1.38)	**0.012**	1.11	(0.96 - 1.29)	0.141
ARV	1.17	(1.02 - 1.34)	**0.026**	1.09	(0.94 - 1.25)	0.251
RMSE	1.23	(1.08 - 1.42)	**0.003**	1.14	(0.98 - 1.31)	0.081

Major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); systolic blood pressure (SBP); blood pressure (BP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); hazard ratio (HR); confidence interval (CI)

Table 3-11 The risk of recurrent major vascular events in relation to clinic BP, HBPM, and ABPM one month after TIA/stroke; mutually adjusted models and goodness of fit

	HR	95% CI	p-value	LR χ^2	p-value
Mean SBP (per SD increase)					
Clinic	1.14	(0.98 - 1.33)	0.096	-	-
HBPM	1.30	(1.13 - 1.51)	**<0.0001**	-	-
Awake ABPM	1.20	(1.03 - 1.39)	**0.020**	-	-
24-hour ABPM	1.23	(1.06 - 1.43)	**0.006**	-	-
Asleep ABPM	1.29	(1.11 - 1.49)	**0.001**	-	-
Adjusted for clinic SBP					
HBPM	1.29	(1.10 - 1.51)	**0.001**	9.81	**0.002**
Awake ABPM	1.16	(0.98 - 1.38)	0.085	2.93	0.090
24-hour ABPM	1.21	(1.02 - 1.44)	**0.030**	4.58	**0.032**
Asleep ABPM	1.27	(1.08 - 1.50)	**0.003**	8.26	**0.004**
Adjusted for HBPM					
Awake ABPM	1.05	(0.88 - 1.25)	0.589	0.29	0.590
24-hour ABPM	1.09	(0.90 - 1.30)	0.378	0.77	0.381
Asleep ABPM	1.16	(0.97 - 1.38)	0.096	2.69	0.101
Adjusted for awake ABPM					
HBPM	1.27	(1.07 - 1.51)	**0.006**	7.43	**0.006**
24-hour ABPM	1.39	(0.91 - 2.12)	0.133	2.23	0.136
Asleep ABPM	1.26	(1.04 - 1.53)	**0.016**	5.62	**0.017**

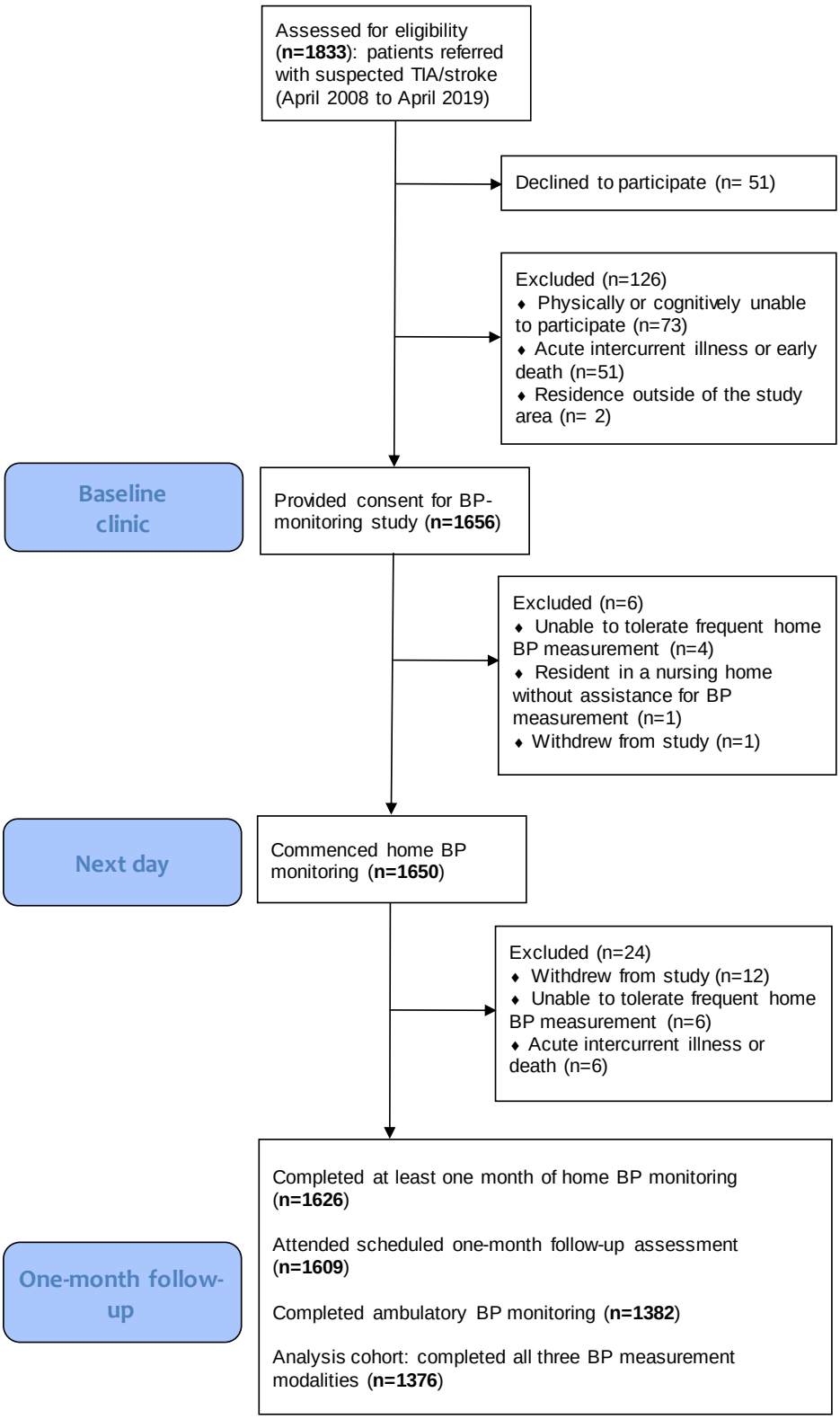
Major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); systolic blood pressure (SBP); blood pressure (BP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); hazard ratio (HR); confidence interval (CI)

Table 3-12 The risk of recurrent major vascular events in relation to clinic BP and residual out-of-office BP, and goodness of fit of sequentially adjusted models

	HR	95% CI	p-value	LR χ^2	p-value
Per SD increase					
Clinic SBP	1.14	(0.98 - 1.33)	0.096	-	-
Residual SBP, adjusted for clinic SBP					
HBPM	1.26	(1.09 - 1.46)	**0.001**	9.81	**0.002**
Awake ABPM	1.14	(0.98 - 1.33)	0.085	2.93	0.087
24-hour ABPM	1.18	(1.02 - 1.37)	**0.030**	4.58	**0.032**
Asleep ABPM	1.25	(1.08 - 1.45)	**0.003**	8.26	**0.004**
Residual SBP, adjusted for awake ABPM					
HBPM	1.26	(1.06 - 1.42)	**0.006**	7.43	**0.006**
24-hour ABPM	1.12	(0.97 - 1.31)	0.133	2.23	0.136
Asleep ABPM	1.20	(1.03 - 1.39)	**0.016**	5.62	**0.018**
Residual SBP, adjusted for HBPM					
Awake ABPM	1.04	(0.89 - 1.21)	0.590	0.29	0.590
24-hour ABPM	1.07	(0.92 - 1.24)	0.378	0.77	0.381
Asleep ABPM	1.14	(0.98 - 1.32)	0.096	2.96	0.101
Residual SBP, sequentially adjusted					
Clinic	1.14	(0.98 - 1.33)	0.096	-	-
+ HBPM	1.26	(1.09 - 1.46)	**0.001**	9.81	**0.002**
+ HBPM + awake ABPM	1.10	(0.94 - 1.28)	0.226	1.45	0.229
+ HBPM + 24-hour ABPM	1.13	(0.97 - 1.31)	0.121	2.34	0.126
+ HBPM + asleep ABPM	1.18	(1.02 - 1.38)	**0.029**	4.61	**0.032**

Major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); systolic blood pressure (SBP); blood pressure (BP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); hazard ratio (HR); confidence interval (CI)

3.7 Figures



Transient ischaemic attack (TIA); blood pressure (BP)

Figure 3-1 Flowchart of study inclusion and exclusion

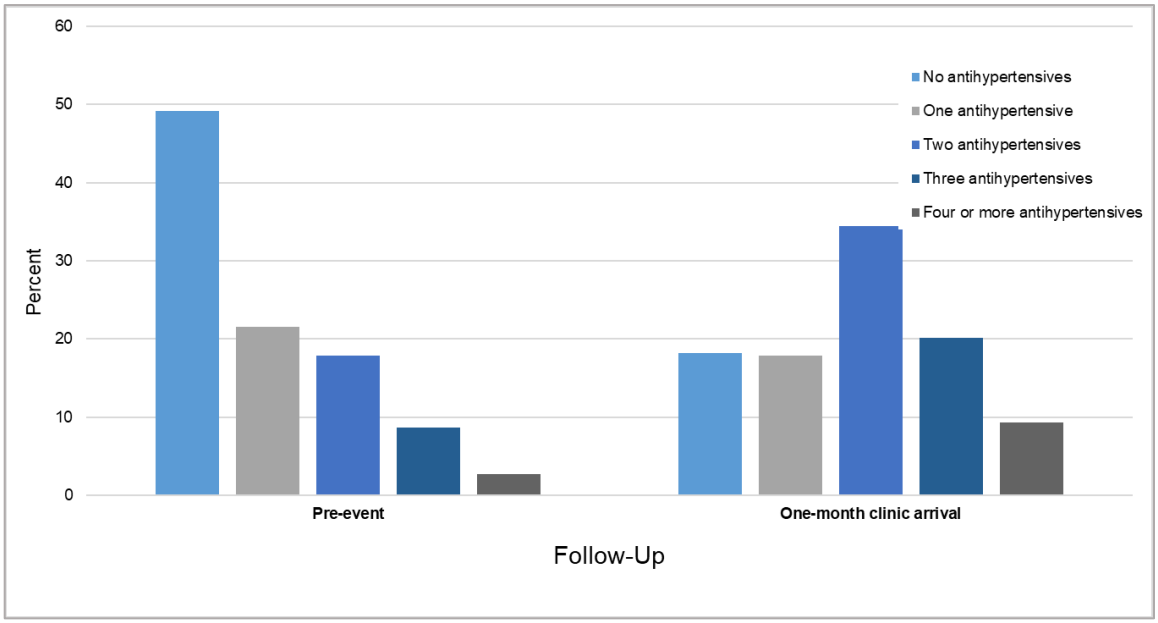
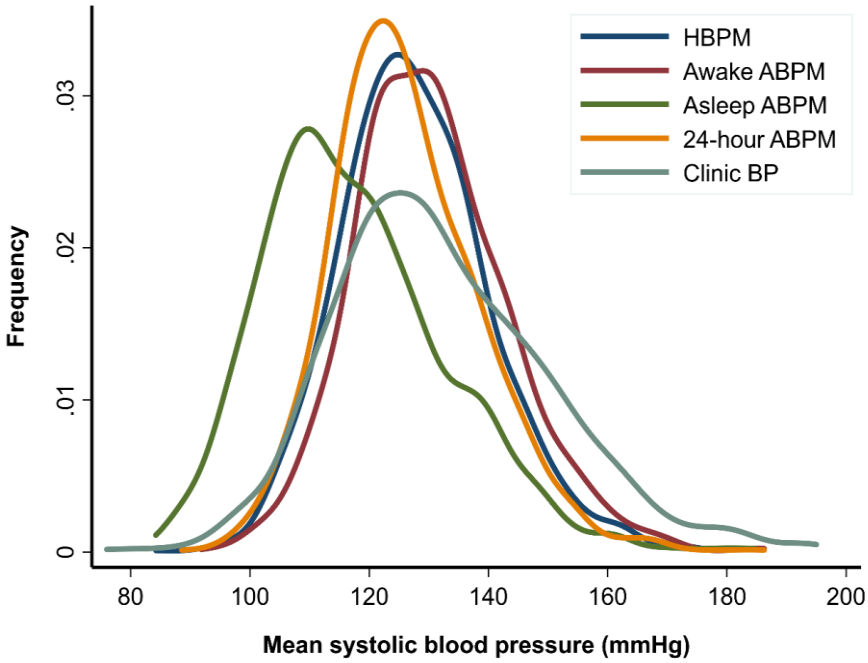


Figure 3-2 Change in the number of prescribed antihypertensive drugs between baseline and one-month follow-up



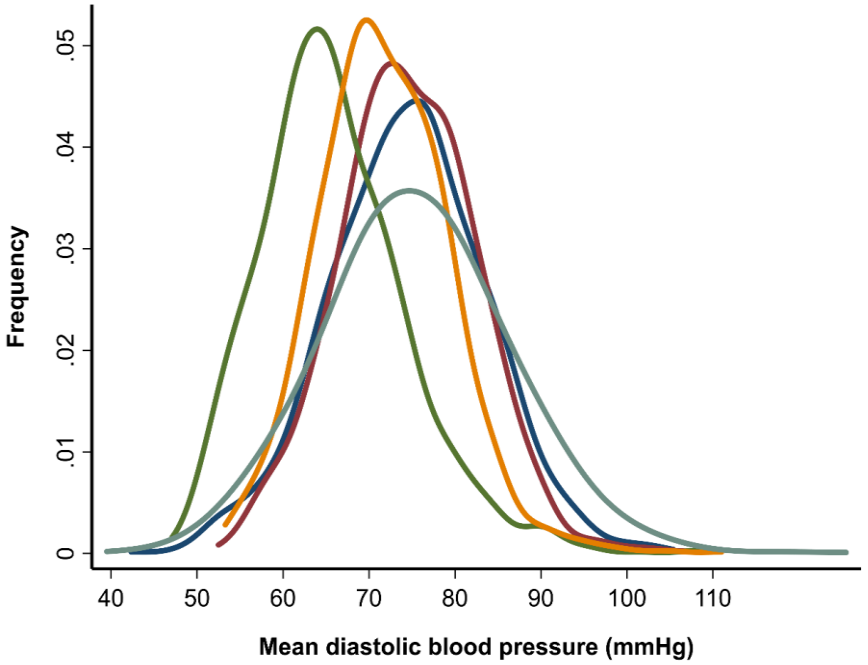


Figure 3-3 Distribution of mean systolic and diastolic blood pressure on 7-day HBPM, awake, asleep and 24-hour ABPM, and clinic recordings at one-month follow-up

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP). Mean BP on HBPM is derived from the seven days prior to the one-month clinic. Clinic BP is calculated from the mean of two sitting readings at one month. Frequencies are given per 3 mmHg and 2 mmHg bands of systolic and diastolic BP, respectively. Only patients with BP data from all measurement modalities are included.

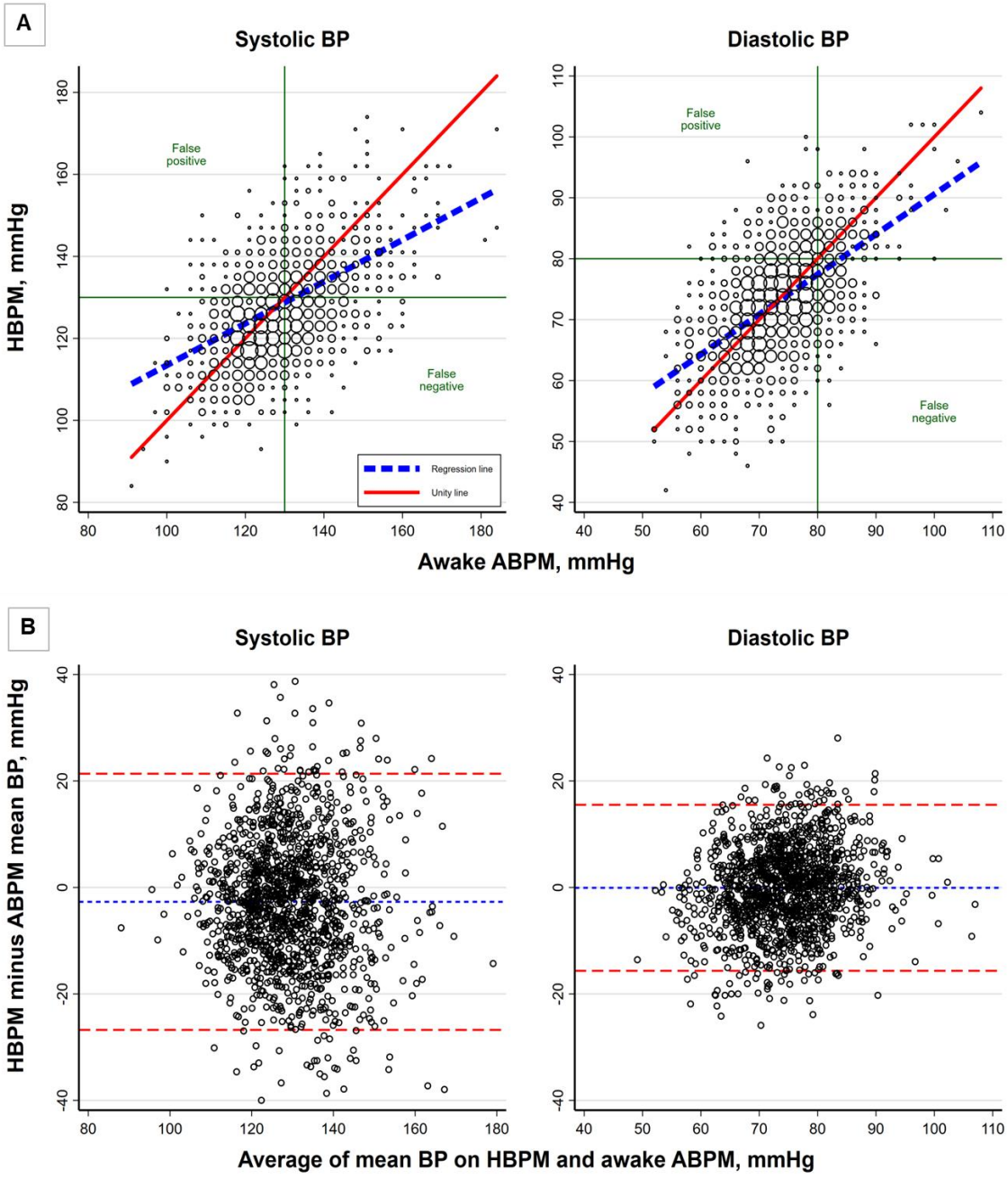


Figure 3-4 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on seven-day HBPM and awake ABPM

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP). The green lines in the scatterplots represent the cut-off points for hypertension (≥130/80 mmHg). ABPM is assumed to be the reference standard to highlight false positives and negatives. The size of the markers in the scatter plots are weighted by the number of cases in each 3 mmHg bin of systolic BP and each 2 mmHg bin of diastolic BP on HBPM and daytime ABPM. The blue dashed lines in the Bland-Altman plots represent the means of the absolute value of the BP difference between modalities. The red dashed lines represent ±1.96 SDs for this range.

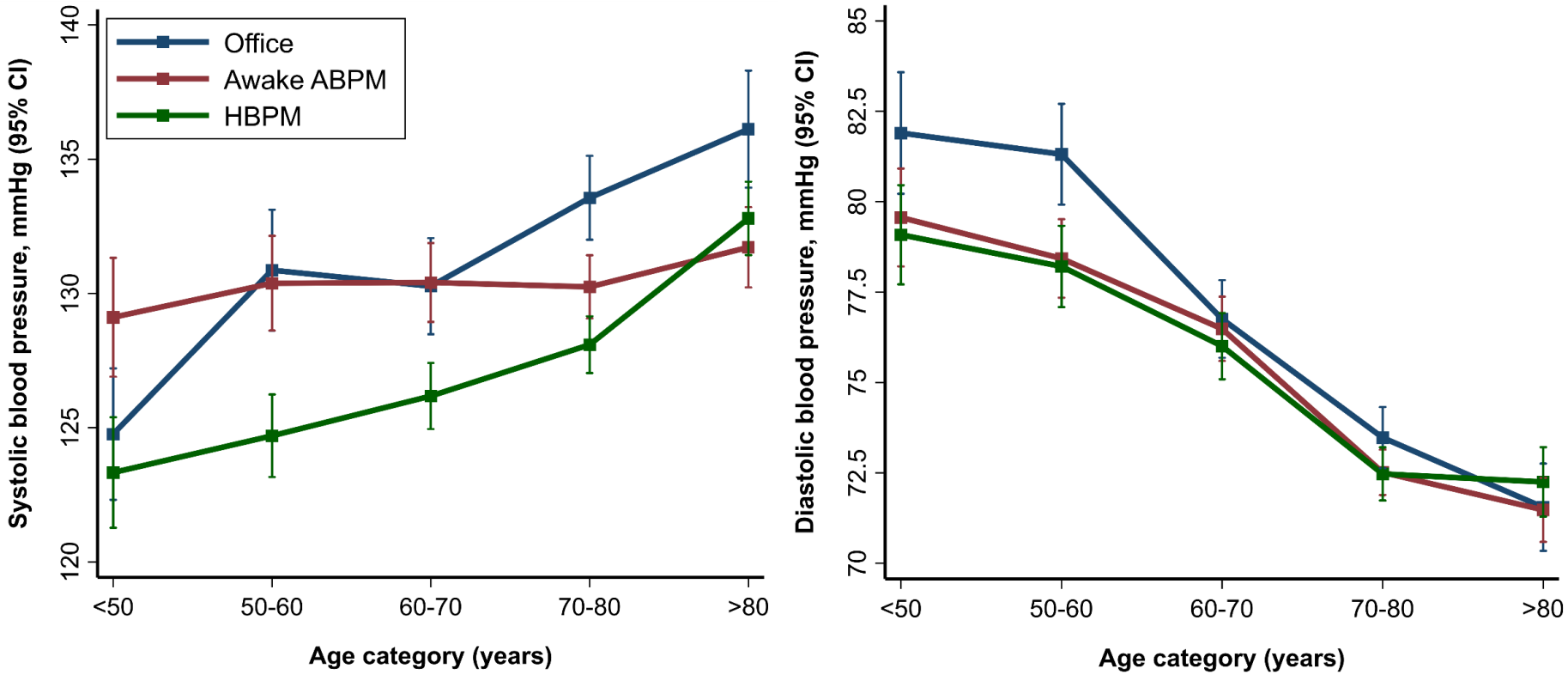


Figure 3-5 Blood pressure measured in the office, on awake ABPM, and on 7-day HBPM, according to age categories

Ambulatory blood pressure monitoring (ABPM); home blood pressure monitoring (HBPM); confidence interval (CI).

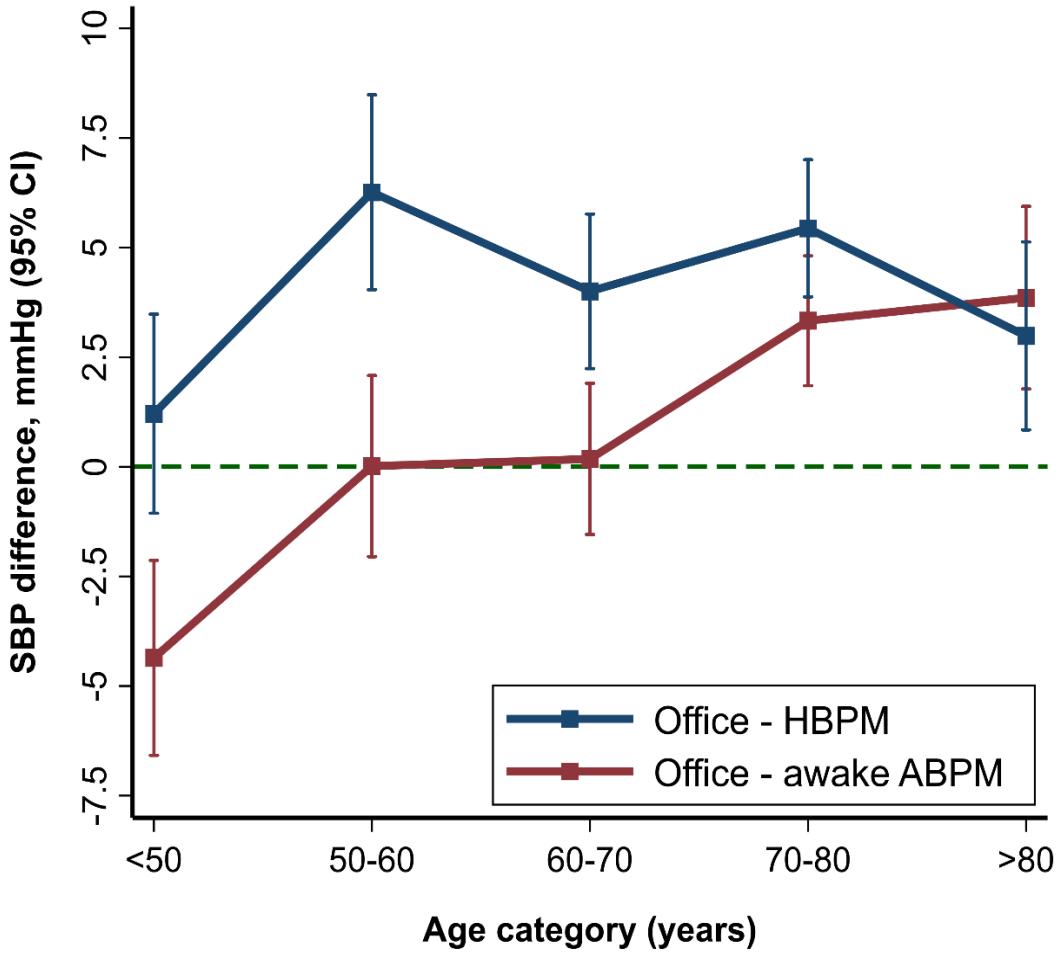


Figure 3-6 Differences in systolic BP between office BP and out-of-office measures, according to age categories

Systolic blood pressure (SBP); ambulatory blood pressure monitoring (ABPM); home blood pressure monitoring (HBPM); confidence interval (CI).

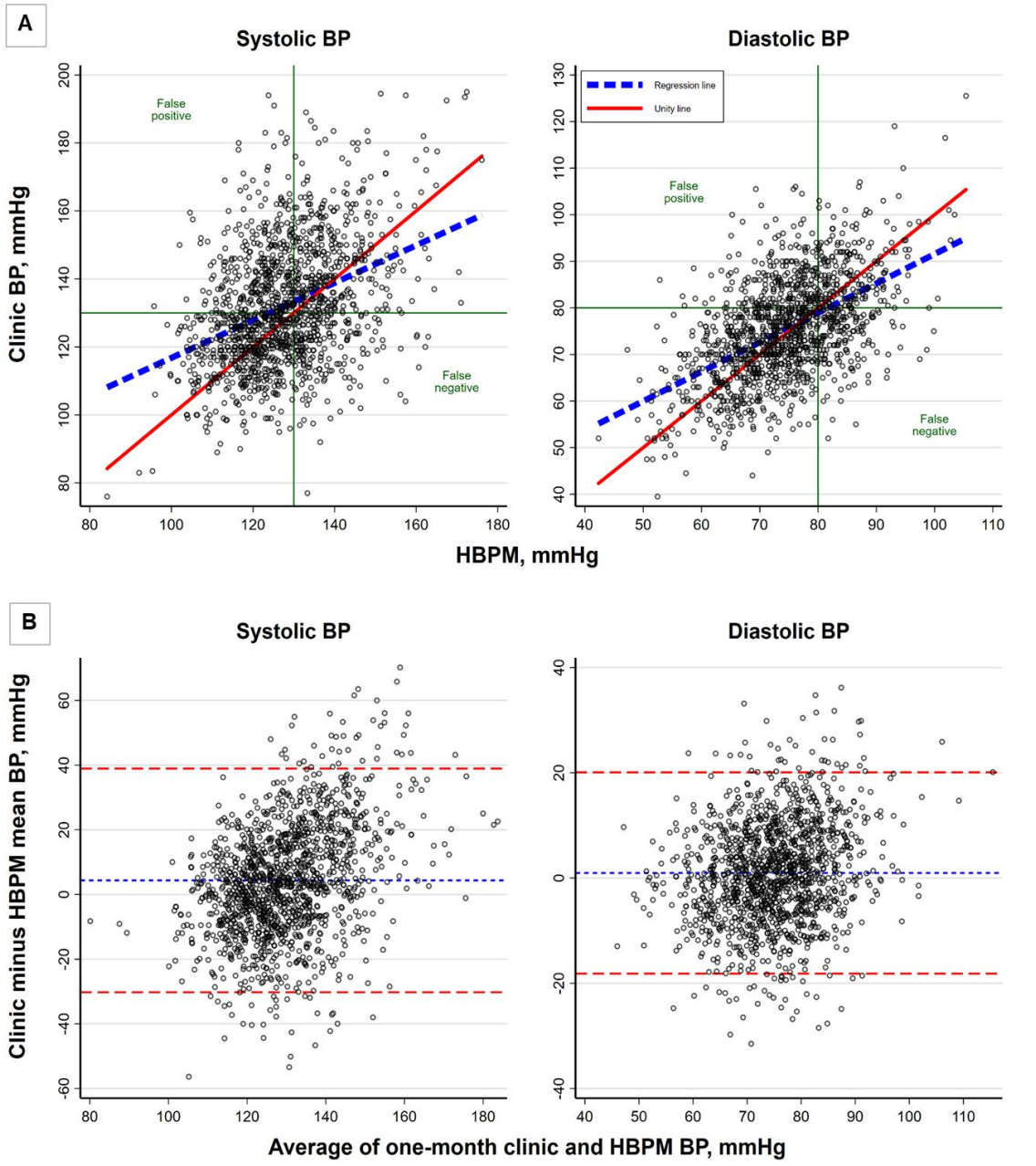


Figure 3-7 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on clinic assessment and seven-day HBPM at one month

Home blood pressure monitoring (HBPM); blood pressure (BP). The green lines in the scatterplots represent the cutoff points for hypertension (≥130/80 mmHg). HBPM is assumed to be the reference standard to highlight false positives and negatives. The blue dashed lines in the Bland-Altman plots represent the means of the absolute value of the BP difference between modalities. The red dashed lines represent ±1.96 SDs for this range.

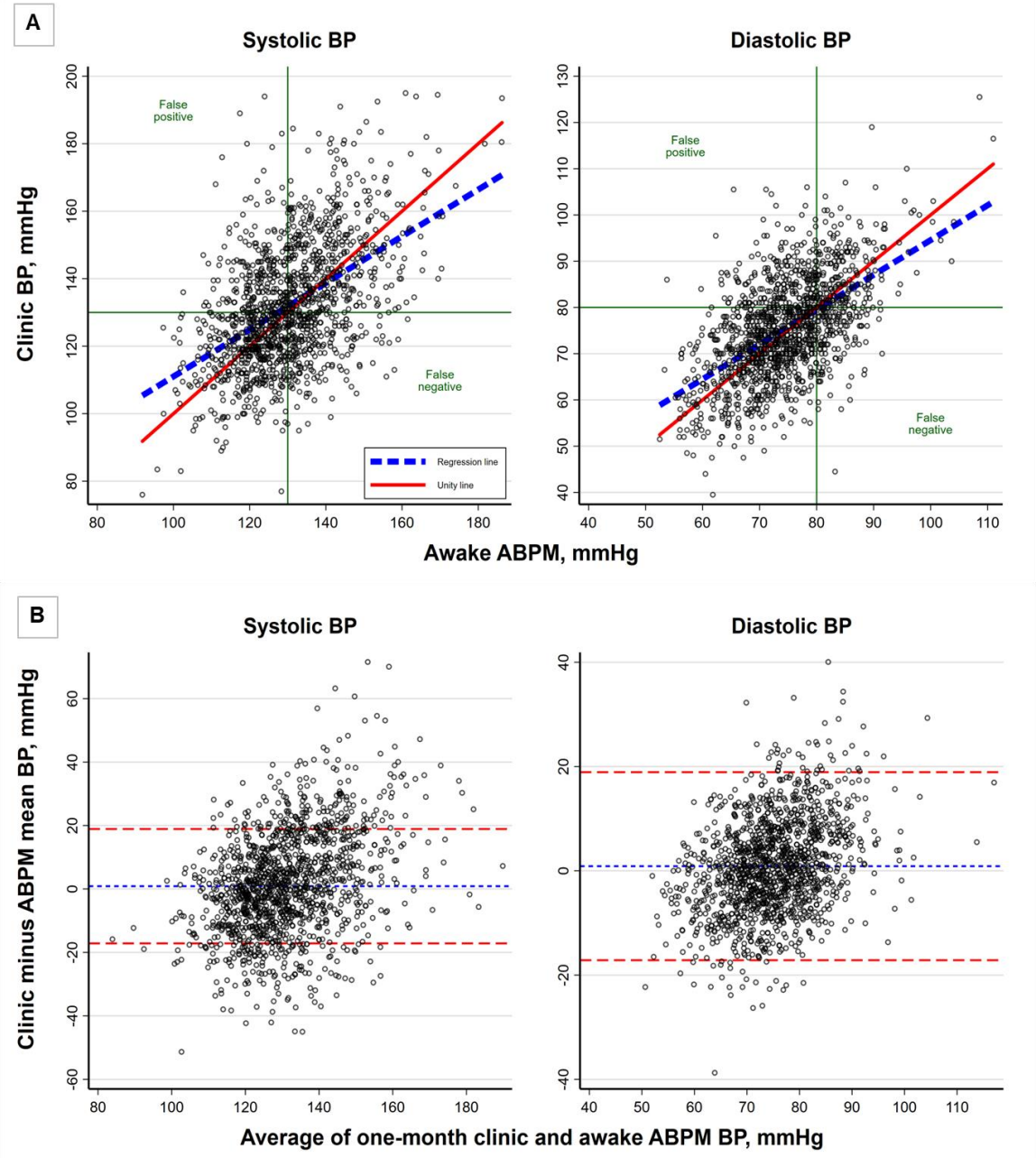


Figure 3-8 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on clinic assessment and awake ABPM at one month

Ambulatory blood pressure monitoring (ABPM); blood pressure (BP). The green lines in the scatterplots represent the cutoff points for hypertension (≥130/80 mmHg). ABPM is assumed to be the reference standard to highlight false positives and negatives. The blue dashed lines in the Bland-Altman plots represent the means of the absolute value of the BP difference between modalities. The red dashed lines represent ±1.96 SDs for this range.

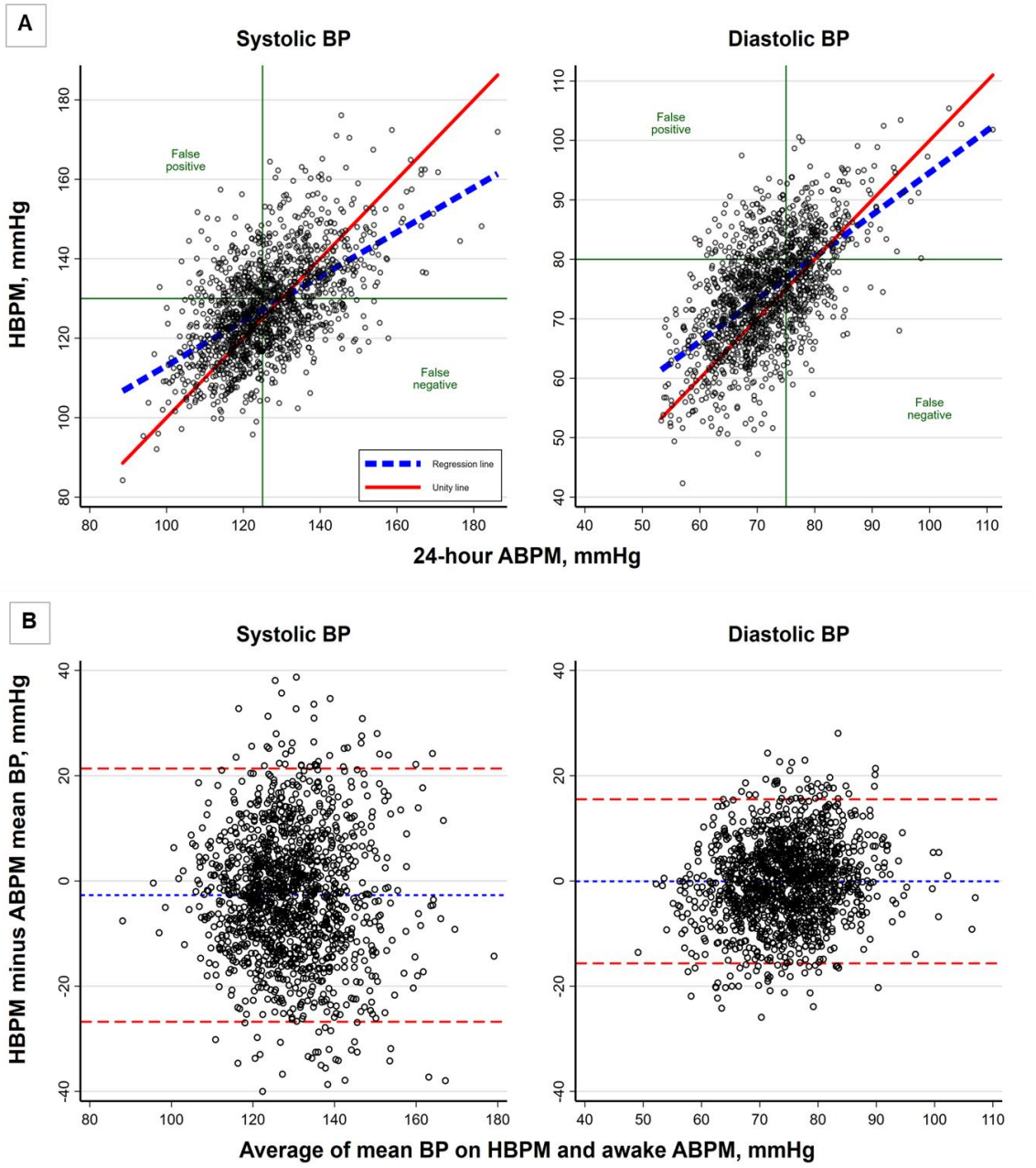


Figure 3-9 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on seven-day HBPM and 24-hour ABPM at one month

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP). The green lines in the scatterplots represent the cutoff points for hypertension (≥130/80 mmHg for HBPM, ≥125/75 for 24-hour ABPM). ABPM is assumed to be the reference standard to highlight false positives and negatives. The blue dashed lines in the Bland-Altman plots represent the means of the absolute value of the BP difference between modalities. The red dashed lines represent ±1.96 SDs for this range.

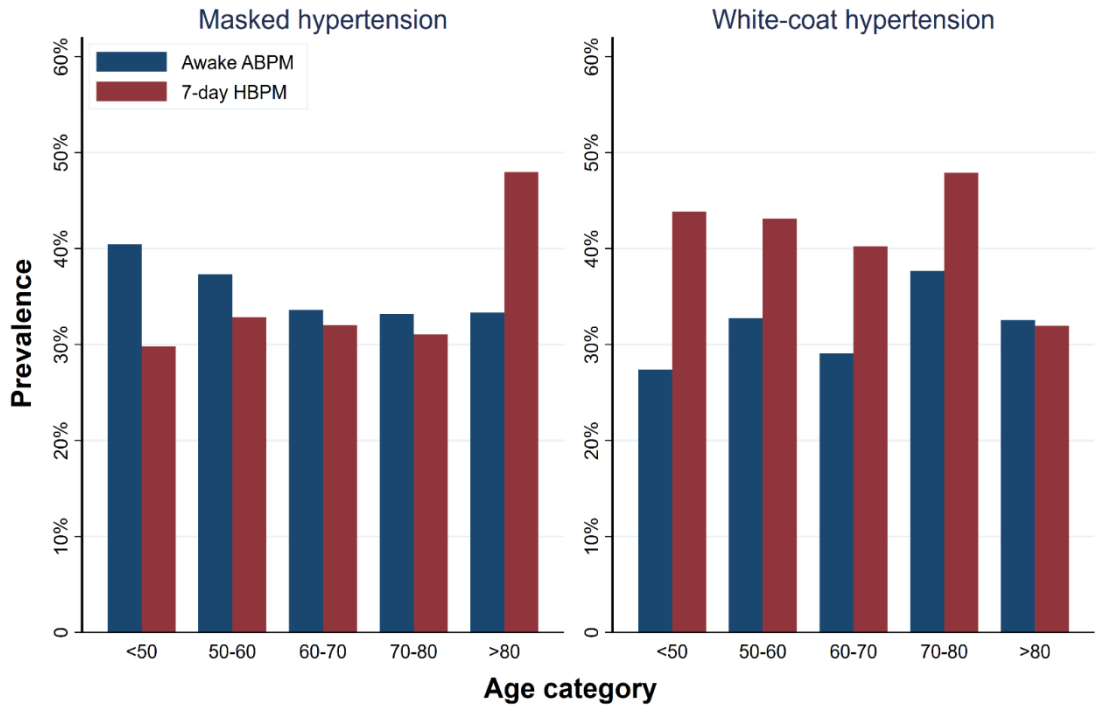


Figure 3-10 Prevalence of masked and white-coat hypertension, defined by HBPM and ABPM, according to age categories

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM). Masked hypertension was defined as clinic BP <130/80 and mean HBPM/ABPM BP ≥130/80 mmHg. White-coat hypertension was defined as clinic BP ≥130/80 mmHg and mean HBPM/ABPM BP <130/80 mmHg.

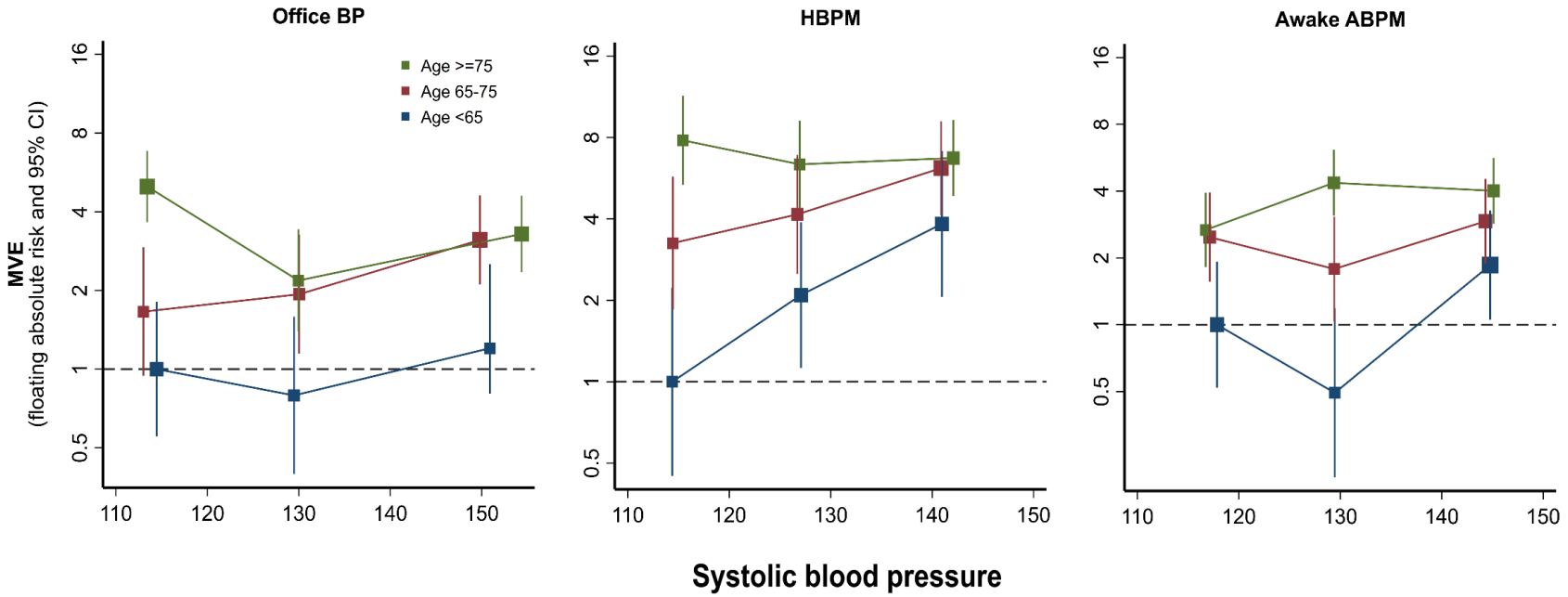


Figure 3-11 Hazard ratios (95% CI) for major vascular events, by tertiles of systolic blood pressure on office, home and awake ambulatory measurement, plotted against the mean systolic BP in each tertile and stratified by age category

Confidence interval (CI); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); major vascular events (MVE). The area of each square is inversely proportional to the variance of the log risk. 95% CIs for floated hazard ratios reflect uncertainty in the log risk for each estimate.

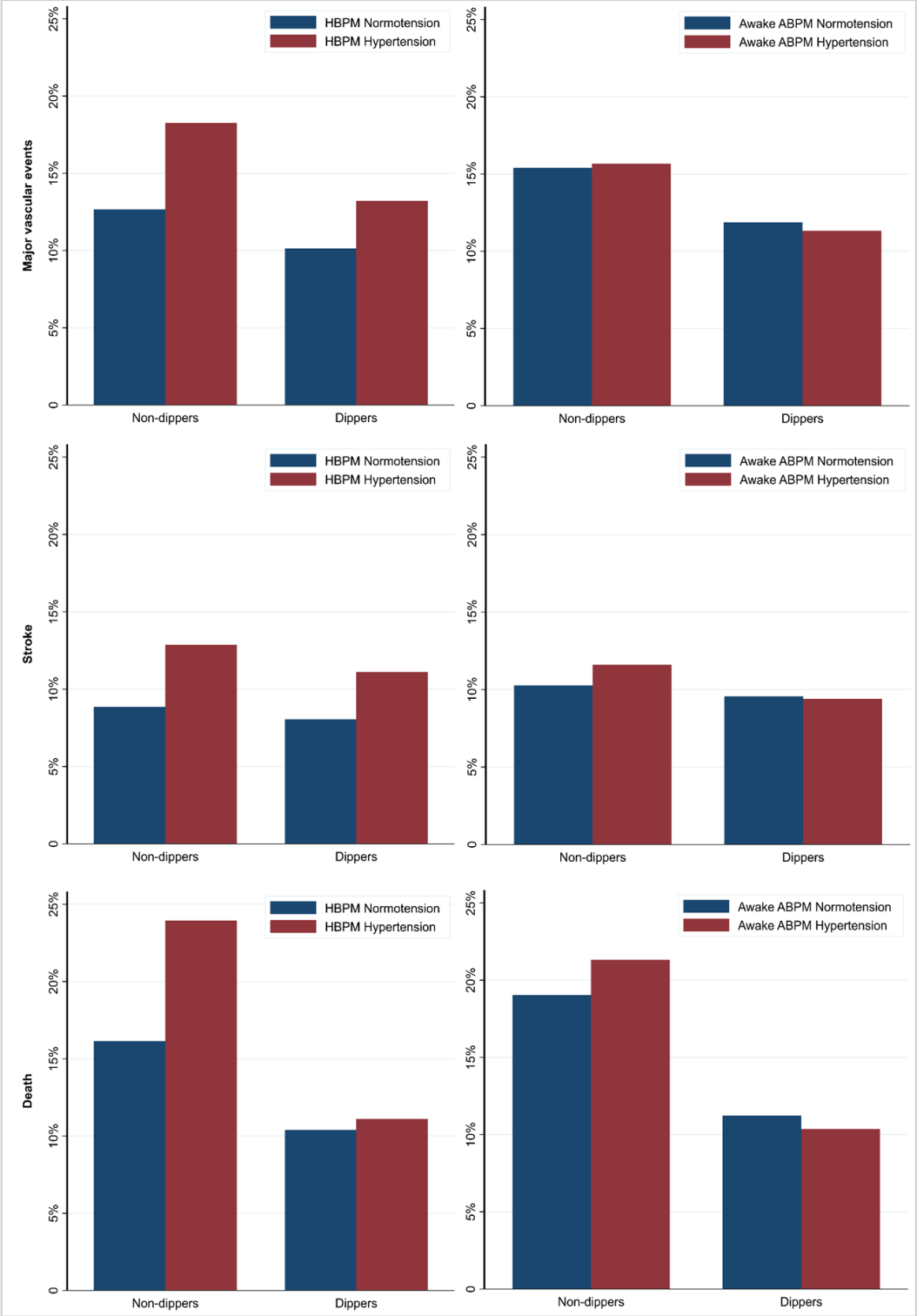


Figure 3-12 Absolute risk of recurrent major vascular events, stroke, and mortality, according to 24-hour ABPM BP dipping pattern, stratified by hypertension on ABPM and HBPM

Blood pressure (BP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM). Major vascular events: combined stroke, myocardial infarction, peripheral vascular events, vascular death. 130/80 mmHg is the threshold for hypertension vs normotension.

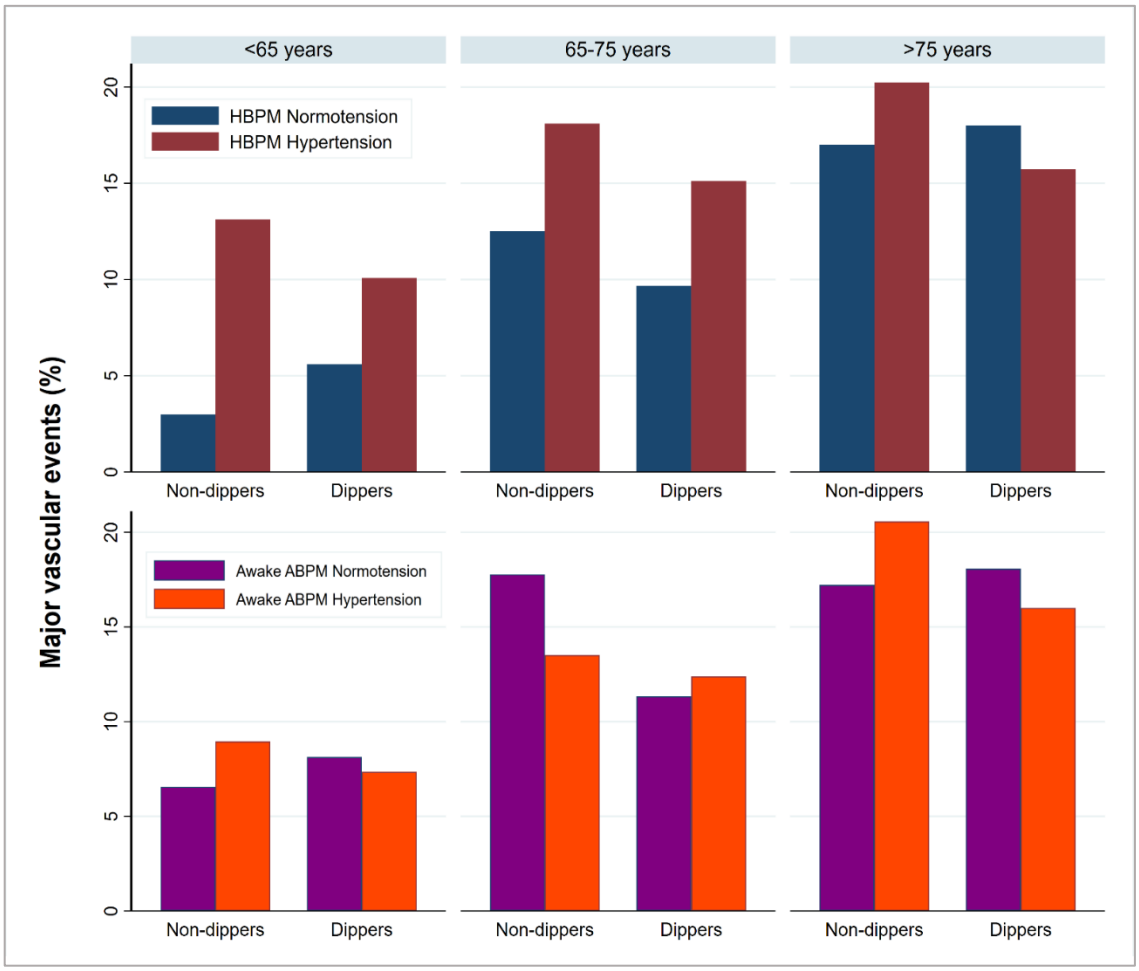


Figure 3-13 Absolute risk of recurrent major vascular events according to 24-hour ABPM BP dipping pattern, stratified by hypertension on ABPM/HBPM and age category

Blood pressure (BP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM). Major vascular events: combined stroke, myocardial infarction, peripheral vascular events, vascular death. 130/80 mmHg is the threshold for hypertension vs normotension.

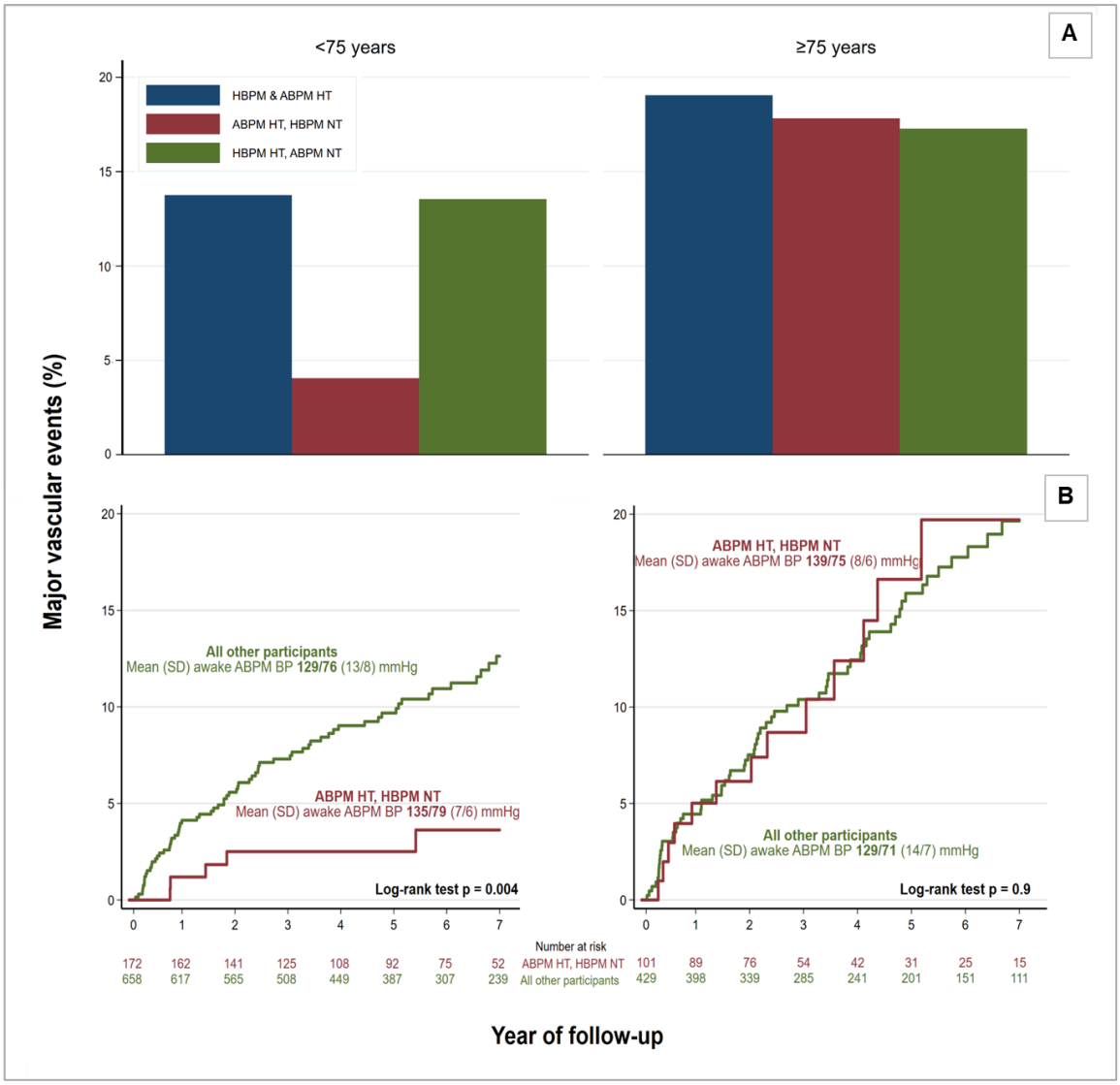


Figure 3-14 Absolute risk (A) and cumulative incidence (B) of recurrent major vascular events according to diagnostic agreement between HBPM and awake ABPM, stratified by age

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); hypertension (HT); normotension (NT). Major vascular events: combined stroke, myocardial infarction, peripheral vascular events, vascular death. 130/80 mmHg is the threshold for hypertension vs normotension.

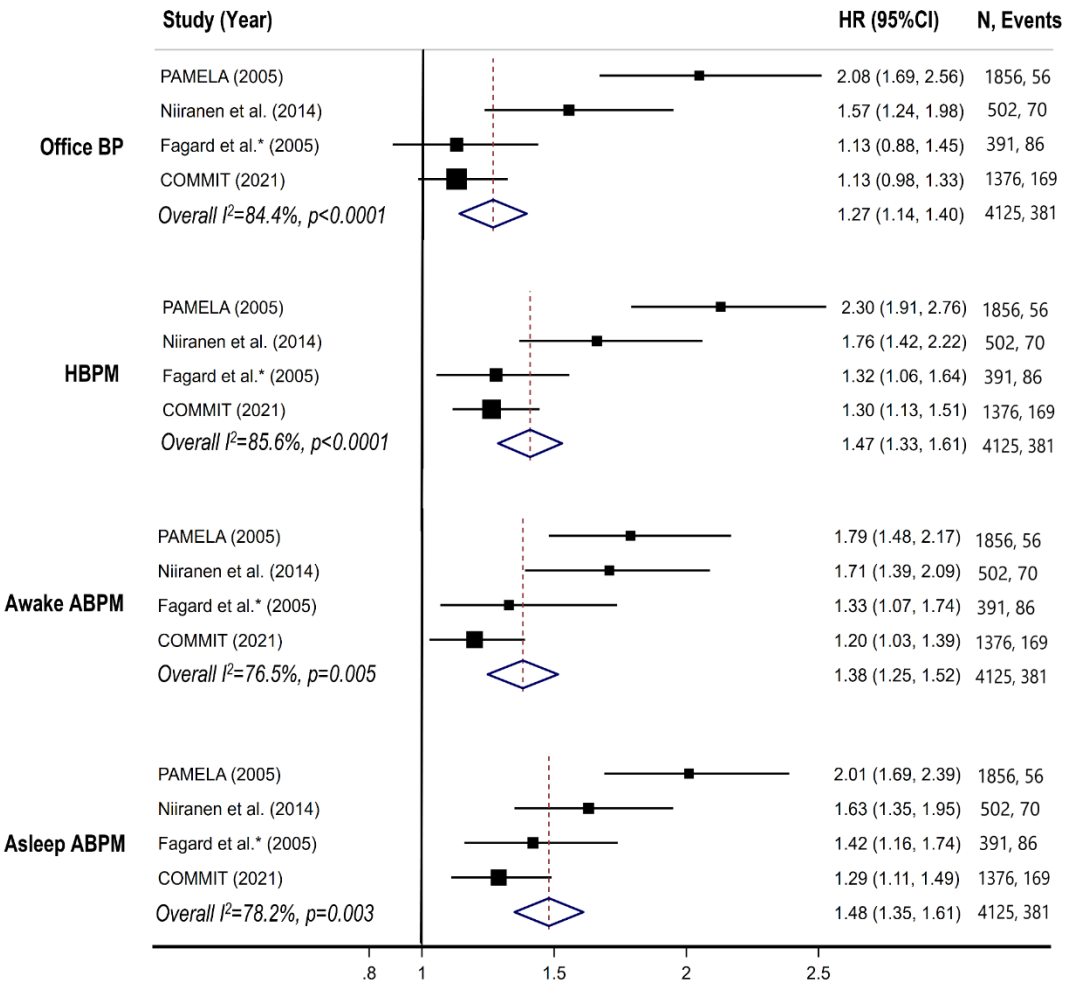


Figure 3-15 Meta-analysis of studies reporting risk of vascular events by continuous systolic BP recorded on office BP, HBPM and ABPM

Blood pressure (BP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); hazard ratio (HR); confidence interval (CI). Unadjusted hazard ratios are reported per standard deviation increase in systolic BP for studies from the general population (PAMELA, Niiranen et al., Fagard et al.), and for our study of people with TIA/stroke (COMMIT). The area of each square is inversely proportional to the within-study variance, and a fixed-effect model has been used to establish overall hazard ratios for each modality. *The study by Fagard et al. only reports hazard ratios adjusted for age, sex, and vascular risk factors. The outcome in the PAMELA study is vascular mortality only (no data are provided on non-fatal vascular outcomes).

Chapter 4: Prognostic value of residual hypertension one month after TIA and stroke: clinic versus home-telemetric and ambulatory blood pressure monitoring (Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study)

4.1 Abstract 155
4.2 Introduction 157
4.3 Methods 159
4.3.1 Study design and participants 159
4.3.2 Procedures 159
4.3.3 Statistical analysis 161
4.4 Results 163
4.5 Discussion 167
4.6 Tables 171
4.7 Figures 184

4.1 Abstract

Background: Guidelines on blood pressure lowering in secondary prevention after stroke advocate treatment even in those with normotension, but cite trials that classified hypertension status using clinic blood pressure measurement, which is prone to misclassification. Ambulatory blood pressure monitoring (ABPM) or home monitoring (HBPM) are deemed essential for accurate blood pressure assessment in primary prevention, but there is a lack of evidence in secondary prevention. Given the uncertainty about the limitations of clinic blood pressure in secondary prevention and the potential of more accurate characterisation, I aimed to compare the predictive values of clinic, 24-hour ABPM, and telemetrically verified HBPM one month after TIA or minor stroke for recurrent vascular events.

Methods: Following initial antihypertensive treatment, consecutive eligible patients with TIA/minor stroke in a population-based study (Oxford Vascular Study) measured their blood pressure three times daily at home with a telemetric device. At the one-month follow-up clinic, patients were fitted for 24-hour ABPM and clinic blood pressure (two readings 5 minutes apart) was measured. Mean blood pressure and hypertension (above guidelines thresholds) on clinic assessment, ABPM, and HBPM (during the seven days prior to clinic) were related to risk of recurrent major vascular events (MVE) on ten-year follow-up.

Results: Among 1656 patients, of whom 1340 (81%) were on antihypertensive treatment at one-month follow-up, residual hypertension (blood pressure ≥130/80 mmHg) was more frequent on clinic readings (60%; 968/1609) than on 7-day HBPM (49%; 799/1626) or daytime ABPM (47%; 655/1382), but clinic-defined hypertension had no prognostic value for MVE during 9116 person-years of follow-up (HR 0.86, 95%CI 0.65-1.14, p=0.30). 7-day HBPM was the strongest predictor of MVE both for hypertensive status (HR 1.47, 1.11-1.94, p=0.008) and mean blood pressure (HR per 20 mmHg 1.64, 1.33-2.01, p<0.0001). Daytime ABPM had intermediate prognostic value

(hypertensive status HR 1.18, 0.87-1.60; p=0.28; HR per 20mmHg 1.32, 1.05-1.67; p=0.019), and did not predict after adjustment for HBPM (HR 1.11, 0.85-1.46; p=0.44), whereas systolic blood pressure on HBPM still predicted MVE after adjustment for both clinic blood pressure and daytime ABPM (HR per 20mmHg 1.44, 1.09-1.90, p=0.009). Systolic blood pressure on HBPM was also highly predictive in the 245 (15%) patients who refused or did not tolerate ABPM (HR=1.98, 1.31-3.00, p=0.001). Of the 60% of patients with apparent hypertension in clinic, 41% were normotensive on HBPM (i.e. 'white-coat hypertension') and had a lower risk of MVE than patients who were hypertensive by both measures (HR 0.54, 0.35-0.82, p=0.004).

Conclusion: Clinic blood pressure one month after TIA and minor stroke had no predictive value for recurrent cardiovascular events. Blood pressure on seven-day HBPM was the strongest predictor and retained prognostic value after adjustment for ABPM. The current practice of clinic-based diagnosis of residual hypertension is suboptimal, and the use of clinic readings in randomised trials of blood pressure lowering will underestimate any impact of true baseline blood pressure on the effect of treatment.

4.2 Introduction

There is a considerable residual risk of recurrent vascular events after stroke or transient ischaemic attack (TIA) despite secondary prevention treatment, with almost a third of all stroke occurring in those with a prior event.[8, 9] It is well established that lowering blood pressure reduces this risk,[61] but blood pressure management after stroke in practice remains poor,[12-14] and the risk of recurrent stroke is high in those with inadequate blood pressure control.[19]

In primary prevention, the validity of hypertension diagnosis using clinic measurements has been questioned,[187, 198] and most guidelines now advocate independent confirmation by ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM).[59, 95, 186, 187, 198-205] In contrast, stroke secondary prevention guidelines do not recommend the use of ABPM/HBPM, and current practice is based on clinic blood pressure measurement.[32, 60, 270, 291, 321, 322] A possible reason for this discrepancy is the recommended practice of prescribing antihypertensive treatment after stroke even when patients' clinic blood pressure is within the 'normal' range,[22, 59] based primarily on the results of the PROGRESS trial,[61] removing the perceived necessity for more detailed characterisation of blood pressure. However, there was little evidence of benefit at systolic blood pressure (systolic blood pressure)<140 mmHg in PROGRESS,[63] and benefits of blood pressure lowering in 'normotension' might be even less apparent if this is defined more rigorously, as clinical practice shifts towards the use of HBPM/ABPM. Indeed, NHS England has recently recommended that all primary care networks implement HBPM in hypertensive patients with previous stroke or TIA,[320] but there is a lack of evidence in a secondary prevention setting to support this, with the few existing comparisons of the prognostic value of HBPM, ABPM, and clinic blood pressure measurements having been performed in primary care.[193, 229, 230, 309, 310, 323-328]

In keeping with clinical guidelines recommending one-month follow-up to assess risk factor control after TIA and stroke,[60, 291, 321, 322] I aimed to assess the diagnosis of residual

hypertension and relative predictive value of clinic blood pressure, HBPM, and ABPM for recurrent vascular events over long-term follow-up, one month after the acute assessment, in a population-based treated cohort of patients with TIA and minor stroke.

4.3 Methods

4.3.1 Study design and participants

The Oxford Vascular Study (OXVASC) is a longitudinal, population-based cohort study of the incidence and outcome of all acute vascular events in a defined population of 92,728 individuals, registered with around 100 general practitioners in nine primary care practices in Oxfordshire, UK.[264, 298] OXVASC was approved by the Oxfordshire research ethics committee, including the HBPM substudy (OREC A: 05/Q1604/70). Written, informed consent or assent from relatives was obtained for all participants for study interview and follow-up, including ongoing review of primary care and hospital records and death certificate data.

4.3.2 Procedures

Consecutive patients with TIA or non-disabling stroke were prospectively recruited to this blood pressure-monitoring study between April 1st 2008 and March 31st 2019 from OXVASC. Case ascertainment of TIA/stroke was done using multiple overlapping methods and is near-complete for events reaching medical attention.[265, 299] These methods included a rapid access daily clinic to which general practitioners and the local emergency department referred individuals with suspected cerebrovascular events, daily searches of emergency departments, relevant hospital wards, eye hospital attendances, radiographic or vascular surgical investigations or procedures, and monthly searches of primary care practice diagnostic codes and referrals to acute and community hospitals.

All consenting patients underwent a standardised medical history and examination, ECG, and blood tests. Patients underwent a stroke protocol MRI brain scan and contrast-enhanced MRA (or CT brain scan and either a carotid Doppler ultrasound or CT-angiogram when MR imaging was contraindicated), an echocardiogram, and five days of ambulatory cardiac monitoring. All patients were assessed by a study physician

and reviewed by the senior study neurologist (Professor Peter Rothwell). Patients were followed up face-to-face at one, three, six, 12, 60, and 120 months. Recurrent cardiovascular events were ascertained at each follow-up and by multiple methods of ascertainment.[265, 299]

Clinic blood pressure was measured in the non-dominant arm by trained personnel, with two measurements made five minutes apart in the sitting position, after five minutes of rest. Patients were provided with a Bluetooth-enabled, regularly-calibrated, telemetric blood pressure monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT, on the day of the baseline clinic assessment. After appropriate training on the day, they were asked to perform three home blood pressure readings over ten minutes, three times daily (after waking, midday, and evening). Measurements were automatically transmitted by Bluetooth to a Raspberry Pi microcomputer hub, for secure transmission via a cellular network to a server hosting a password-protected website for review and download (OBS Medical, Abingdon, UK). Patients continued monitoring for at least one month.

The day before the one-month follow-up visit, ABPM was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by trained study personnel. Blood pressure was measured at 30-minute intervals during the day (06:00 to 23:00) and 60-minute intervals at night. Patients were asked to refrain from excessive activity during recordings and were asked to keep a diary of their day.

Hypertension was treated according to current guidelines,[95] initially based on baseline clinic readings and then according to HBPM, aiming for a target blood pressure <130/80 mmHg. Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a morning dose of perindopril arginine 5mg plus indapamide 1.25mg, or amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician’s discretion.

4.3.3 Statistical analysis

Clinic blood pressure at one-month follow-up was calculated as the mean of the two sitting measurements during the assessment. HBPM readings for each participant were downloaded from the encrypted website and manually assessed to remove those with erroneous measures or incorrect date/time stamps (n=87, <0.1%). Recordings with systolic blood pressure <50 mmHg (n=3), diastolic blood pressure (diastolic blood pressure) >140 mmHg if pulse pressure <40 mmHg (n=5), and any pulse pressure <10 mmHg (n=6) were excluded. Seven days of HBPM prior to ABPM were used to compare the three modalities, according to guidelines on HBPM.[59, 303] In patients who refused ABPM, the HBPM period was taken as the seven days prior to the one-month follow-up assessment, or days 23-29 in those who did not attend.

Mean blood pressure on ABPM was derived after the exclusion of artefactual measurements according to predefined criteria,[312] analogous to those used for HBPM.

Prior hypertension was defined as a diagnosis reported by the patient, prior antihypertensive treatment, or hypertension listed on the primary care list of diagnoses. Hypertension was defined at each time-point as mean blood pressure ≥130/80 mmHg for clinic blood pressure, HBPM, and daytime ABPM, with lower thresholds for 24-hour ABPM (≥125/75 mmHg) and night-time ABPM (≥110/65 mmHg), according to guidelines.[95] Missing data are reported and were not imputed.

Means, medians, and proportions of baseline characteristics were stratified according to completion of HBPM and ABPM at one month and compared using t-tests, Wilcoxon rank-sum tests, and chi-square tests, respectively. The risk of major vascular events (MVE: cardiovascular death, stroke, myocardial infarction, acute peripheral vascular events), stroke, and coronary events were determined by Cox regression for hypertension on clinic blood pressure, HBPM, and ABPM, and by fitting blood pressure as a continuous variable to determine the hazard ratios per 20 mmHg systolic blood pressure/10 mmHg diastolic blood pressure and per one standard deviation increment

of blood pressure (to address any differences in the shape of the blood pressure distribution in the population across modalities).

Models were not adjusted, since comparisons of each measurement modality were made within the same population. Combination models were used to assess the additional value of one modality over another. The time at risk commenced from the day of the one-month follow-up assessment, or day 30 in patients who did not attend.

Participants aged <75 years were chosen as an additional subgroup in which to examine risk prediction, as there are weak associations of systolic blood pressure with cardiovascular events and death in people aged above 75 years,[315] despite a large beneficial effect of antihypertensive treatment in trials of the very elderly in primary prevention,[316] but strong associations in observational studies at younger ages.[176] All analyses were performed using Stata version 16.1.

4.4 Results

Of 1833 patients with TIA or minor stroke in the OXVASC clinic during the study period, 51 (2.8%) declined to take part in the blood pressure-monitoring study, and 126 (6.9%) were excluded due to early death, acute intercurrent illness, severe dementia, excessive physical disability, or residence outside of the study area (Figure 4-1). 1656 (90.3%) consented to home telemetric blood pressure monitoring, of whom 1626 (98.2%) continued measuring until their one-month follow-up clinic assessment. 30 (1.8%) patients took an insufficient number of home readings to be included in comparative predictive analyses at one month. Of these, 13 withdrew from the study, nine were unable to tolerate HBPM for one month, four had acute intercurrent illness precluding blood pressure measurement, three died, and one was a resident in a nursing home in which assistance for HBPM was not available.

Median follow-up was 5.4 years (IQR 2.9-7.9), with 9116 total patient-years. 1609 (97.2%) attended their scheduled one-month follow-up assessment, of whom 1382 (85.9%) agreed to be fitted for 24-hour ABPM and tolerated monitoring, 118 (8.5%) refused, and 109 (7.9%) didn't tolerate the machine for a sufficient number of readings to be used for the calculation of daytime mean blood pressure. 22 (1.6%) patients removed the ABPM device during or before night-time readings so that only daytime blood pressure data were available.

Mean age of the consenting patients at baseline clinic was 69.7 (SD 13) years, and 51.4% of participants were men (Table 4-1). Baseline demographic characteristics of patients who underwent both ABPM and HBPM were generally similar to those who refused, did not tolerate, or were not reviewed at one-month follow-up to be fitted for ABPM (Table 4-2).

Mean blood pressure decreased substantially across the month of home monitoring (Table 4-1), with significant reductions in clinic blood pressure between baseline and one-

month assessments (19.2/9.5 mmHg, p<0.0001). Mean blood pressure measured in clinic, on HBMP, or ABPM was generally similar in those who underwent both ABPM and HBPM compared with those who had only one of these assessments (Table 4-3). Of 802 (48.4%) participants not taking antihypertensive treatment at baseline, 537 (67.0%) were prescribed at least one agent before the one-month follow-up clinic, such that 1340 (80.9%) of patients were treated. Overall, 1108 (66.9%) patients had their antihypertensive medications changed (i.e. either started, new agents prescribed, dosage alterations, or stopped) between their initial clinic assessment and one-month follow-up, of which 94.2% (1044) was a net dosage increase (Figure 4-2).

The proportion of patients with hypertension (blood pressure ≥130/80 mmHg) at one-month clinic blood pressure assessment was 60.2% (n=968) and was lower when defined by seven-day HBPM (n=672, 48.8%, p<0.0001), with a similar proportion on daytime ABPM (n=650, 47.2%, p=0.149) when restricted to those with both tests (Table 4-4). Mean blood pressure in clinic at one month was 4.3/1.0 mmHg higher than on HBPM, 2.9/1.6 mmHg higher than on daytime ABPM, and 5.9/3.7 mmHg higher than on 24-hour ABPM (all comparisons p<0.0001, Figure 4-1) in participants who had both tests for each comparison. Systolic blood pressure was lower on seven-day HBPM than daytime ABPM (-1.5 mmHg, 95%CI -0.8--2.1, p<0.0001) but diastolic blood pressure was higher (0.7, 0.3-1.1, p=0.002).

There was only moderate correlation between mean systolic blood pressure on seven-day HBPM with daytime ABPM (r^2=0.28, p<0.0001, Figure 4-3) and 24-hour ABPM (r^2=0.31, p<0.0001, Figure 4-4). There was also relatively weak agreement for the diagnosis of hypertension at one month (HBPM vs daytime ABPM kappa=0.29, 95%CI 0.24-0.34; HBPM vs 24-hour ABPM [threshold 125/75 mmHg] k=0.32, 0.27-0.37; HBPM vs clinic blood pressure k=0.23, 0.18-0.27, Figure 4-5**,** Figure 4-6**,** Figure 4-7).

The predictive value of mean systolic blood pressure and hypertension for the risk of recurrent cardiovascular events was greatest on HBPM (Table 4-5). A 20 mmHg

increment in systolic blood pressure on seven-day HBPM was associated with a 64% (95% CI 33-201, p<0.0001) higher risk of recurrent MVE, a 41% (10-81, p=0.007) higher risk of recurrent stroke, and a 67% (10-255, p=0.016) higher risk of recurrent MI or cardiac death (Table 4-6). The associations of systolic blood pressure on HBPM with MVE were particularly strong in participants aged <75 years (Table 4-5).

In contrast, no significant predictive value for recurrent MVE was found for clinic hypertension (HR 0.86, 0.65-1.14, p=0.304) or clinic systolic blood pressure (HR 1.15 per 20 mmHg, 95%CI 0.99-1.34, p=0.065). In addition, neither hypertension on daytime ABPM nor on 24-hour ABPM had significant prognostic value (daytime ABPM HR 1.18, 0.87-1.60, p=0.280; 24-hour ABPM HR 1.06, 0.78-1.43, 0.703), but nocturnal hypertension did have some predictive value (night-time ABPM HR 1.43, 1.02-2.02, p=0.038). However, daytime, night-time, and 24-hour ABPM were predictive of recurrent MVE in continuous analyses (Table 4-5). Similar results were found when restricting to only those participants with complete blood pressure data for all three modalities (Table 4-7), and when expressed per standard deviation increase in blood pressure (Table 4-8). Systolic blood pressure on HBPM was also highly predictive of MVE in patients who refused or could not tolerate ABPM (HR 1.98 per 20mmHg, 1.31-3.00, p=0.001, Table 4-9).

Of patients found to be hypertensive in clinic, 394/955 (41.3%) had white-coat hypertension based on HBPM, and 342/825 (41.5%) based on daytime ABPM (i.e. were found to be normotensive on these modalities). White-coat hypertension was associated with a significantly lower risk of recurrent MVE for seven-day HBPM (HR 0.54, 0.35-0.82, p=0.004), but not for daytime ABPM (HR 0.67, 0.44-1.04, p=0.072, Figure 4-8), compared with correctly-diagnosed hypertension.

In models combining methods of monitoring, mean systolic blood pressure on HBPM was independently predictive of MVE after adjustment for clinic blood pressure (HR 1.58 per 20 mmHg, 1.26-1.98, p<0.0001), daytime ABPM (HR 1.45, 1.10-1.90, p=0.008), or

both clinic blood pressure and daytime ABPM in combination (HR 1.44, 1.09-1.90, p=0.009, Table 4-5). In contrast, daytime ABPM had no significant independent predictive value after adjustment either for HBPM (HR 1.11, 0.85-1.46, p=0.438) or for clinic blood pressure (HR 1.28, 0.98-1.67, p=0.067). Systolic blood pressure on night-time and 24-hour ABPM had independent predictive value after adjustment for clinic blood pressure, but not after adjustment for HBPM (Table 4-5).

4.5 Discussion

Despite guideline recommendations in primary prevention that ABPM or HBPM be used in addition to clinic blood pressure to diagnose hypertension and guide treatment,[59, 95, 199] there is no such recommendation in secondary prevention,[32, 60, 291] in the absence of any data on comparative prognostic value before this study, to our knowledge. I have shown that clinic blood pressure overdiagnosed residual hypertension one month after TIA and minor stroke, and had little predictive value for recurrent cardiovascular events. Mean systolic blood pressure was lower on HBPM than on clinic blood pressure and daytime ABPM, but HBPM was the strongest predictor of the risk of recurrent vascular events, was highly predictive in the 15% of patients who refused or did not tolerate ABPM, and had independent predictive value over and above clinic blood pressure and 24-hour ABPM. The strongest associations for each modality were found in patients aged <75 years, as would be expected from observational studies in primary prevention.[176]

My findings have a number of clinical implications. First, clinic blood pressure, which is still the clinical standard after TIA and stroke,[59, 60, 95, 291, 321, 322] inaccurately characterised blood pressure at one-month follow-up. This has important implications for the generalisability of secondary prevention trials of blood pressure lowering after stroke to current practice since such trials were based on clinic blood pressure measured after the sub-acute phase at a similar time point to this study,[329] and clinic blood pressure measurement used in predictive analyses in this study (i.e. the mean of two seated measures, taken five minutes apart and after five minutes of rest) was to a similar protocolised standard. The largest meta-analysis of blood pressure-lowering effects on vascular events, published this year, calls for treatment for vascular risk reduction irrespective of blood pressure,[22] consistent with the findings of the PROGRESS trial.[61] However, the definition of 'non-hypertensive' used in PROGRESS was clinic blood pressure<160/90 mmHg,[61] the guideline-recommended target of systolic blood pressure<130 mmHg has not been achieved in any of the main

trials,[98] and the SPS3 trial failed to show a significant risk-reducing effect of a target systolic blood pressure of <130mmHg where baseline clinic blood pressure was characterised in more detail across multiple visits.[29] Because I have shown that clinic blood pressure is unreliable for the diagnosis of hypertension compared to HBPM/ABPM, benefits of blood pressure lowering in apparent 'normotension' might therefore not be observed when blood pressure is accurately characterised using HBPM/ABPM, thus there is a need for randomised evidence of blood pressure lowering in accurately-designated normotension. Moreover, the measurement error inherent in clinic blood pressure, which I have uncovered by its prognostic inferiority, will lead to an underestimation of the association of baseline blood pressure with risk reduction due to antihypertensive treatment in randomised trials, where bigger effect sizes are likely at higher baseline blood pressure and smaller effect sizes at lower baseline blood pressure.[330] Second, there was weak agreement between HBPM and ABPM for the diagnosis of hypertension in my cohort. This finding is consistent with the only other study examining ABPM and telemetric HBPM in treated stroke and TIA patients, a small study of 80 participants with no clinical outcome data, and suggests that these should not be considered interchangeable methods of blood pressure evaluation in this population.[236] Third, HBPM was the strongest predictor of recurrent cardiovascular events, supporting its use first-line at follow-up for TIA and minor stroke, both to detect residual hypertension and to monitor the response to antihypertensive treatment. Specifically, ABPM had no additional prognostic value over HBPM and appeared to be less predictive of recurrent vascular events. This has clinical significance, as HBPM is less expensive, more widely available, and better tolerated by patients than ABPM,[211, 303] and can be used to improve blood pressure control.[227, 237, 238] Finally, hypertension on all modalities was common one month after TIA/minor stroke despite intensive treatment, identifying a large subgroup who are at-risk yet potentially treatable. However, over 40% of patients had white-coat hypertension in clinic based on HBPM, and these patients had a substantially reduced risk of recurrent vascular events compared to those with correctly diagnosed hypertension. High levels of visit-to-visit blood pressure variability[162, 232] and

persistent anxiety[302] may particularly detract from the utility of clinic blood pressure measurement among patients with TIA/stroke. A week of HBPM just before the one-month follow-up assessment allows identification of prognostically important hypertension while preventing overdiagnosis, and could therefore be used to improve secondary prevention.

The main strengths of my study include the large number of patients and outcome events compared to previous studies in lower-risk primary prevention settings,[215, 228] the contemporaneous comparison of all three blood pressure measurement modalities, and the use of home blood pressure telemonitoring, which provides valid and reliable blood pressure data without compromising acceptability.[220-222] However, my analyses had some potential shortcomings. First, HBPM was performed for the full duration of the first month after TIA/stroke, while ABPM was performed for the first time at one-month follow-up. An acclimatisation effect may thus have contributed to the marginally lower systolic blood pressure recorded on HBPM versus ABPM, which contrasts with the pattern seen in some, but not all, previous studies performed in primary prevention.[229, 309, 319] However, the differences in mean blood pressure may be accounted for by the clinical characteristics of the cohort. Since patients were advised to relax in a chair prior to HBPM measurement, as is recommended for clinic readings, HBPM was effectively a measure of resting blood pressure. In contrast, ABPM, as a measure of active blood pressure, may have been more affected by sporadic blood pressure elevations of uncertain prognostic significance, especially in this high-risk elderly population with increased blood pressure variability. Second, since blood pressure treatment was subsequently altered based on clinic, HBPM, and ABPM measurements at one month, I will have reduced the predictive value for recurrent vascular events for each modality. Third, risk associations for one-month clinic blood pressure are subject to regression dilution bias. However, I aimed to compare the prognostic value of HBPM and ABPM to the modality of blood pressure assessment (single clinic measurements) used in current clinical practice. Finally, I used telemetric HBPM to ensure the reliability of readings for comparisons with ABPM and clinic blood pressure,

which is more expensive than conventional HBPM.[221] However, this is consistent with the preferred choice in NHS England's primary care HBPM protocol currently being implemented, including patients with previous stroke or TIA.[320]

In conclusion, mean blood pressure on seven-day HBPM was the strongest predictor of recurrent vascular events one month after TIA and minor stroke, and clinic blood pressure had little prognostic value. Guidelines advocating treatment irrespective of blood pressure after stroke should be interpreted with caution as the use of HBPM/ABPM increases in practice, and randomised trials of blood pressure lowering based on clinic blood pressure will have underestimated any impact of true baseline blood pressure on the effect of treatment.

4.6 Tables

Table 4-1 Characteristics and blood pressure of patients, by completion of HBPM and ABPM at one-month follow-up

Patient characteristics ***n (% whole cohort)***	**HBPM cohort** ***1656 (100%)***	**HBPM and ABPM** ***1376 (83.1%)***
Male sex, n (%)	851 (51.4%)	725 (52.7%)
Age, mean (SD)	69.7 (13.1)	69.6 (12.8)
Event type, n (%)		
Stroke	652 (39.4%)	531 (38.6%)
TIA	1004 (60.6%)	845 (61.4%)
Medical history prior to event, n (%)		
Hypertension (prior history/treatment)	1042 (62.9%)	854 (62.1%)
Angina	191 (11.5%)	156 (11.3%)
Diabetes mellitus	218 (13.2%)	166 (12.1%)
Hyperlipidaemia	524 (31.7%)	439 (31.9%)
Myocardial infarction	51 (3.1%)	38 (2.8%)
Atrial fibrillation	193 (11.7%)	158 (11.5%)
Heart failure	69 (4.2%)	57 (4.1%)
Peripheral vascular disease	53 (3.2%)	48 (3.5%)
Prior stroke	94 (5.7%)	78 (5.7%)
Prior TIA	240 (14.5%)	206 (15.0%)
Lifestyle factors (self-reported)		
Current smoker, n (%)	251 (15.2%)	206 (15.0%)
Ever-smoker, n (%)	887 (53.6%)	734 (53.3%)
Alcohol intake u/week, median (IQR)ǂ	2 (10)	2 (11)
Antihypertensive use, n (%)		
Baseline	854 (51.6%)	700 (50.9%)
One-month follow-up	1340 (80.9%)	1125 (81.8%)
Baseline BP mmHg, mean (SD)		
Clinic, systolic	151.4 (22.9)	152.0 (22.9)
Clinic, diastolic	85.1 (13.3)	85.3 (13.2)
HBPM first day of monitoring, systolic*	138.1 (17.4)	138.2 (17.3)
HBPM first day of monitoring, diastolic	80.6 (11.1)	80.7 (11.0)
HBPM first 3 days of monitoring, systolic	135.5 (16.2)	135.4 (16.0)
HBPM first 3 days of monitoring, diastolic	79.0 (10.3)	78.9 (10.2)
One-month follow-up BP mmHg, mean (SD)		
Clinic, systolic¶	132.3 (18.6)	132.5 (21.5)
Clinic, diastolic	75.6 (11.2)	75.3 (10.9)
HBPM 3 days prior to one-month clinic, systolic¥	127.3 (12.7)	127.2 (12.4)
HBPM 3 days prior to one-month clinic, diastolic	74.3 (9.2)	74.2 (9.1)
HBPM 7 days prior to one-month clinic, systolic	127.8 (12.8)	127.8 (12.5)
HBPM 7 days prior to one-month clinic, diastolic	74.6 (9.2)	74.5 (9.1)

ABPM daytime, systolic§	129.3 (12.8)	129.2 (12.8)
ABPM daytime, diastolic	73.8 (8.1)	73.8 (8.1)
ABPM night-time, systolic	116.7 (15.4)	116.6 (15.4)
ABPM night-time, diastolic	65.1 (8.6)	65.1 (8.6)
ABPM 24-hour, systolic	126.1 (12.4)	126.2 (12.4)
ABPM 24-hour, diastolic	71.7 (7.6)	71.7 (7.6)

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP)). ǂ Data missing for 87 participants * Baseline HBPM n=1650; ¶ one-month clinic BP n=1609; ¥ one-month HBPM n=1626; § one-month ABPM n=1382.

Table 4-2 Differences in baseline characteristics of patients based on their completion of ABPM and HBPM at one-month follow-up

Baseline characteristics	Whole cohort	HBPM only*	HBPM and ABPM*	p-value (HBPM only versus HBPM & ABPM)
n (% whole cohort)	1656 (100%)	250 (15.0%)	1376 (83.1%)	
Male sex, n (%)	851 (51.4%)	118 (47.2%)	725 (52.7%)	0.110
Age, mean (SD)	69.7 (13.1)	69.7 (14.7)	69.6 (12.8)	0.911
Event type, n (%)				
Stroke	652 (39.4%)	110 (44.0%)	531 (38.6%)	0.107
TIA	1004 (60.6%)	140 (56.0%)	845 (61.4%)	
Medical history prior to event, n (%)				
Hypertension (prior history/treatment)	1042 (62.9%)	163 (65.2%)	854 (62.1%)	0.346
Angina	191 (11.5%)	32 (12.8%)	156 (11.3%)	0.506
Diabetes mellitus	218 (13.2%)	48 (19.2%)	166 (12.1%)	**0.002**
Hyperlipidaemia	524 (31.7%)	74 (29.6%)	439 (31.9%)	0.471
Myocardial infarction	51 (3.1%)	11 (4.4%)	38 (2.8%)	0.163
Atrial fibrillation	193 (11.7%)	30 (12.0%)	158 (11.5%)	0.814
Heart failure	69 (4.2%)	8 (3.2%)	57 (4.1%)	0.484
Peripheral vascular disease	53 (3.2%)	4 (1.6%)	48 (3.5%)	0.119
Prior stroke	94 (5.7%)	15 (6.0%)	78 (5.7%)	0.836
Prior TIA	240 (14.5%)	33 (13.2%)	206 (15.0%)	0.467
Lifestyle factors (self-reported)				
Current smoker, n (%)	251 (15.2%)	39 (15.6%)	206 (15.0%)	0.789
Ever-smoker, n (%)	887 (53.6%)	143 (57.2%)	734 (53.3%)	0.260
Alcohol intake u/week, median (IQR) ǂ	2 (10)	1 (7)	2 (11)	**0.020**
Baseline antihypertensive use, n (%)	854 (51.6%)	134 (53.6%)	700 (50.9%)	0.427

Ambulatory blood pressure monitoring (ABPM); home blood pressure monitoring (HBPM); standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP). * Total does not make 1656, as only those 250 participants who completed at least one whole month of HBPM are included for the purposes of comparison with ABPM at one month. ǂ Data missing for 87 participants.

Table 4-3 Clinic, HBPM, and ABPM mean blood pressure of patients based on their completion of ABPM and HBPM at one-month follow-up

Blood pressure mmHg, mean (SD)	Whole cohort	n	HBPM only	n	ABPM and HBPM	n	p-value (HBPM & ABPM versus HBPM only)
Baseline clinic, systolic	151.4 (22.9)	1656	147.8 (23.0)	250	152.0 (22.9)	1376	**0.007**
Baseline clinic, diastolic	85.1 (13.3)	1656	84.0 (13.8)	250	85.3 (13.2)	1376	0.150
One-month follow-up clinic, systolic	132.3 (18.6)	1609	132.1 (18.1)	216	132.5 (21.5)	1376	0.751
One-month follow-up clinic, diastolic	75.6 (11.2)	1609	76.1 (12.9)	216	75.3 (10.9)	1376	0.076
Home telemetric BP monitoring							
First day of monitoring, systolic	138.1 (17.4)	1650	137.0 (17.4)	250	138.2 (17.3)	1376	0.292
First day of monitoring, diastolic	80.6 (11.1)	1650	80.1 (11.2)	250	80.7 (11.0)	1376	0.427
First 3 days of monitoring, systolic	135.5 (16.2)	1650	134.9 (16.9)	250	135.4 (16.0)	1376	0.631
First 3 days of monitoring, diastolic	79.0 (10.3)	1650	78.8 (10.5)	250	78.9 (10.2)	1376	0.894
3 days prior to one-month clinic, systolic	127.3 (12.7)	1626	127.7 (14.5)	250	127.2 (12.4)	1376	0.594
3 days prior to one-month clinic, diastolic	74.3 (9.2)	1626	74.9 (9.7)	250	74.2 (9.1)	1376	0.242
7 days prior to one-month clinic, systolic	127.8 (12.8)	1626	128.2 (14.5)	250	127.8 (12.5)	1376	0.653
7 days prior to one-month clinic, diastolic	74.6 (9.2)	1626	75.1 (9.6)	250	74.5 (9.1)	1376	0.367
	Whole cohort	**n**	**ABPM only**	**n**	**ABPM and HBPM**	**n**	**p-value (HBPM & ABPM versus ABPM only)**
One-month ABPM							
Daytime, systolic	129.3 (12.8)	1382	137.8 (13.5)	6	129.2 (12.8)	1376	0.105
Daytime, diastolic	73.8 (8.1)	1382	79.2 (6.9)	6	73.8 (8.1)	1376	0.108
Night-time, systolic	116.7 (15.4)	1360	122.1 (15.3)	6	116.6 (15.4)	1376	0.388
Night-time, diastolic	65.1 (8.6)	1360	70.7 (9.3)	6	65.1 (8.6)	1376	0.110
24-hour, systolic	126.1 (12.4)	1382	133.4 (14.6)	6	126.2 (12.4)	1376	0.157
24-hour, diastolic	71.7 (7.6)	1382	76.8 (7.2)	6	71.7 (7.6)	1376	0.100

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); standard deviation (SD); blood pressure (BP).

Table 4-4 Blood pressure and hypertension on HBPM, ABPM, and clinic BP based on antihypertensive use at one-month follow-up

Blood pressure measurement ***n (% whole cohort)***	**Whole cohort** ***1656 (100%)***	**No antihypertensive use** ***316 (19.1%)***
Clinic		
n (% whole cohort)	1609 (97.2%)	305 (19.6%)
BP mean (SD), mmHg	132.3/75.6 (18.6/11.2)	127.9/76.3 (16.7/11.4)
Hypertension [≥130/80 mmHg], n (%)	968 (60.2%)	157 (51.6%)
7-day HBPM		
n (% whole cohort)	1626 (98.2%)	310 (19.1%)
BP mean (SD), mmHg	127.8/74.6 (12.8/9.2)	122.2/73.6 (11.4/8.4)
Hypertension [≥130/80 mmHg], n (%)	799 (49.1%)	102 (32.9%)
Daytime ABPM		
n (% whole cohort)	1382 (83.4%)	251 (18.2%)
BP mean (SD), mmHg	129.3/73.8 (12.8/8.1)	127.1/74.7 (12.1/7.0)
Hypertension [≥130/80 mmHg], n (%)	655 (47.4%)	102 (40.6%)
Night-time ABPM		
n (% whole cohort)	1360 (82.1%)	246 (18.1%)
BP mean (SD), mmHg	116.7/65.1 (15.4/8.6)	111.8/64.0 (14.3/8.0)
Hypertension [≥110/65 mmHg], n (%)	926 (68.1%)	132 (53.7%)
24-hour ABPM		
n (% whole cohort)	1382 (83.4%)	251 (18.2%)
BP mean (SD), mmHg	126.2/71.7 (12.5/7.6)	123.3/72.1 (11.3/6.3)
Hypertension [≥125/75 mmHg], n (%)	778 (56.3%)	128 (51.0%)

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); standard deviation (SD).

Table 4-5 The risk of recurrent MVE in relation to clinic BP, HBPM, and ABPM one month after TIA/stroke

	All participants				Age < 75 years			
	Event number	**HR**	**95% CI**	**p-value**	**Event number**	**HR**	**95% CI**	**p-value**
Hypertension								
Clinic (≥130/80 mmHg)	198	0.86	(0.65 - 1.14)	0.304	89	1.02	(0.67 - 1.55)	0.942
HBPM (≥130/80 mmHg)	198	1.47	(1.11 - 1.94)	**0.008**	89	1.89	(1.23 - 2.90)	**0.004**
Daytime ABPM (≥130/80 mmHg)	170	1.18	(0.87 - 1.60)	0.280	78	1.12	(0.72 - 1.75)	0.613
24-hour ABPM (≥125/75 mmHg)	170	1.06	(0.78 - 1.43)	0.703	78	0.94	(0.60 - 1.47)	0.789
Night-time ABPM (≥110/65 mmHg)	167	1.43	(1.02 - 2.02)	**0.038**	76	1.36	(0.84 - 2.19)	**0.038**
SBP (20 mmHg higher)								
Clinic	198	1.15	(0.99 - 1.34)	0.065	89	1.37	(1.09 - 1.73)	**0.008**
HBPM	198	1.64	(1.33 - 2.01)	**<0.0001**	89	2.16	(1.61 - 2.90)	**<0.0001**
Daytime ABPM	170	1.32	(1.05 - 1.67)	**0.019**	78	1.54	(1.09 - 2.17)	**0.013**
24-hour ABPM	170	1.37	(1.08 - 1.75)	**0.010**	78	1.57	(1.11 - 2.22)	**0.011**
Night-time ABPM	167	1.34	(1.11 - 1.62)	**0.003**	76	1.46	(1.11 - 1.91)	**0.007**
HBPM adjusted for clinic BP	197	1.58	(1.26 - 1.98)	**<0.0001**	88	1.95	(1.40 - 2.70)	**<0.0001**
HBPM adjusted for daytime ABPM	169	1.45	(1.10 - 1.90)	**0.008**	77	1.92	(1.28 - 2.87)	**0.002**
HBPM adjusted for clinic BP and daytime ABPM	169	1.44	(1.09 - 1.90)	**0.009**	77	1.85	(1.23 - 2.79)	**0.003**
HBPM adjusted for 24-hour ABPM	169	1.43	(1.07 - 1.89)	**0.013**	77	1.94	(1.28 - 2.93)	**0.002**
HBPM adjusted for night-time ABPM	166	1.45	(1.10 - 1.89)	**0.008**	75	1.96	(1.32 - 2.93)	**0.001**
Daytime ABPM adjusted for clinic BP	170	1.28	(0.98 - 1.67)	0.067	78	1.35	(0.91 - 1.99)	0.139
Daytime ABPM adjusted for HBPM	169	1.11	(0.85 - 1.46)	0.438	77	1.10	(0.73 - 1.67)	0.649
24-hour ABPM adjusted for clinic BP	170	1.34	(1.02 - 1.78)	**0.037**	78	1.37	(0.91 - 2.05)	0.126
24-hour ABPM adjusted for HBPM	170	1.14	(0.85 - 1.53)	0.378	77	1.08	(0.70 - 1.67)	0.734
Night-time ABPM adjusted for clinic BP	167	1.32	(1.08 - 1.63)	**0.008**	76	1.33	(0.99 - 1.80)	0.058
Night-time ABPM adjusted for HBPM	166	1.17	(0.94 - 1.46)	0.165	75	1.13	(0.81 - 1.57)	0.465

Major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); systolic blood pressure (SBP); blood pressure (BP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); hazard ratio (HR); confidence interval (CI)

Table 4-6 The risk of recurrent vascular events associated with hypertension or a 20 or 10 mmHg higher SBP or DBP, respectively, on clinic BP, HBPM, and ABPM at one month post-TIA/stroke

	HBPM				Daytime ABPM				24-hour ABPM				Night-time ABPM				Clinic			
Outcome	Events	HR	95% CI	p-value	Events	HR	95% CI	p-value	Events	HR	95% CI	p-value	Events	HR	95% CI	p-value	Events	HR	95% CI	p-value
Hypertension																				
MVE	198	1.47	(1.11 - 1.94)	**0.008**	170	1.18	(0.87 - 1.60)	0.280	170	1.06	(0.78 - 1.43)	0.703	167	1.43	(1.02 - 2.02)	**0.038**	198	0.86	(0.65 - 1.14)	0.304
All cause stroke	140	1.39	(1.00 - 1.94)	0.053	124	1.26	(0.89 - 1.80)	0.195	124	1.08	(0.75 - 1.53)	0.691	122	1.48	(0.99 - 2.22)	0.058	141	0.94	(0.67 - 1.31)	0.706
MI, SCD & IHD Death	48	1.24	(0.70 - 2.20)	0.451	40	0.87	(0.46 - 1.63)	0.656	40	0.80	(0.43 - 1.48)	0.473	39	1.08	(0.55 - 2.10)	0.827	48	0.63	(0.36 - 1.11)	0.112
SBP (20 mmHg higher)																				
MVE	198	1.64	(1.33 - 2.01)	**<0.0001**	170	1.32	(1.05 - 1.67)	**0.019**	170	1.37	(1.08 - 1.75)	**0.010**	167	1.34	(1.11 - 1.62)	**0.003**	198	1.15	(0.99 - 1.34)	0.065
All cause stroke	140	1.41	(1.10 - 1.81)	**0.007**	124	1.30	(0.99 - 1.71)	0.056	124	1.34	(1.01 - 1.78)	**0.042**	122	1.27	(1.01 - 1.60)	**0.037**	141	1.13	(0.95 - 1.36)	0.170
MI, SCD & IHD Death	48	1.67	(1.10 - 2.55)	**0.016**	40	1.33	(0.83 - 2.15)	0.238	40	1.33	(0.81 - 2.18)	0.267	40	1.30	(0.87 - 1.93)	0.202	48	1.11	(0.81 - 1.52)	0.528

DBP (10 mmHg higher)																			
MVE	198	0.89	(0.77 - 1.04)	0.155	170	0.89	(0.73 - 1.07)	0.214	170	0.91	(0.74 - 1.12)	0.369	167	1.10	(0.92 - 1.32)	0.286	198	0.82	(0.72 - 0.94)	**0.004**
All cause stroke	140	1.00	(0.84 - 1.21)	0.964	124	1.01	(0.81 - 1.25)	0.955	124	1.03	(0.81 - 1.31)	0.800	122	1.10	(0.89 - 1.36)	0.361	141	0.92	(0.79 - 1.08)	0.307
MI, SCD & IHD Death	48	0.62	(0.45 - 0.85)	**0.003**	40	0.66	(0.44 - 0.98)	**0.037**	40	0.64	(0.41 - 0.99)	**0.043**	39	0.97	(0.66 - 1.42)	0.880	48	0.59	(0.44 - 0.77)	**<0.0001**

Systolic blood pressure (SBP); diastolic blood pressure (DBP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); confidence interval (CI); hazard ratio (HR); major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); myocardial infarction (MI); sudden cardiac death (SCD); ischaemic heart disease (IHD).

Table 4-7 The risk of recurrent vascular events associated with hypertension or a 20 or 10 mmHg higher SBP or DBP, respectively, on clinic BP, HBPM, and ABPM at one month post-TIA/stroke, in patients with all three measurements at one month

		HBPM			Daytime ABPM			24-hour ABPM			Night-time ABPM			Clinic		
Outcome	Events	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Hypertension																
MVE	169	1.36	(1.00 - 1.84)	**0.048**	1.18	(0.87 - 1.59)	0.288	1.06	(0.78 - 1.43)	0.716	1.43	(1.02 - 2.02)	**0.040**	0.86	(0.63 - 1.16)	0.316
All cause stroke	123	1.38	(0.97 - 1.97)	0.076	1.25	(0.88 - 1.79)	0.210	1.06	(0.75 - 1.52)	0.720	1.47	(0.98 - 2.20)	0.062	0.96	(0.67 - 1.38)	0.838
MI, SCD & IHD Death	40	1.05	(0.57 - 1.96)	0.866	0.87	(0.46 - 1.65)	0.681	0.80	(0.43 - 1.50)	0.491	1.08	(0.56 - 2.11)	0.811	0.50	(0.27 - 0.95)	**0.034**
SBP (20 mmHg higher)																
MVE	169	1.53	(1.21 - 1.93)	**<0.0001**	1.35	(1.07 - 1.70)	**0.012**	1.40	(1.10 - 1.78)	**0.006**	1.35	(1.12 - 1.64)	**0.002**	1.15	(0.97 - 1.37)	0.096
All cause stroke	123	1.40	(1.06 - 1.84)	**0.016**	1.34	(1.02 - 1.75)	**0.037**	1.37	(1.03 - 1.82)	**0.029**	1.28	(1.02 - 1.61)	**0.030**	1.12	(0.92 - 1.37)	0.266

MI, SCD & IHD Death	40	1.51	(0.93 - 2.45)	0.093	1.35	(0.84 - 2.17)	0.238	1.34	(0.81 - 2.20)	0.251	1.30	(0.87 - 1.93)	0.195	1.07	(0.74 - 1.53)	0.725
DBP (10 mmHg higher)																
MVE	169	0.83	(0.70 - 0.99)	**0.033**	0.88	(0.73 - 1.07)	0.202	0.90	(0.73 - 1.11)	0.341	1.10	(0.92 - 1.31)	0.315	0.81	(0.70 - 0.94)	**0.005**
All cause stroke	123	0.96	(0.79 - 1.17)	0.666	1.01	(0.80 - 1.25)	0.998	1.02	(0.80 - 1.30)	0.862	1.09	(0.89 - 1.35)	0.411	0.92	(0.78 - 1.09)	0.329
MI, SCD & IHD Death	40	0.53	(0.38 - 0.74)	**<0.0001**	0.66	(0.44 - 0.98)	**0.040**	0.64	(0.41 - 0.99)	**0.047**	0.98	(0.67 - 1.43)	0.903	0.55	(0.41 - 0.75)	**<0.0001**

Systolic blood pressure (SBP); diastolic blood pressure (DBP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); confidence interval (CI); hazard ratio (HR); major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); myocardial infarction (MI); sudden cardiac death (SCD); ischaemic heart disease (IHD).

Table 4-8 The risk of recurrent vascular events associated with hypertension or per standard deviation higher SBP or DBP, respectively, on clinic BP, HBPM, and ABPM at one month post-TIA/stroke, in patients with all three measurements at one month

		HBPM			Daytime ABPM			24-hour ABPM			Night-time ABPM			Clinic		
Outcome	Events	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Hypertension																
MVE	169	1.36	(1.00 - 1.84)	**0.048**	1.18	(0.87 - 1.59)	0.288	1.06	(0.78 - 1.43)	0.716	1.43	(1.02 - 2.02)	**0.040**	0.86	(0.63 - 1.16)	0.316
All cause stroke	123	1.38	(0.97 - 1.97)	0.076	1.25	(0.88 - 1.79)	0.210	1.06	(0.75 - 1.52)	0.720	1.47	(0.98 - 2.20)	0.062	0.96	(0.67 - 1.38)	0.838
MI, SCD & IHD Death	40	1.05	(0.57 - 1.96)	0.866	0.87	(0.46 - 1.65)	0.681	0.80	(0.43 - 1.50)	0.491	1.08	(0.56 - 2.11)	0.811	0.50	(0.27 - 0.95)	**0.034**
SBP (per SD increase)																
MVE	169	1.30	(1.13 - 1.51)	**<0.0001**	1.21	(1.04 - 1.41)	**0.012**	1.23	(1.06 - 1.43)	**0.006**	1.26	(1.09 - 1.46)	**0.002**	1.15	(0.98 - 1.35)	0.096
All cause stroke	123	1.23	(1.04 - 1.46)	**0.016**	1.20	(1.01 - 1.3)	**0.037**	1.22	(1.02 - 1.45)	**0.029**	1.21	(1.02 - 1.45)	**0.030**	1.35	(0.92 - 1.37)	0.266

MI, SCD & IHD Death	40	1.29	(0.96 - 1.75)	0.093	1.21	(0.89 - 1.65)	0.238	1.20	(0.88 - 1.63)	0.251	1.22	(0.90 - 1.66)	0.195	1.06	(0.75 - 1.50)	0.725
DBP (per SD increase)																
MVE	169	0.85	(0.73 - 0.99)	**0.033**	0.90	(0.77 - 1.06)	0.202	0.93	(0.79 - 1.08)	0.341	1.08	(0.93 - 1.26)	0.315	0.79	(0.68 - 0.94)	**0.005**
All cause stroke	123	0.96	(0.80 - 1.15)	0.666	1.00	(0.84 - 1.20)	0.998	1.02	(0.85 - 1.22)	0.862	1.08	(0.90 - 1.29)	0.411	0.91	(0.76 - 1.10)	0.329
MI, SCD & IHD Death	40	0.56	(0.41 - 0.76)	**<0.0001**	0.71	(0.52 - 0.99)	**0.040**	0.72	(0.51 - 0.99)	**0.047**	0.98	(0.71 - 1.36)	0.903	0.52	(0.38 - 0.73)	**<0.0001**

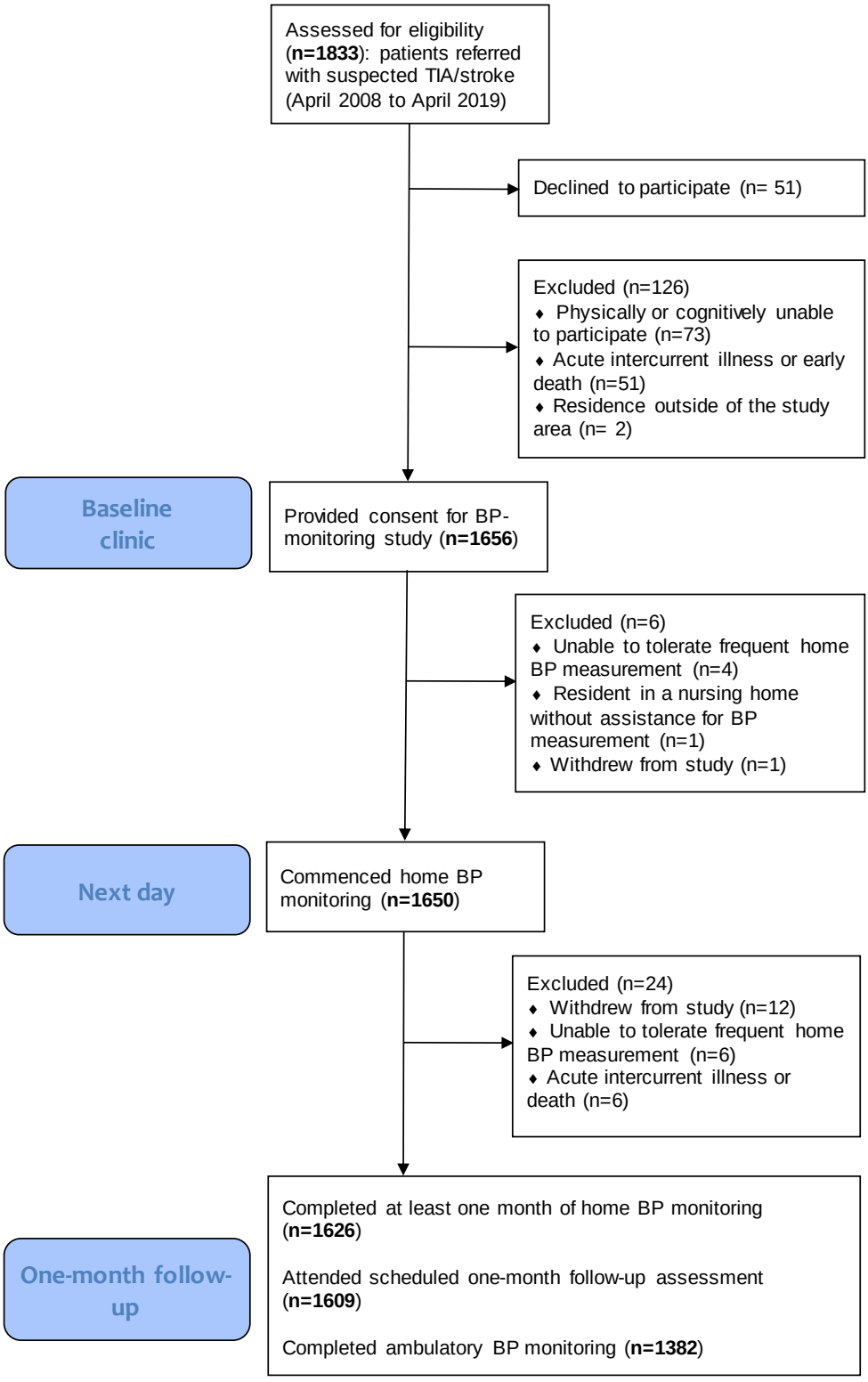
Systolic blood pressure (SBP); diastolic blood pressure (DBP); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); confidence interval (CI); hazard ratio (HR); major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); myocardial infarction (MI); sudden cardiac death (SCD); ischaemic heart disease (IHD).

Table 4-9 The risk of recurrent vascular events associated with hypertension or a 20 or 10 mmHg higher SBP or DBP, respectively, on clinic BP and HBPM in patients who refused or did not tolerate ABPM

	HBPM (n=250)				Clinic (n=216)			
Outcome	Events	HR	95% CI	p-value	Events	HR	95% CI	p-value
Hypertension								
MVE	29	2.27	(1.03 - 4.98)	**0.042**	28	1.03	(0.48 - 2.20)	0.939
All cause stroke	17	1.43	(0.54 - 3.76)	0.467	17	0.94	(0.36 - 2.46)	0.893
MI, SCD & IHD Death	8	3.09	(0.62 - 15.33)	0.451	8	2.14	(0.43 - 10.66)	0.112
SBP (20 mmHg higher)								
MVE	29	1.98	(1.31 - 3.00)	**0.001**	28	1.15	(0.88 - 1.69)	0.231
All cause stroke	17	1.42	(0.79 - 2.57)	0.246	17	1.30	(0.87 - 1.95)	0.205
MI, SCD & IHD Death	8	2.09	(0.97 - 4.51)	0.061	8	1.25	(0.69 - 2.27)	0.463
DBP (10 mmHg higher)								
MVE	29	1.25	(0.87 - 1.80)	0.229	28	0.88	(0.64 - 1.19)	0.401
All cause stroke	17	1.30	(0.81 - 2.08)	0.270	17	0.94	(0.63 - 1.38)	0.741
MI, SCD & IHD Death	8	1.28	(0.96 - 2.52)	0.477	8	0.78	(0.43 - 1.43)	0.426

Systolic blood pressure (SBP); diastolic blood pressure (DBP); home blood pressure monitoring (HBPM); blood pressure (BP); ambulatory blood pressure monitoring (ABPM); confidence interval (CI); hazard ratio (HR); major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); myocardial infarction (MI); sudden cardiac death (SCD); ischaemic heart disease (IHD).

4.7 Figures



Transient ischaemic attack (TIA); blood pressure (BP)

Figure 4-1 Flowchart of study inclusion and exclusion

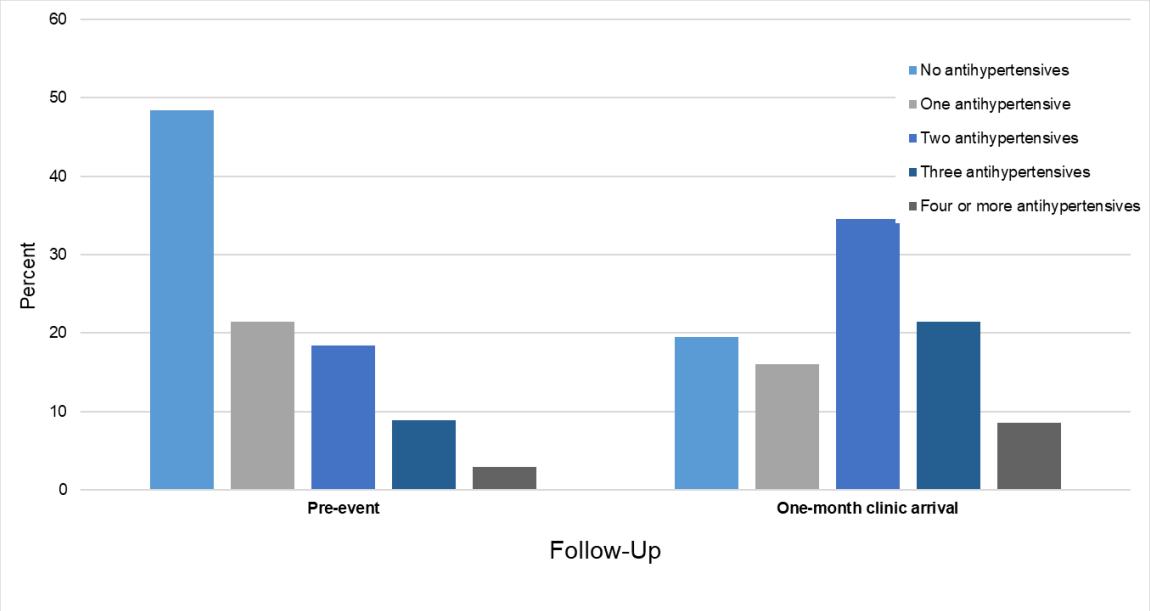


Figure 4-2 Change in the number of prescribed antihypertensive medications between baseline clinic and the arrival to the one-month follow-up clinic

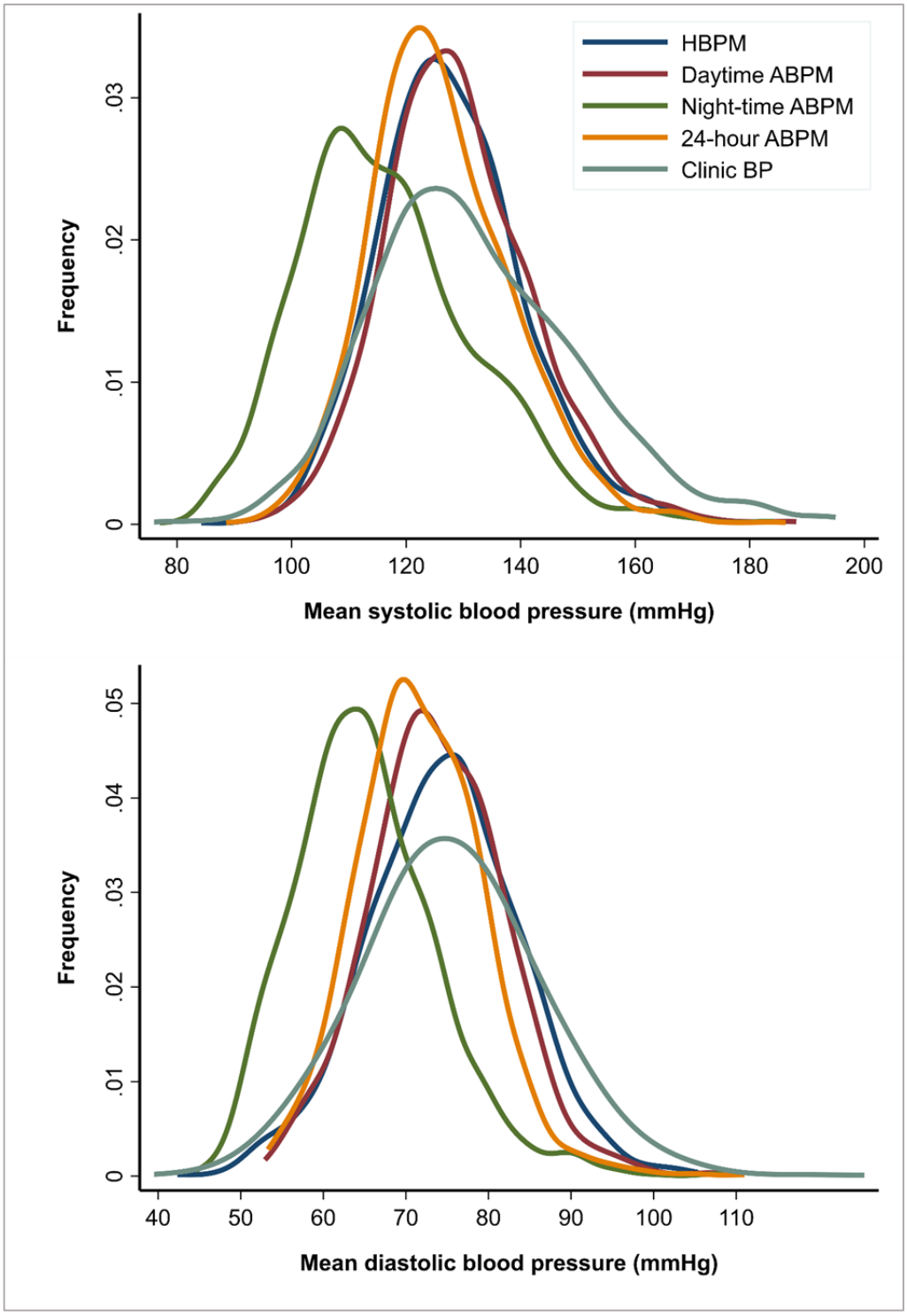


Figure 4-3 Distribution of mean systolic and diastolic blood pressure on 7-day HBPM, daytime, night-time and 24-hour ABPM, and clinic recordings at one-month follow-up

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP). Mean BP on HBPM is derived from the seven days prior to the one-month clinic. Clinic BP is calculated from the mean of two sitting readings at one month. Frequencies are given per 3 mmHg and 2 mmHg bands of systolic and diastolic BP, respectively. Only patients with BP data from all measurement modalities are included.

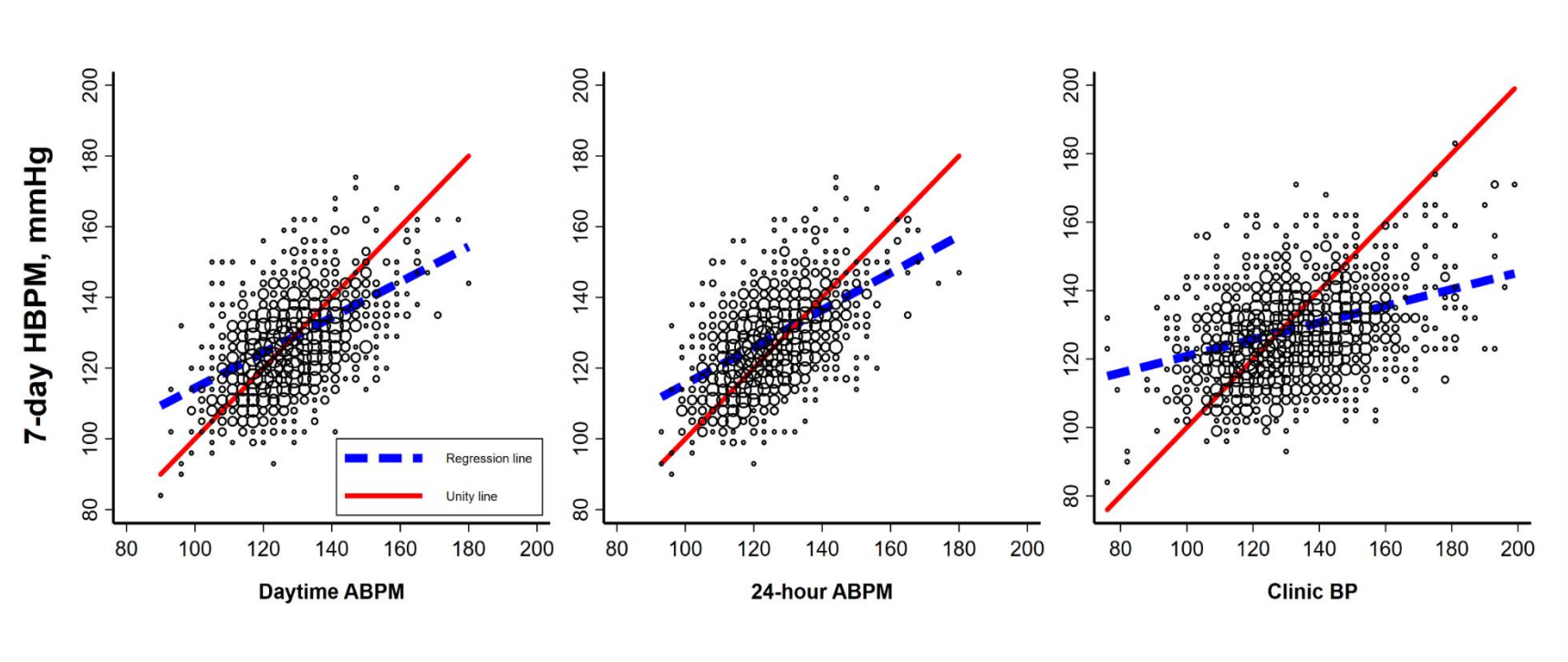


Figure 4-4 Scatter plots of mean systolic blood pressure on seven-day HBPM with daytime ABPM, 24-hour ABPM, and clinic BP at one month

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP). The size of the markers in the scatter plots are weighted by the number of cases in each 3 mmHg bin of systolic BP on each modality.

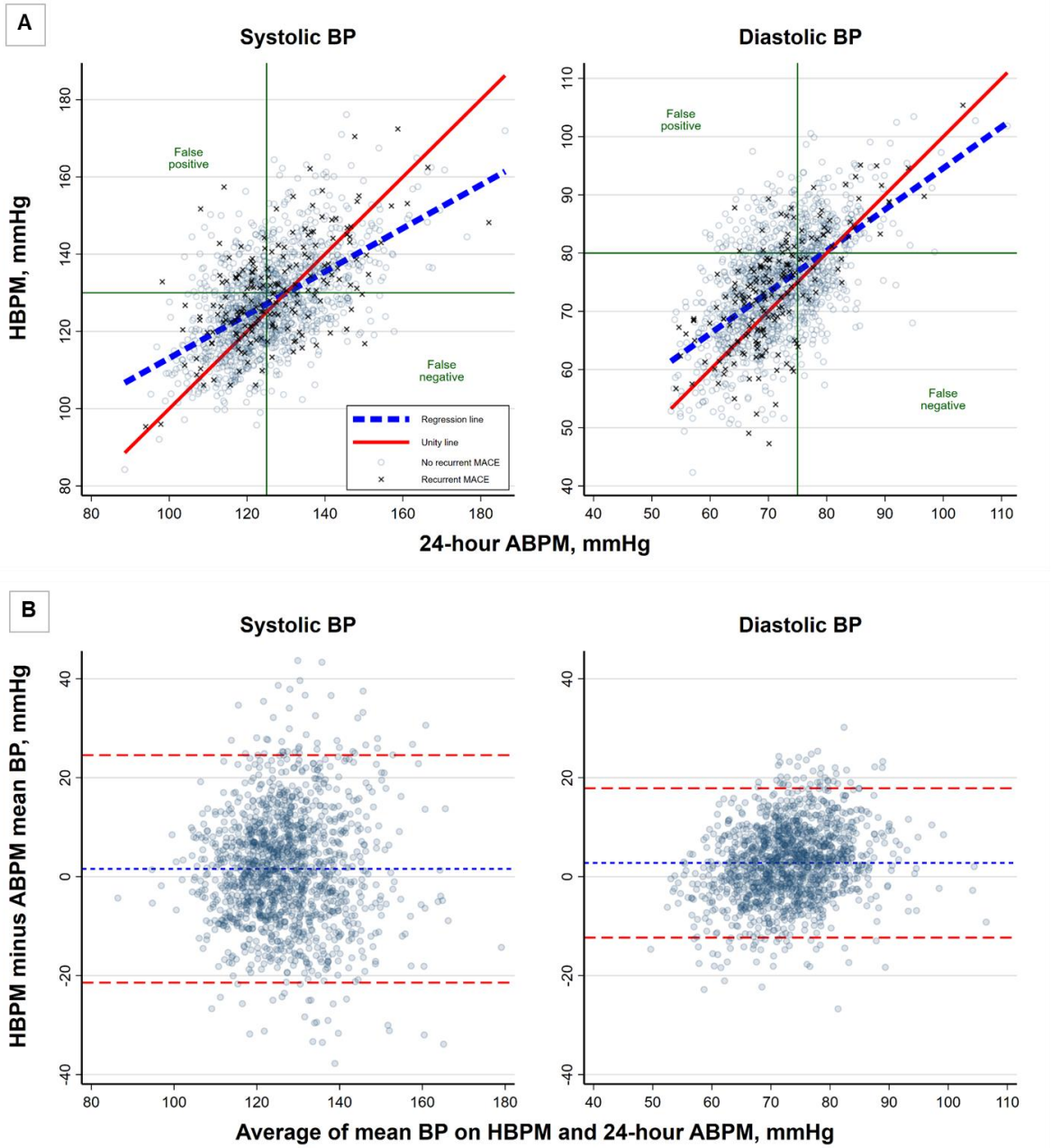


Figure 4-5 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on seven-day HBPM and 24-hour ABPM at one month

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); major adverse cardiovascular events (MACE). The green lines in the scatterplots represent the cut-off points for hypertension (≥130/80 mmHg for HBPM, ≥125/75 for 24-hour ABPM). ABPM is assumed to be the reference standard to highlight false positives and negatives. The blue dashed lines in the Bland-Altman plots represent the means of the absolute value of the BP difference between modalities. The red dashed lines represent ±1.96 SDs for this range.

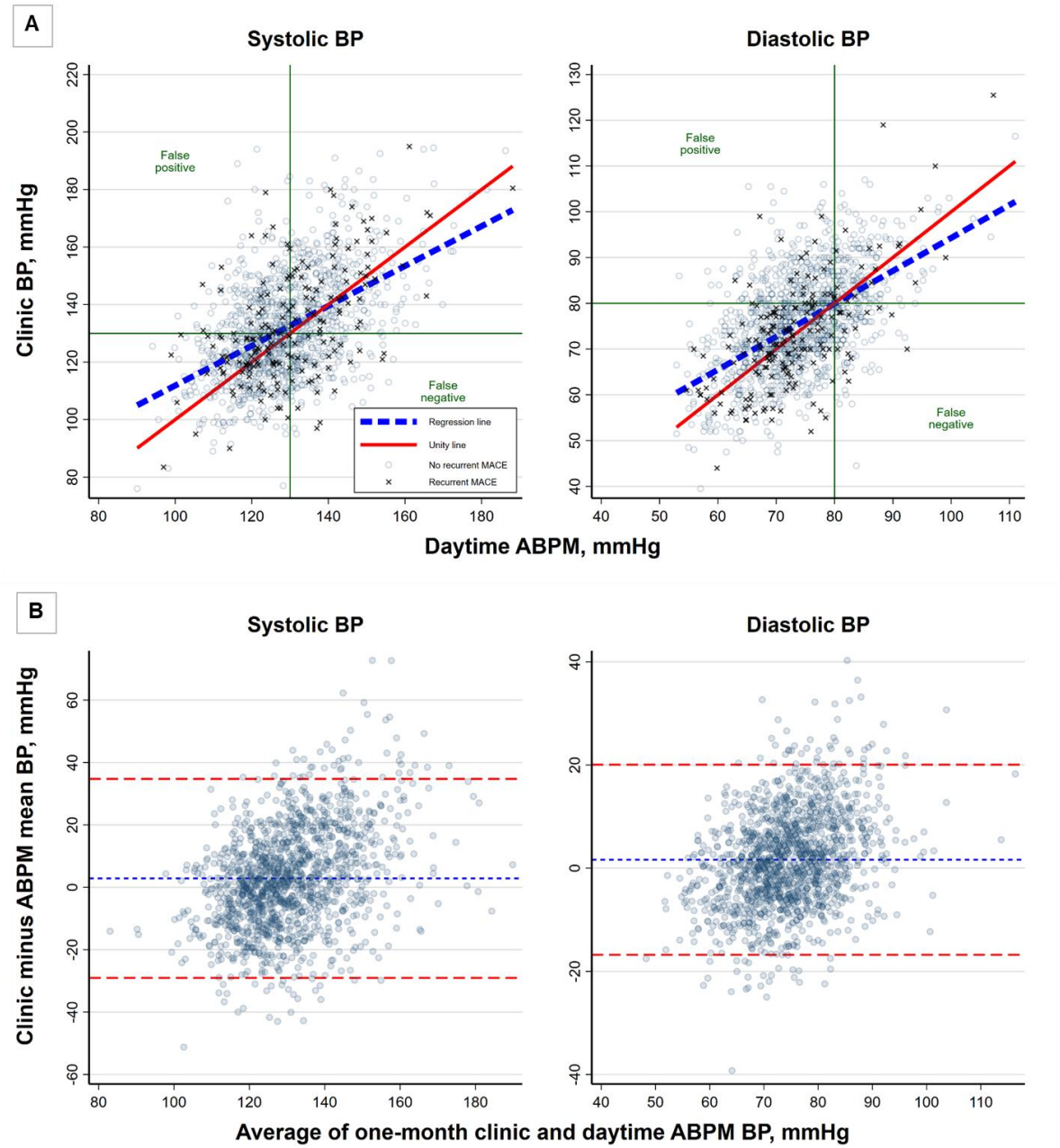


Figure 4-6 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on clinic assessment and daytime ABPM at one month

Ambulatory blood pressure monitoring (ABPM); blood pressure (BP); major adverse cardiovascular events (MACE). The green lines in the scatterplots represent the cut-off points for hypertension (≥130/80 mmHg). ABPM is assumed to be the reference standard to highlight false positives and negatives. The blue dashed lines in the Bland-Altman plots represent the means of the absolute value of the BP difference between modalities. The red dashed lines represent ±1.96 SDs for this range.

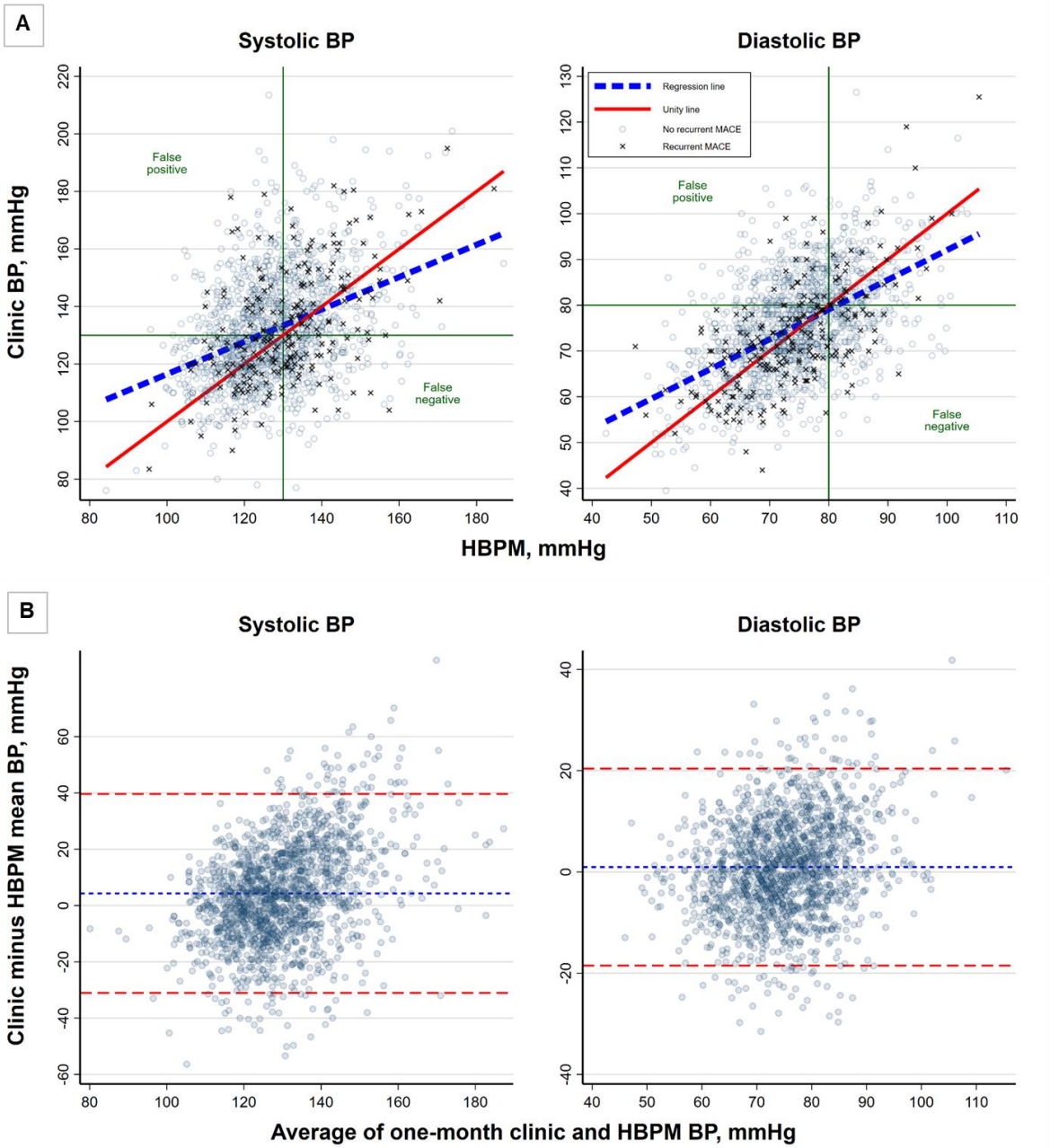


Figure 4-7 Scatter plots (A) and Bland-Altman plots (B) of mean systolic and diastolic blood pressure on clinic assessment and seven-day HBPM at one month

Home blood pressure monitoring (HBPM); blood pressure (BP); major adverse cardiovascular events (MACE). The green lines in the scatterplots represent the cut-off points for hypertension (≥130/80 mmHg). HBPM is assumed to be the reference standard to highlight false positives and negatives. The blue dashed lines in the Bland-Altman plots represent the means of the absolute value of the BP difference between modalities. The red dashed lines represent ±1.96 SDs for this range.

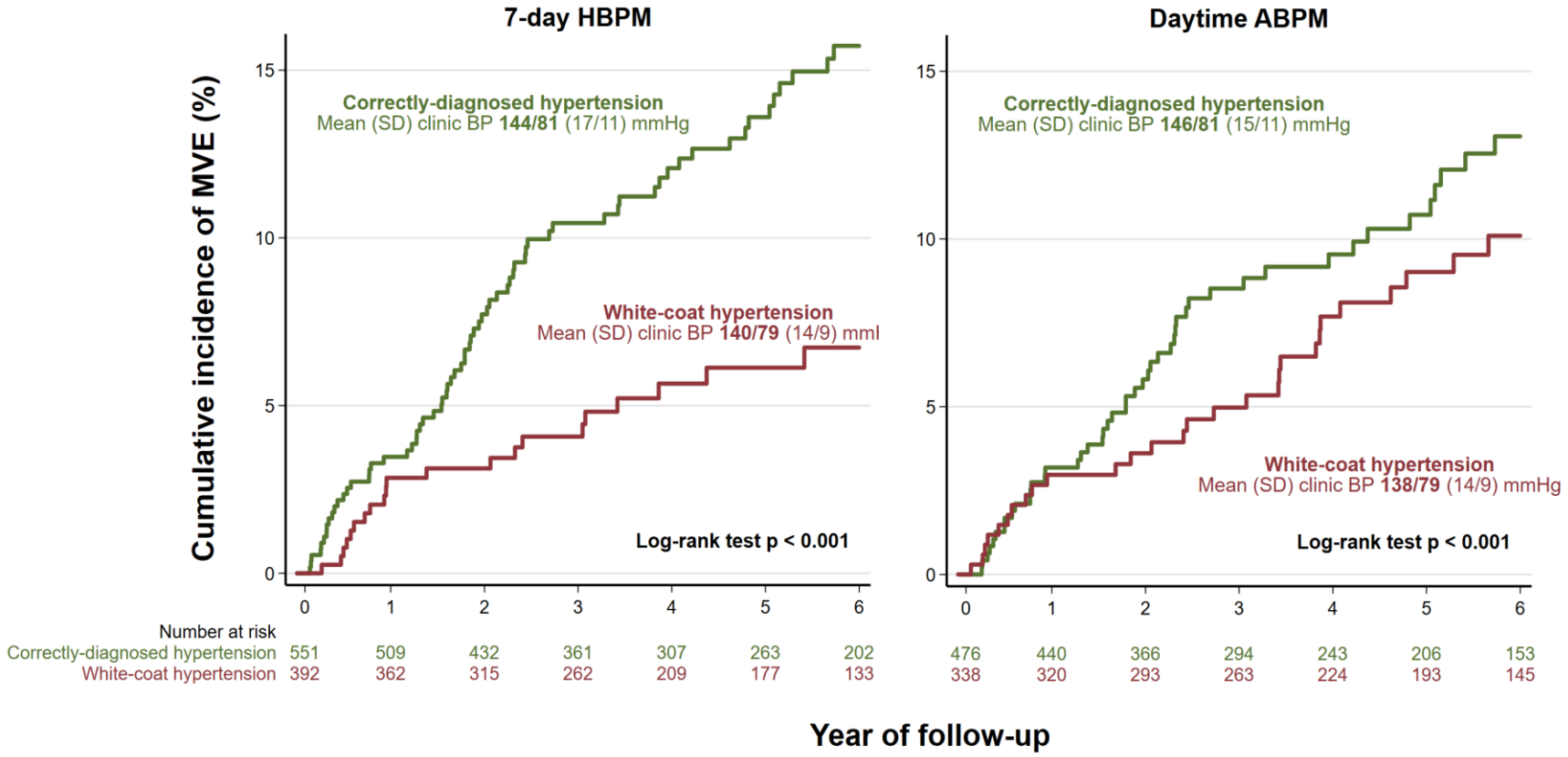


Figure 4-8 Risk of recurrent major vascular events associated with white-coat hypertension versus correctly diagnosed hypertension at one-month clinic assessment, according to HBPM and ABPM

Major vascular events (MVE: combined stroke, myocardial infarction, peripheral vascular events, vascular death); home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); blood pressure (BP); standard deviation (SD). Correctly diagnosed hypertension was defined as clinic BP ≥130/80 and mean 7-day HBPM/daytime ABPM BP ≥130/80 mmHg. White-coat hypertension was defined as clinic BP ≥130/80 mmHg and mean 7-day HBPM/daytime ABPM BP <130/80 mmHg.

Chapter 5: Home telemonitoring-guided blood pressure control after TIA and stroke: Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study

5.1 Abstract 193
5.2 Introduction 195
5.3 Methods 197
5.3.1 Study design and participants..... 197
5.3.2 Procedures..... 197
5.3.3 Statistical analysis: 199
5.4 Results 201
5.5 Discussion 206
5.6 Tables 210
5.7 Figures 219

5.1 Abstract

Background: Clinical guidelines recommend a strict blood pressure target of <130/80 mmHg for secondary prevention after transient ischaemic attack (TIA) and stroke, but do not address how this should be achieved. In practice, blood pressure control is poor, and there remains a considerable residual risk of recurrent vascular events. Home blood pressure monitoring (HBPM) combined with guided antihypertensive therapy improves blood pressure control in primary prevention, but evidence is lacking after TIA/stroke, where usual practice is still based on clinic blood pressure surveillance. I aimed to assess blood pressure control, safety, and acceptability of a telemetric HBPM-guided blood pressure treatment programme in TIA and minor stroke.

Methods: After prescription of antihypertensive treatment based on initial clinic blood pressure, consecutive eligible patients with TIA or minor stroke in a population-based study (Oxford Vascular Study) measured their blood pressure three times daily at home with a telemetric device for at least one month. Antihypertensive therapy was tailored to the blood pressure response during HBPM to a target blood pressure of <130/80 mmHg. 24-hour ambulatory blood pressure monitoring (ABPM) was performed at one-month and one-year follow-up, and clinic blood pressure was measured at regular follow-up intervals. Acceptability was determined by anonymised questionnaires.

Results: 1656 patients (mean/SD age=69.7/13.1) were recruited over 11 years, of whom 854 (52%) were taking antihypertensive treatment at baseline. 1108 (66.9%) had their antihypertensive treatment changed by one-month follow-up, of whom 1044 (94.2%) had a net dosage increase. Mean blood pressure decreased by 24.2/11.9 mmHg ($p<0.0001$) between baseline and three-month follow-up clinic assessment, with approximately double the blood pressure reduction observed in those who had their antihypertensive treatment increased during the monitoring period compared to those who did not (29.2/16.6 vs 15.6/7.4 mmHg, $p<0.0001$). Measurements of day-to-day blood pressure variability that were independent of reductions in mean blood pressure

also decreased during the HBPM period (systolic blood pressure mean [SD] coefficient of variation first 3 days 9.3 [3.2]% vs last 7 days 7.6 [3.0]%, p<0.0001). Target blood pressure was sustained to one-year follow-up (daytime ABPM mean [SD] 129.5/74.3 [13.3/8.0], clinic blood pressure 130.1/73.7 [17.6/16.5] mmHg), and both patient and primary care physician satisfaction rates of the telemetric HBPM programme were over 90%. Overall, reductions in mean clinic blood pressure between baseline and one-year follow-up were significantly greater during the first six years of the HBPM-guided blood pressure treatment programme compared to an equivalent matched population during the preceding six years (20.6/11.2 vs 14.4/6.3 mmHg, p<0.0001).

Conclusion: A month of telemetric-HBPM guided blood pressure treatment was well tolerated by patients and achieved sustained blood pressure control <130/80 mmHg after TIA and minor stroke.

5.2 Introduction

Elevated blood pressure is the strongest modifiable risk factor for stroke,[3] but there has been little research on optimal assessment and control of blood pressure in secondary prevention where the risk of recurrent vascular events is highest.[9] The PROGRESS trial showed that treatment to lower blood pressure after transient ischaemic attack (TIA) and stroke reduces this risk.[61] However, although guidelines recommend a blood pressure target of less than 130/80 mmHg, they provide no recommendations on how this should be achieved.[59, 60, 95] In practice, only a third of patients achieve the guideline blood pressure standard,[15-17] and over 20% of patients discontinue their antihypertensive treatment within the first year.[18]

Home blood pressure monitoring (HBPM) has been identified as a promising strategy in primary prevention to improve long-term blood pressure control, but only when combined with co-interventions such as systematic antihypertensive medication titration or patient education.[227, 238] NHS England has recently recommended that all primary care networks implement HBPM, with a particular focus on hypertensive patients with previous stroke or TIA,[320] but there is a lack of evidence in this population. The very few trials of HBPM that included patients with a history of TIA or stroke showed no effect in terms of blood pressure lowering, with or without telemonitoring and co-interventions, and this was not explained by more intensive treatment prior to randomisation in these patients.[238-241]

To address this need for evidence and the inadequate blood pressure control in current practice after TIA/stroke, where the benefits of optimised control will be largest,[97] the Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study was designed. This prospective observational study, nested in a population-based TIA/stroke cohort, had two specific aims. First, can telemetric HBPM be used to achieve the guideline blood pressure target (<130/80 mmHg) after

TIA/stroke, and second, is a programme of HBPM-guided treatment feasible, safe, and acceptable to patients and their primary care physicians.

5.3 Methods

5.3.1 Study design and participants

The Oxford Vascular Study (OXVASC) is a longitudinal, population-based cohort study of the incidence and outcome of all acute vascular events in a defined population of 92,728 individuals, registered with around 100 general practitioners in nine primary care practices in Oxfordshire, UK.[264, 298] OXVASC was approved by the Oxfordshire research ethics committee, including the HBPM sub-study (OREC A: 05/Q1604/70). Written, informed consent or assent from relatives was obtained for all participants for study interview and follow-up, including ongoing review of primary care and hospital records and death certificate data.

5.3.2 Procedures

Consecutive patients with TIA or non-disabling stroke were prospectively recruited to this blood pressure-monitoring sub-study (COMMIT: Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment) between April 1st 2008 and March 31st 2019 from OXVASC. Case ascertainment of TIA/stroke was done using multiple overlapping methods and is near-complete for events reaching medical attention.[265, 299] These methods included a rapid access daily clinic to which general practitioners and the local emergency department referred individuals with suspected cerebrovascular events, daily searches of emergency departments, relevant hospital wards, eye hospital attendances, radiographic or vascular surgical investigations or procedures, and monthly searches of primary care practice diagnostic codes and referrals to acute and community hospitals.

All consenting patients underwent a standardised medical history and examination, ECG, and blood tests. Patients underwent a stroke protocol MRI brain scan and contrast-enhanced MRA (or CT brain scan and either a carotid Doppler ultrasound or

CT-angiogram when MR imaging was contraindicated), an echocardiogram, and five days of ambulatory cardiac monitoring.

All patients were assessed by a study physician and reviewed by the senior study neurologist (Professor Peter Rothwell). Patients were followed up face-to-face at one, three, six, 12, 60, and 120 months. Recurrent vascular events were ascertained at each follow-up and by multiple methods of ascertainment.[265, 299]

Clinic blood pressure at baseline and follow-up was measured in the non-dominant arm by trained personnel, with two measurements made five minutes apart in the sitting position, after five minutes of rest. Patients were provided with a Bluetooth-enabled, regularly-calibrated, telemetric blood pressure monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT, on the day of the baseline clinic assessment. After appropriate training on the day, they were asked to perform three home blood pressure readings over ten minutes, three times daily (after waking, midday, and evening).

Measurements were automatically transmitted by Bluetooth to a Raspberry Pi microcomputer hub, for secure transmission via a cellular network to a server hosting a password-protected website for review and download (OBS Medical, Abingdon, UK). Patients continued monitoring for at least one month.

The day before the one-month and one-year follow-up visits, ABPM was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by trained study personnel. Blood pressure was measured at 30-minute intervals during the day (07:00 to 23:00) and 60-minute intervals at night. Patients were asked to refrain from excessive activity during recordings and were asked to keep a diary of their day.

Hypertension was treated according to current guidelines,[95] initially based on baseline clinic readings and then according to HBPM, aiming for a target blood pressure <130/80 mmHg. Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a combination of perindopril arginine 5mg and indapamide

1.25mg, followed by amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion. Patients were generally advised to take their antihypertensive medication in the morning.

For sequential comparisons of follow-up blood pressure in the COMMIT study versus the pre-COMMIT study period, all non-hospitalised patients with confirmed cerebrovascular events in OXVASC from the beginning of the study to the start of the COMMIT study (April 1, 2002, to March 31 2008) and patients with confirmed cerebrovascular events across an equivalent period in the COMMIT study (April 1, 2008, to March 31 2014) were included.

5.3.3 Statistical analysis:

Clinic blood pressure was calculated as the mean of the two sitting measurements during each assessment. HBPM readings for each participant were downloaded from the encrypted website and manually assessed to remove those with erroneous measures or incorrect date/time stamps (n=87, <0.1%). Recordings with systolic blood pressure <50 mmHg (n=3), diastolic blood pressure >140 mmHg if pulse pressure <40 mmHg (n=5), and any pulse pressure <10 mmHg (n=6) were excluded.

The first three days of HBPM at baseline and the last 7 days of HBPM for each participant were used to assess mean blood pressure and blood pressure variability changes over the monitoring period, both to minimise effects of blood pressure treatment at baseline clinic and to equalise any diminution in the number of daily readings among participants at the end of the HBPM programme.

Mean blood pressure on ABPM was derived after the exclusion of artefactual measurements according to predefined criteria,[312] analogous to those used for HBPM.

Prior hypertension was defined as a diagnosis reported by the patient, or hypertension listed on the primary care list of diagnoses. Hypertension was defined at each time-point

as mean blood pressure ≥130/80 mmHg for clinic blood pressure, HBPM, and daytime ABPM, according to guidelines.[95]

Day-to-day blood pressure variability on HBPM was quantified by calculating the standard deviation (SD), coefficient of variation (*CV-100 x SD/mean*), and root mean square error (RMSE: blood pressure variability around the fitted linear regression line of blood pressure and day of HBPM, to account for any trend in blood pressure particularly any reductions due to early treatment effects across the first three days). Missing data are reported, and were not imputed.

Means, medians, and proportions of baseline characteristics were stratified according to commencement or up-titration of antihypertensive medication during the first month of HBPM and compared using t-tests, Wilcoxon rank-sum tests, and chi-square tests, respectively. Mean blood pressure and blood pressure variability were compared between baseline and follow-up, and between the COMMIT study and pre-COMMIT study phases using paired t-tests, and the prevalence of hypertension was compared using McNemar's tests. All analyses were performed using Stata version 16.1.

5.4 Results

Of 1833 patients with TIA or minor stroke in the OXVASC clinic during the study period, 51 (2.8%) refused to take part in the COMMIT study, and 126 (6.9%) were excluded due to early death, acute intercurrent illness, severe dementia, excessive physical disability, or residence outside of the study area (Figure 5-1). 1656 (90.3%) consented to home telemetric blood pressure monitoring, of whom 1626 (98.2%) continued measuring until at least their one-month follow-up clinic assessment. 736 (44.4%) patients were maintained on telemetric HBPM beyond six weeks, and 236 (14.3%) up to or beyond three months due to intermissions in monitoring or delays in achieving target blood pressure control. Of 30 (1.8%) participants who discontinued HBPM prior to one-month follow-up, 13 withdrew from the study, nine were unable to tolerate HBPM for one month, four had acute intercurrent illness precluding blood pressure measurement, three died, and one was a resident in a nursing home in which assistance for HBPM was not available.

Mean age at baseline clinic was 69.7 (SD 13) years, and 51.4% of participants were men (Table 5-1). 1609 (97.2%) attended their scheduled one-month follow-up assessment, of whom 1382 (85.9%) agreed to be fitted for 24-hour ABPM and tolerated monitoring. 1327 (80.1%) attended their one-year follow-up assessment, of whom 962 (72.5%) agreed to be fitted for repeat 24-hour ABPM and tolerated monitoring.

Of 802 (48.4%) participants not taking antihypertensive treatment at baseline, 537 (67.0%) were prescribed at least one agent before the one-month follow-up clinic, such that 1340 (80.9%) of patients were treated. Overall, 1108 (66.9%) patients had their antihypertensive medications changed (i.e. either started, new agents prescribed, dosage alterations, or stopped) during the first month of the HBPM period, of which 1044 (94.2%) was a net dosage increase and 64 (5.8%) was a net dosage decrease. By three-month follow-up, 1158/1344 (86.2%) patients assessed were taking antihypertensive

treatment, and this proportion was relatively stable by six-month follow-up (1139/1355, 84.1%, Figure 5-2).

Mean blood pressure decreased across the period of telemetric HBPM-guided treatment, with significant reductions in clinic blood pressure between baseline and three-month assessments (24.3/11.9 mmHg, p<0.0001), with greater reductions (p<0.0001) among those who had their antihypertensive medications increased during this time (29.2/14.6 mmHg, p<0.0001) compared to those who did not (15.6/7.4 mmHg, p<0.0001, Table 5-2**,** Table 5-3).

Significant decreases were also achieved for mean home blood pressure between three days of monitoring at baseline and seven days at the end of the HBPM period for each participant (9.6/5.5 mmHg, p<0.0001, Table 5-2**,** Figure 5-3), with a bigger reduction (p<0.0001) again observed among those with a net treatment dose increase (12.6/7.0 mmHg, p<0.0001, Table 5-3**,** Figure 5-4). Target mean blood pressure (<130/80 mmHg) was achieved regardless of the measurement modality: three-month follow-up clinic mean (SD) 127.1/73.0 (16.5/10.7); last week of HBPM 125.8/73.5 (12.0/8.9); one-month daytime ABPM 129.2/73.8 (12.8/8.1); one-year daytime ABPM 129.5/74.3 (13.3/8.0) mmHg.

Day-to-day blood pressure variability measured on HBPM also decreased across the monitoring period (Table 5-2), with greater reductions among patients whose antihypertensive treatment was increased (Table 5-3). For some variability metrics, this might have been partly attributable to the substantial reductions in mean blood pressure, as maximum (R^2=0.65, p<0.0001), minimum (R^2=0.63, p<0.0001), SD (R^2=0.08, p<0.0001), and RMSE (R^2=0.07, p<0.0001) were highly correlated with mean systolic blood pressure on the last seven days of HBPM. However, CV was not significantly correlated with mean systolic blood pressure (R^2=0.002, p=0.07), nor was the difference in CV with the difference in mean systolic blood pressure between the start and the end of monitoring (R^2=0.0004, p=0.40). Similarly, no significant correlation was observed

between mean systolic blood pressure and CV(RMSE) (R^2=0.001, p=0.15), nor for the difference in mean systolic blood pressure versus CV(RMSE) between baseline and follow up (R^2<0.0001, p=0.92). Despite this, there were also significant reductions in systolic blood pressure CV (1.8%, p<0.0001, Figure 5-5) and CV(RMSE) (1.4%, p<0.0001) during the monitoring period. The decrease in systolic blood pressure CV was modestly greater among patients in whom treatment was increased compared to those in whom there was no treatment increase (1.9% vs 1.5%, p=0.036), but a significant difference by treatment intensification was not observed for diastolic blood pressure (Table 5-3, Figure 5-6).

Despite rapid blood pressure control to target, only 3.4% (56/1626) of patients fell during the first month of HBPM-guided treatment, of which no falls resulted in significant trauma. Nine (16.1%) falls were associated with treatment-induced hypotension. Two of these patients with hypotension-related falls required a reduction in antihypertensive medication, and there were a further 13 medication changes due to other possible hypotension-related symptoms (postural dizziness, presyncopal symptoms, general fatigue). Between one- and three-month follow-up, there were a further 48 falls. Six (12.5%) were associated with hypotension, of which three resulted in medication changes, and there were eight further reductions due to possible hypotension-related symptoms.

Of the first 1200 patients recruited, who were sent an anonymised questionnaire, 688 (57.3%) returned this after one month of telemetric HBPM-guided treatment (Figure 5-7, Table 5-4). 669 (97.2%) of patients were highly satisfied with monitoring. Mean (SD) overall satisfaction on a visual analogue scale (0%-extremely dissatisfied to 100%-extremely satisfied) was 89.7(15.4)%. 628 (91.3%) strongly approved of HBPM, 649 (94.3%) felt reassured by central surveillance, and 641 (93.2%) thought it helpful to be able to discuss their blood pressure readings and treatment by telephone. Only 25 (3.6%) patients strongly felt that taking their blood pressure was uncomfortable.

However, 107 (15.5%) patients reported that intensive monitoring contributed to increased anxiety levels, and 89 (12.9%) reported that the process was too time-consuming.

Thirty-nine primary care physicians returned the physician satisfaction questionnaire (Table 5-5). Median (IQR) overall satisfaction on a visual analogue scale (0-extremely dissatisfied to 10-extremely satisfied) was high 9 (8-10). None felt that the majority of patients were unable to perform HBPM. 36 physicians (92.3%) felt that blood pressure control was better, and 37 (94.9%) reported that HBPM reflected underlying blood pressure more accurately than clinic blood pressure assessment. Although 26 (66.7%) reported that blood pressure control was moderately or overly aggressive, only one (2.6%) preferred standard care.

Of 1790 patients included in sequential comparisons of follow-up blood pressure in the COMMIT study versus the pre-COMMIT OXVASC study period, 880 (49.2%) had confirmed outpatient TIA/stroke before the initiation of the COMMIT study, and 910 (50.8%) had equivalent events in the first six years of the COMMIT study. Patients in the pre-COMMIT phase were marginally older on average (mean age 72.4 vs 69.7 years, $p<0.0001$), but were otherwise well-matched to the COMMIT comparator population in terms of vascular risk factors, including a similar prevalence of pre-event hypertension and antihypertensive use (Table 5-6). Mean [SD] baseline clinic systolic blood pressure was also similar between the two cohorts (151.1 [26.8] pre-COMMIT vs 149.6 [23.6] mmHg COMMIT, $p=0.23$), but diastolic blood pressure was higher in the COMMIT cohort (83.9 [13.6] vs 81.7 [11.6], $p=0.0004$, Table 5-7).

One-month follow-up blood pressure was significantly lower in the COMMIT cohort than in the pre-COMMIT cohort (130.0/74.1 [17.9/11.1]] vs 138.3/76.7 [21.4/10.1], $p<0.0001$), and this difference persisted to one-year follow-up (129.4/72.8 [17.9/10.6]] vs 137.1/76.0 [20.2/9.9], $p<0.0001$, Figure 5-8**,** Figure 5-9). Accordingly, the blood pressure reduction between baseline and one-year follow-up clinic was greater in the six-year COMMIT

phase than in the pre-COMMIT phase (20.6/11.2 vs 14.4/6.3 mmHg, p<0.0001, Figure 5-10), consistent with a higher proportion of patients prescribed at least one antihypertensive agent by one-year follow-up in the COMMIT phase (82.7% vs 69.3%, p<0.0001). When restricting to two years pre- and post-COMMIT study initiation to minimise any role of temporal blood pressure trends in the general population, similar reductions in mean follow-up clinic blood pressure were observed (Table 5-7).

5.5 Discussion

Centralised telemetric HBPM-guided blood pressure treatment achieved sustained control to guideline target blood pressure (<130/80 mmHg) in unselected patients with recent TIA or minor stroke, with substantial reductions in mean blood pressure and day-to-day blood pressure variability during the monitoring period, greater than any reductions observed in the population before the initiation of the HBPM programme. Satisfaction among both patients and primary care physicians was high and there were few adverse events during monitoring.

My findings have a number of clinical implications. First, although there is irrefutable evidence from large randomised controlled trials that intensive blood pressure control after TIA/stroke is associated with reductions in recurrent vascular events,[11] few patients attain the guideline blood pressure standard in current practice.[15-17] I have shown that this blood pressure target after TIA/stroke is achievable with around a month of HBPM and guided antihypertensive treatment. I observed an instantaneous and substantial reduction in follow-up blood pressure in the OXVASC population after the initiation of the HBPM programme, despite minimal change in baseline clinic blood pressure or the demographic and clinical characteristics of the population, suggesting a direct effect of the programme rather than a temporal shift in the population. Moreover, such reductions in blood pressure occurred in the context of a substantial increase in the proportion of the population being prescribed antihypertensive therapy. Mean blood pressure at one-year follow-up revealed sustained normotension when measured in clinic or using ABPM in my study, suggesting that close liaison between physicians and patients, patient engagement in their own care, and direct feedback regarding the efficacy of treatment provided by self-monitoring results in long-term control. HBPM has previously been shown to improve blood pressure control when combined with systematic antihypertensive medication titration in primary care, but this has not been observed in those with a history of stroke/TIA, where there appears to be reduced effectiveness of

HBPM for systolic blood pressure lowering in the very few studies that included such people.[238] In fact, in the two small randomised trials performed specifically in people with a history of TIA/stroke, HBPM (with or without guided therapy) did not result in lower blood pressure levels at follow-up compared with usual care.[239, 331] Moreover, the blood pressure reductions in my study between baseline and follow-up were greater than those observed in the intervention arm of any of the trials comparing HBPM after stroke to usual care (systolic blood pressure reduction range 1.7-10.2 mmHg).[239, 290, 331] However, these previous studies recruited much later after TIA/stroke, where baseline blood pressure may already be partly controlled and the motivating effects of a recent cerebrovascular event might have diminished. In addition, they implemented guided antihypertensive treatment that was arguably less intensive than that provided in the COMMIT study. Second, there were few falls despite a substantial reduction in mean blood pressure, occurring at approximately the expected frequency for the population,[332] and few medication changes due to hypotension-related symptoms. Blood pressure lowering in the acute phase after major stroke is associated with little benefit or even harm,[79-87] but there is little evidence in minor stroke/TIA, and guidelines provide conflicting recommendations about the timing of commencement of treatment.[59, 95] Indeed, even in the general population, rapid initiation or titration of medication in elderly patients with multiple comorbidities may increase the risk of falls.[67] However, I have shown that regular communication with patients and daily assessment of blood pressure readings facilitating tailored titration of medications allows intensive blood pressure control without excessive risk of adverse events after TIA and minor stroke. Third, the high rates of patient engagement (over 90%) and completion of at least a month of HBPM (98%), as well as high levels of satisfaction reported by both patients and primary care physicians demonstrate that intensive HBPM in acute TIA and minor stroke patients is feasible and acceptable. This is consistent with the limited previous evidence of acceptability of HBPM,[290, 333, 334] but the motivating effects of a recent cerebrovascular event might have further increased acceptability in my older, frailer study population.

Our analyses had some potential shortcomings. First, patients who declined to take part or who were excluded from the COMMIT sub-study due to comorbidity would have been unlikely to tolerate frequent HBPM and intensive blood pressure management. However, this population was small (<10%), and the mean age of the included cohort was 70 years, reflecting the high inclusivity of this population-based cohort compared to selectively recruiting HBPM cohort studies with comparably low participation rates.[326, 328, 335] Second, this study is not a randomised trial, so was not intended to prove that HBPM-guided blood pressure treatment is superior to usual care for the control of blood pressure after TIA and stroke. However, the fact that target blood pressure control was attained and sustained in this study, despite rarely being achieved in current secondary prevention practice, as well as my observations of a dramatic reduction in follow-up blood pressure in the study population after the initiation of HBPM, indicate the effectiveness of the intervention in achieving blood pressure control at the population level. Moreover, an advantage of this prospective population-based methodology in comparison to a randomised trial is the inclusion of a broad range of patients, many of whom would not meet the stringent inclusion criteria of trials of blood pressure-lowering interventions, thereby maximising the generalisability of these results to the wider secondary prevention population. Third, a rise in blood pressure of uncertain prognostic significance immediately after TIA/stroke that decreases spontaneously within days, 'post-stroke hypertension', is present in many patients,[336] and might have contributed to the large apparent reductions in blood pressure achieved between baseline and follow-up in my study compared to previous trials of HBPM, which recruited after the sub-acute phase.[239, 290, 331] However, my observations of significantly greater blood pressure reductions among patients whose blood pressure treatment was increased, and larger reductions between baseline and follow-up than those recorded prior to the initiation of the HBPM programme, suggest a causal role for this intervention. Finally, the high cost and implementation challenges of blood pressure telemonitoring technologies[221] pose barriers to the application of the strategy used in this study to routine secondary

prevention practice. In addition, this centrally administered model of HBPM-guided treatment required a full-time nurse and some daily physician time for reviewing readings and enacting interventions. However, telemetric patient-recorded HBPM has been endorsed as the preferred choice in NHS England's primary care HBPM protocol currently being implemented, including among patients with previous stroke or TIA,[320] and my approach of central monitoring could be readily adapted to a primary care setting, where feasibility has previously been established.[290]

In conclusion, centrally managed, telemetric HBPM-guided, blood pressure lowering after TIA or minor stroke was feasible, safe, acceptable to patients and their primary care physicians, and achieved sustained blood pressure control to guideline targets. In light of the well-established vascular risk-reducing benefits of blood pressure lowering after TIA/stroke, this study lends support to the use of HBPM-guided early intensive blood pressure lowering for improving secondary prevention.

5.6 Tables

Table 5-1 Characteristics of patients according to antihypertensive treatment status between baseline assessment and one-month follow-up

Patient characteristics	Whole cohort	Antihypertensive treatment¶ commenced/up-titrated	Antihypertensive treatment not commenced/up-titrated	p-value
n (% whole cohort)	1656 (100%)	1044 (63.0%)	612 (37.0%)	-
Male sex, n (%)	851 (51.4%)	539 (51.6%)	300 (51.0%)	0.799
Age, mean (SD)	69.7 (13.1)	70.6 (12.7)	68.2 (13.7)	**<0.0001**
Event type, n (%)				
Stroke	652 (39.4%)	393 (37.6%)	258 (42.2%)	0.070
TIA	1004 (60.6%)	651 (62.4%)	354 (57.8%)	
Medical history prior to event, n (%)				
Hypertension (prior history/treatment)	1038 (62.7%)	677 (64.9%)	361 (60.0%)	**0.017**
Angina	191 (11.5%)	126 (12.1%)	65 (10.6%)	0.373
Diabetes mellitus	218 (13.2%)	140 (13.4%)	78 (12.8%)	0.669
Hyperlipidaemia	524 (31.7%)	338 (32.4%)	186 (30.4%)	0.402
Myocardial infarction	51 (3.1%)	34 (3.3%)	17 (2.8%)	0.586
Atrial fibrillation	193 (11.7%)	115 (11.0%)	78 (12.8%)	0.290
Heart failure	69 (4.2%)	40 (3.8%)	29 (4.7%)	0.373
Peripheral vascular disease	53 (3.2%)	29 (2.8%)	24 (3.9%)	0.202
Prior stroke	94 (5.7%)	55 (5.3%)	39 (6.4%)	0.349
Prior TIA	240 (14.5%)	159 (15.2%)	81 (13.2%)	0.266
Lifestyle factors (self-reported)				
Current smoker, n (%)	251 (15.2%)	154 (14.8%)	97 (15.9%)	0.547
Ever-smoker, n (%)	887 (53.6%)	543 (52.0%)	344 (56.2%)	0.098
Alcohol intake u/wk, median (IQR) ǂ	2 (10)	2 (10)	2 (12)	0.166

Blood pressure, mmHg, mean (SD)				
Clinic, systolic	151.4 (22.9)	156.8 (22.2)	142.0 (21.0)	**<0.0001**
Clinic, diastolic	85.1 (13.3)	87.6 (13.2)	80.7 (12.4)	**<0.0001**
Hypertension (BP ≥130/80 mmHg), n (%)	1468 (88.7%)	891 (94.0%)	487 (79.6%)	0.366
HBPM first 3 days of monitoring, systolic*	135.5 (16.2)	139.4 (15.7)	128.7 (14.7)	**<0.0001**
HBPM first 3 days of monitoring, diastolic	79.0 (10.3)	80.8 (10.5)	75.8 (9.2)	**<0.0001**
Hypertension (BP ≥130/80 mmHg), n (%)	1123 (68.1%)	822 (78.9%)	301 (49.5%)	**<0.0001**

Standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP). ¶ Antihypertensive treatment was defined as any medication specifically prescribed for reducing blood pressure. ǂ Data missing for 87 participants. * Complete HBPM n=1650

Table 5-2 Blood pressure of participants between baseline and follow-up

Blood pressure, mmHg	Baseline	Follow-up	p-value
Mean BP (SD)			
Clinic (*baseline to* ***one-month FU***), systolic¶	151.4 (22.9)	132.3 (18.6)	**<0.0001**
Clinic (*baseline to* ***one-month FU***), diastolic	85.1 (13.3)	75.6 (11.2)	**<0.0001**
Clinic hypertension (BP ≥130/80 mmHg), n (%)	1426 (88.6%)	968 (60.2%)	**<0.0001**
Clinic (*baseline to* ***three-month FU***), systolic¥	151.3 (23.0)	127.1 (16.5)	**<0.0001**
Clinic (*baseline to* ***three-month FU***), diastolic	85.0 (13.4)	73.0 (10.7)	**<0.0001**
Clinic hypertension (BP ≥130/80 mmHg), n (%)	1182 (88.3%)	659 (49.2%)	**<0.0001**
Clinic (*baseline to* ***one-year FU***), systolic§	151.2 (22.9)	130.1 (17.6)	**<0.0001**
Clinic (*baseline to* ***one-year FU***), diastolic	85.0 (13.4)	73.7 (10.6)	**<0.0001**
Clinic hypertension (BP ≥130/80 mmHg), n (%)	1134 (88.3%)	685 (53.4%)	**<0.0001**
HBPM, systolicǂ	135.4 (16.1)	125.8 (12.0)	**<0.0001**
HBPM, diastolic	78.9 (10.3)	73.4 (8.9)	**<0.0001**
HBPM hypertension (BP ≥130/80 mmHg), n (%)	1101 (67.7%)	695 (42.7%)	**<0.0001**
*Day-to-day HBPM BP variability, mean (SD)**			
Max, systolic	161.9 (21.7)	142.6 (16.1)	**<0.0001**
Max, diastolic	94.6 (13.0)	83.5 (10.9)	**<0.0001**
Min, systolic	113.4 (15.1)	110.7 (13.1)	**<0.0001**
Min, diastolic	65.0 (11.1)	63.7 (9.9)	**<0.0001**
SD, systolic	12.7 (4.8)	9.5 (4.0)	**<0.0001**
SD, diastolic	7.6 (2.7)	5.9 (2.5)	**<0.0001**
CV, systolic (%)	9.3 (3.2)	7.6 (3.0)	**<0.0001**
CV, diastolic (%)	9.7 (3.5)	8.1 (3.4)	**<0.0001**
RMSE, systolic	11.8 (4.5)	9.2 (3.9)	**<0.0001**
RMSE, diastolic	7.1 (2.5)	5.7 (2.4)	**<0.0001**
CV(RMSE), systolic (%)	8.7 (3.0)	7.3 (3.0)	**<0.0001**
CV(RMSE), diastolic (%)	9.1 (3.3)	7.8 (3.4)	**<0.0001**

Standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP). Analyses are restricted to those participants with complete BP data at baseline and follow-up for each modality: ¶ n=1609 ¥ n=1339 § n=1284 ǂ n=1626. * n=1621

Table 5-3 Blood pressure reduction between baseline and follow-up according to BP-lowering treatment status during intensive monitoring

Blood pressure difference, mmHg	Overall	Antihypertensive treatment commenced/up-titrated	Antihypertensive treatment not commenced/up-titrated	p-value
Mean BP (SD)				
Clinic (*baseline to one-month FU*), systolic¶	19.2 (23.2)	23.5 (23.8)	11.5 (19.8)	**<0.0001**
Clinic (*baseline to one-month FU*), diastolic	9.5 (12.2)	11.6 (12.4)	5.8 (11.1)	**<0.0001**
Clinic (*baseline to three-month FU*), systolic¥	24.2 (23.6)	29.2 (23.6)	15.6 (21.1)	**<0.0001**
Clinic (*baseline to one-month FU*), diastolic	11.9 (13.0)	14.6 (12.7)	7.4 (12.1)	**<0.0001**
HBPM, systolic£	9.6 (13.5)	12.6 (14.0)	4.3 (10.9)	**<0.0001**
HBPM, diastolic	5.5 (7.6)	7.0 (7.7)	2.9 (6.7)	**<0.0001**
*Day-to-day HBPM BP variability, mean (SD)**				
Max, systolic	19.3 (20.3)	22.5 (21.2)	13.8 (17.4)	**<0.0001**
Max, diastolic	11.2 (12.5)	13.0 (12.5)	7.9 (10.1)	**<0.0001**
Min, systolic	2.8 (15.1)	5.3 (15.2)	-1.6 (13.7)	**<0.0001**
Min, diastolic	1.3 (10.0)	3.0 (9.8)	-1.5 (9.6)	**<0.0001**
SD, systolic	3.1 (5.2)	3.6 (5.3)	2.3 (4.8)	**<0.0001**
SD, diastolic	1.7 (3.1)	2.0 (3.2)	1.3 (3.0)	**<0.0001**
CV, systolic (%)	1.8 (3.7)	1.9 (3.8)	1.5 (3.7)	**0.036**
CV, diastolic (%)	1.6 (4.2)	1.8 (4.2)	1.4 (4.2)	0.129
RMSE, systolic	2.6 (4.9)	3.1 (5.1)	1.8 (4.4)	**<0.0001**
RMSE, diastolic	1.4 (2.9)	1.6 (2.9)	1.0 (2.8)	**0.0001**
CV(RMSE), systolic (%)	1.4 (3.6)	1.5 (3.7)	1.2 (3.4)	0.063
CV(RMSE), diastolic (%)	1.3 (3.9)	1.4 (3.9	1.1 (3.9)	0.165

Standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP). Analyses are restricted to those participants with complete BP data at baseline and follow-up for each modality: ¶ n=1609 ¥ n=1339 £ n=1626. * n=1621

Table 5-4 Summary of results from patient HBPM satisfaction questionnaire

Question	Definitely agree	Moderately agree	Neither agree or disagree	Moderately Disagree	Definitely disagree	Total responses
Liked that regular readings would provide better information about their BP						
n	628	43	7	2	2	**682**
% total responses	92.1%	6.3%	1.0%	0.3%	0.3%	**100%**
% overall	91.3%	6.3%	1.0%	0.3%	0.3%	**99.1%**
Felt reassured that their blood pressure was transmitted directly to the hospital						
n	611	38	18	2	3	**672**
% total	90.9%	5.7%	2.7%	0.3%	0.4%	**100%**
% overall	88.8%	5.5%	2.6%	0.3%	0.4%	**97.7%**
Found it helpful to be able to discuss BP readings and treatment						
n	586	55	26	5	1	**673**
% total	87.1%	8.2%	3.9%	0.7%	0.1%	**100%**
% overall	85.2%	8.0%	3.8%	0.7%	0.1%	**97.8%**
Found it uncomfortable						
n	25	57	71	74	406	**633**
% total	3.9%	9.0%	11.2%	11.7%	64.1%	**100%**
% overall	3.6%	8.3%	10.3%	10.8%	59.0%	**92.0%**
Found it too time-consuming						
n	21	68	66	125	353	**633**
% total	3.3%	10.7%	10.4%	19.7%	55.8%	**100%**
% overall	3.1%	9.9%	9.6%	18.2%	51.3%	**92.0%**
Found it increased anxiety						
n	31	76	59	57	408	**631**
% total	4.9%	12.0%	9.4%	9.0%	64.7%	**100%**
% overall	4.5%	11.0%	8.6%	8.3%	59.3%	**91.7%**
Found it difficult to remember						
n	32	70	56	135	353	**646**
% total	5.0%	10.8%	8.7%	20.9%	54.6%	**100%**
% overall	4.7%	10.2%	8.1%	19.6%	51.3%	**93.9%**

Home blood pressure monitoring (HBPM); blood pressure (BP).

Table 5-5 Primary care physicians' HBPM satisfaction questionnaires

Question topics	n	% overall
Effectiveness of the HBPM-guided BP management programme versus standard care		
Much more effective	19	48.7
Somewhat more effective	13	33.3
Slightly more effective	4	10.3
About as effective	2	5.1
Slightly less effective	0	0.0
Somewhat less effective	0	0.0
Much less effective	0	0.0
Total responses	38	97.4
Communication of medication changes with GP		
Extremely well	24	61.5
Quite well	13	33.3
Moderately well	1	2.6
Slightly well	0	0.0
Not at all well	0	0.0
Total responses	38	97.4
Level of BP management		
Too conservative	0	0.0
Moderately conservative	1	2.6
About right	12	30.8
Moderately aggressive	21	53.8
Too aggressive	5	12.8
Total responses	39	100.0
Period of HBPM as a reflection of overall control		
Extremely well	27	69.2
Quite well	10	25.6
Moderately well	2	5.1
Slightly well	0	0.0
Not at all well	0	0.0
Total responses	39	100.0

Home blood pressure monitoring (HBPM); blood pressure (BP)

Table 5-6 Characteristics of OXVASC patients in the pre-COMMIT study period (6 years) and the first 6 years of the COMMIT study

Patient characteristics ***n (%)***	**Combined cohorts** ***1790 (100%)***	**COMMIT cohort** ***910 (50.8%)***	**Pre-COMMIT cohort** ***880 (49.2%)***	**p-value (COMMIT vs pre-COMMIT)**
Male sex, n (%)	902 (50.4%)	491 (54.0%)	411 (46.7%)	**0.002**
Age, mean (SD)	71.0 (12.9)	69.7 (13.0)	72.4 (12.7)	**<0.0001**
Event type, n(%)				
Stroke	853 (47.7%)	418 (45.9%)	435 (49.4%)	0.139
TIA	937 (42.4%)	492 (54.1%)	445 (50.6%)	
Medical history prior to event, n (%)				
Hypertension (prior history)	971 (54.3%)	501 (55.1%)	470 (53.4%)	0.485
Angina	229 (12.8%)	109 (12.0%)	120 (13.6%)	0.294
Diabetes mellitus	227 (12.7%)	123 (13.5%)	104 (11.8%)	0.280
Hyperlipidaemia	534 (29.9%)	288 (31.7%)	246 (28.0%)	0.094
Atrial fibrillation	238 (13.3%)	118 (13.6%)	120 (13.6%)	0.677
Heart failure	116 (6.5%)	43 (4.7%)	73 (8.3%)	**0.002**
Peripheral vascular disease	89 (5.0%)	40 (4.4%)	49 (5.6%)	0.236
Lifestyle factors (self-reported)				
Current smoker, n (%)	271 (15.1%)	147 (16.2%)	124 (14.1%)	0.223
Ever-smoker, n (%)	989 (55.3%)	513 (56.4%)	476 (54.1%)	0.332
Antihypertensive use, n (%)				
Baseline	942 (52.6%)	466 (51.2%)	476 (54.1%)	0.222
One-month follow-up*	1295 (75.6%)	708 (77.8%)	587 (73.1%)	**0.024**
One-year follow-up¶	1161 (76.5%)	673 (82.7%)	415 (69.3%)	**<0.0001**

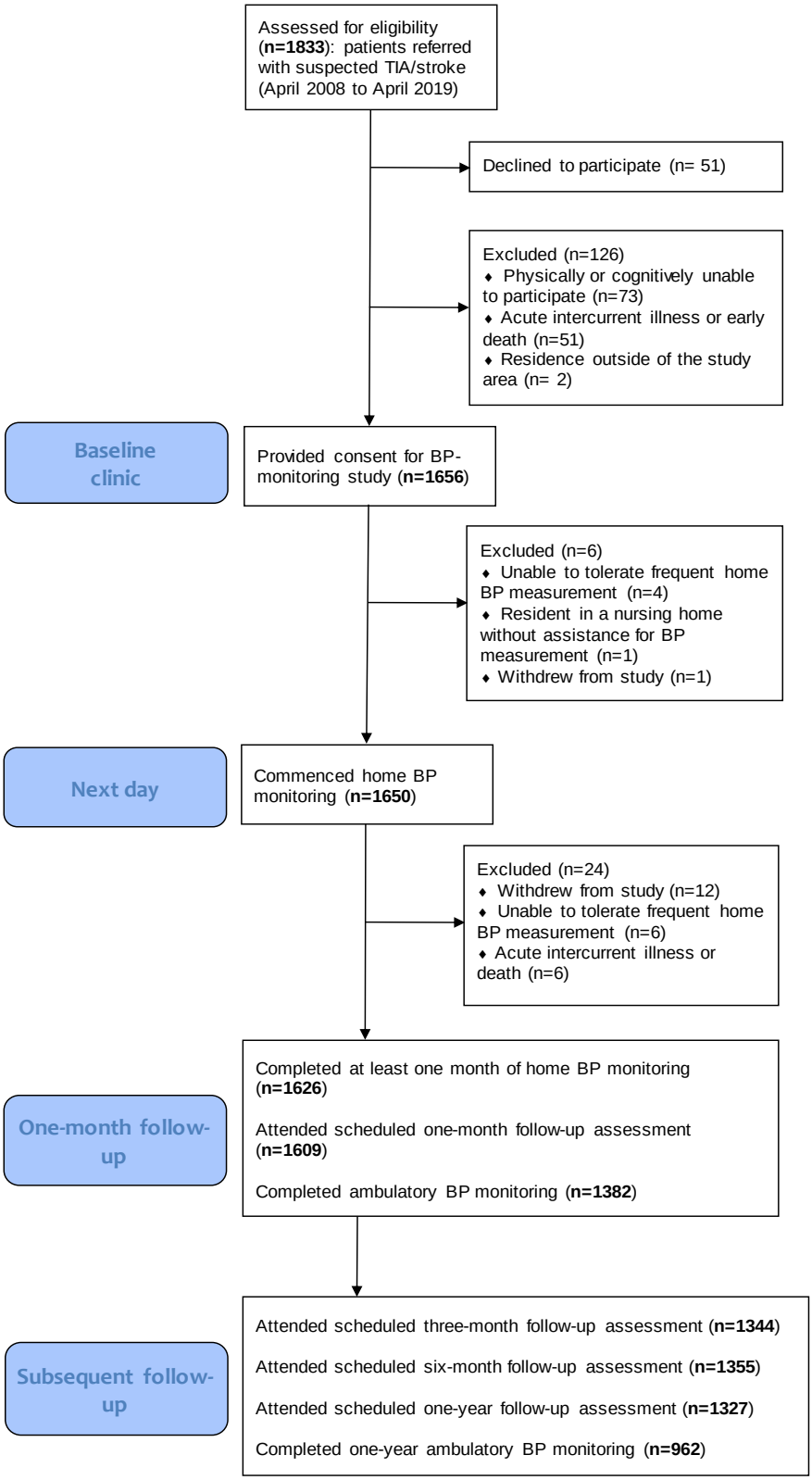
Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT); standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP). Available clinic BP data: * Combined cohorts n=1713, COMMIT cohort n=910, pre-COMMIT cohort n=803; ¶ Combined cohorts n=1518, COMMIT cohort n=814, pre-COMMIT cohort n=704.

Table 5-7 Baseline and follow-up clinic blood pressure of OXVASC patients in the pre-COMMIT study period (6 years) and the first 6 years of the COMMIT study

Blood pressure, mean (SD), mmHg	COMMIT cohort	Pre-COMMIT cohort	p-value (COMMIT vs pre-COMMIT)
Full comparison cohort (6 years pre- to post-COMMIT initiation), n (%)	***910 (50.8%)***	***880 (49.2%)***	
Baseline clinic systolic BP*	149.6 (23.6)	151.1 (26.8)	0.230
Baseline clinic diastolic BP	83.9 (13.6)	81.7 (11.6)	**0.0004**
One-month clinic systolic BP¶	130.0 (17.9)	138.3 (21.4)	**<0.0001**
One-month clinic diastolic BP	74.1 (11.1)	76.7 (10.1)	**<0.0001**
One-year clinic systolic BPǂ	129.4 (17.9)	137.1 (20.2)	**<0.0001**
One-year clinic diastolic BP	72.8 (10.6)	76.0 (9.9)	**<0.0001**
2 years pre- to post-COMMIT initiation, n (%)	***230 (44.5%)***	***287 (55.5%)***	
Baseline clinic systolic BP*	149.1 (23.9)	149.3 (27.3)	0.911
Baseline clinic diastolic BP	83.0 (12.8)	81.7 (10.1)	0.219
One-month clinic systolic BP¶	131.9 (17.2)	136.6 (22.4)	**0.012**
One-month clinic diastolic BP	74.5 (9.8)	75.7 (10.1)	0.211
One-year clinic systolic BPǂ	128.5 (17.8)	136.7 (20.0)	**0.0001**
One-year clinic diastolic BP	72.2 (10.5)	74.7 (9.2)	**0.018**

Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT); standard deviation (SD); transient ischaemic attack (TIA); blood pressure (BP). Available clinic BP data: full comparison cohort: * n=717 in the pre-COMMIT cohort; ¶ n=892 in COMMIT cohort, n=654 in the pre-COMMIT cohort; ǂ n=797 in COMMIT cohort, n=510 in the pre-COMMIT cohort. Missing data: 2 years pre- to post-COMMIT cohort: * n=236 in pre-COMMIT cohort; ¶ n=228 in COMMIT cohort, n=209 in pre-COMMIT cohort; ǂ n=207 in COMMIT cohort, n=145 in pre-COMMIT cohort.

5.7 Figures



Transient ischaemic attack (TIA); blood pressure (BP)

Figure 5-1 Flowchart of study inclusion and exclusion

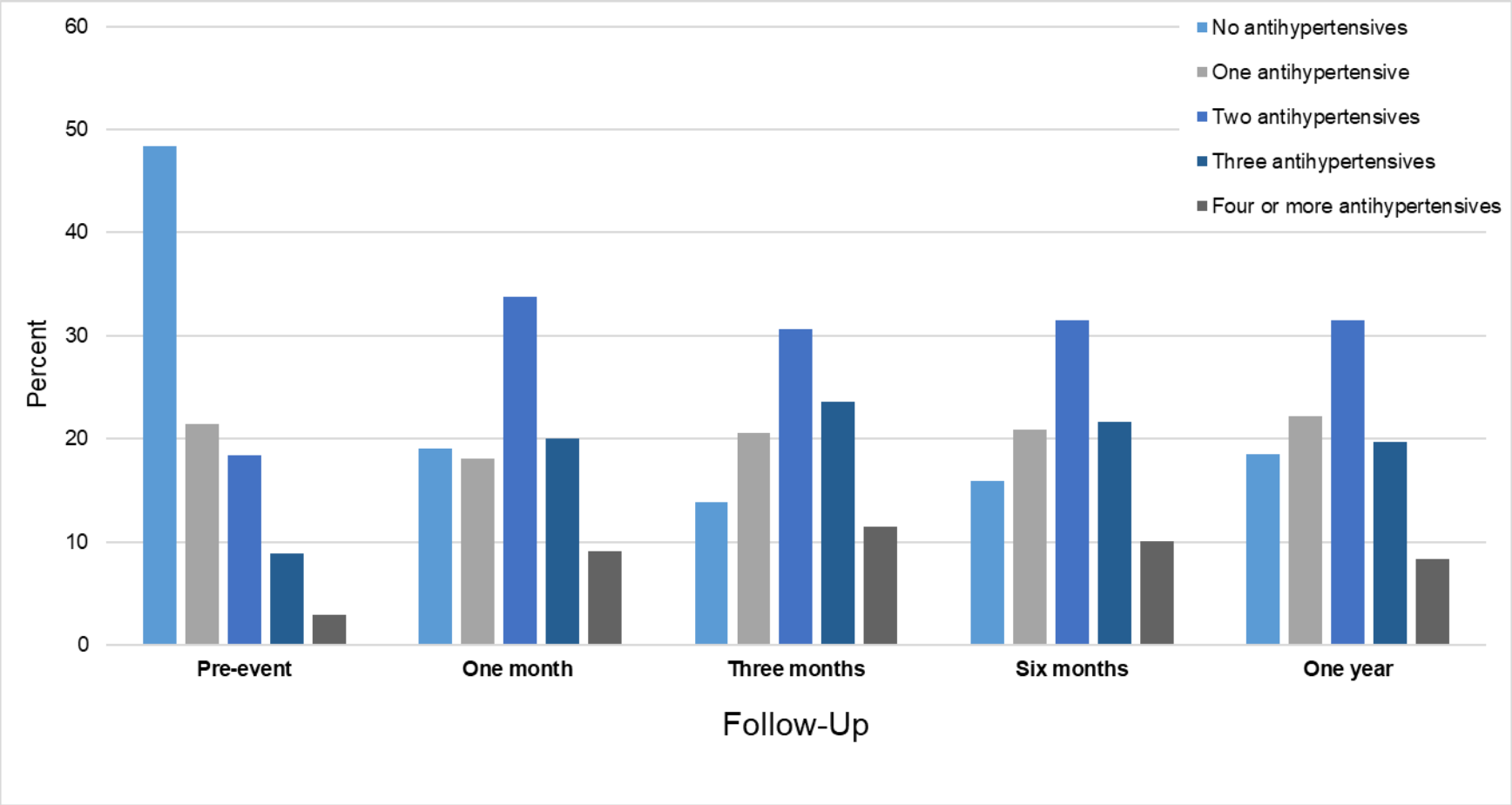


Figure 5-2 Changes in antihypertensive treatment use during and following the intensive monitoring period

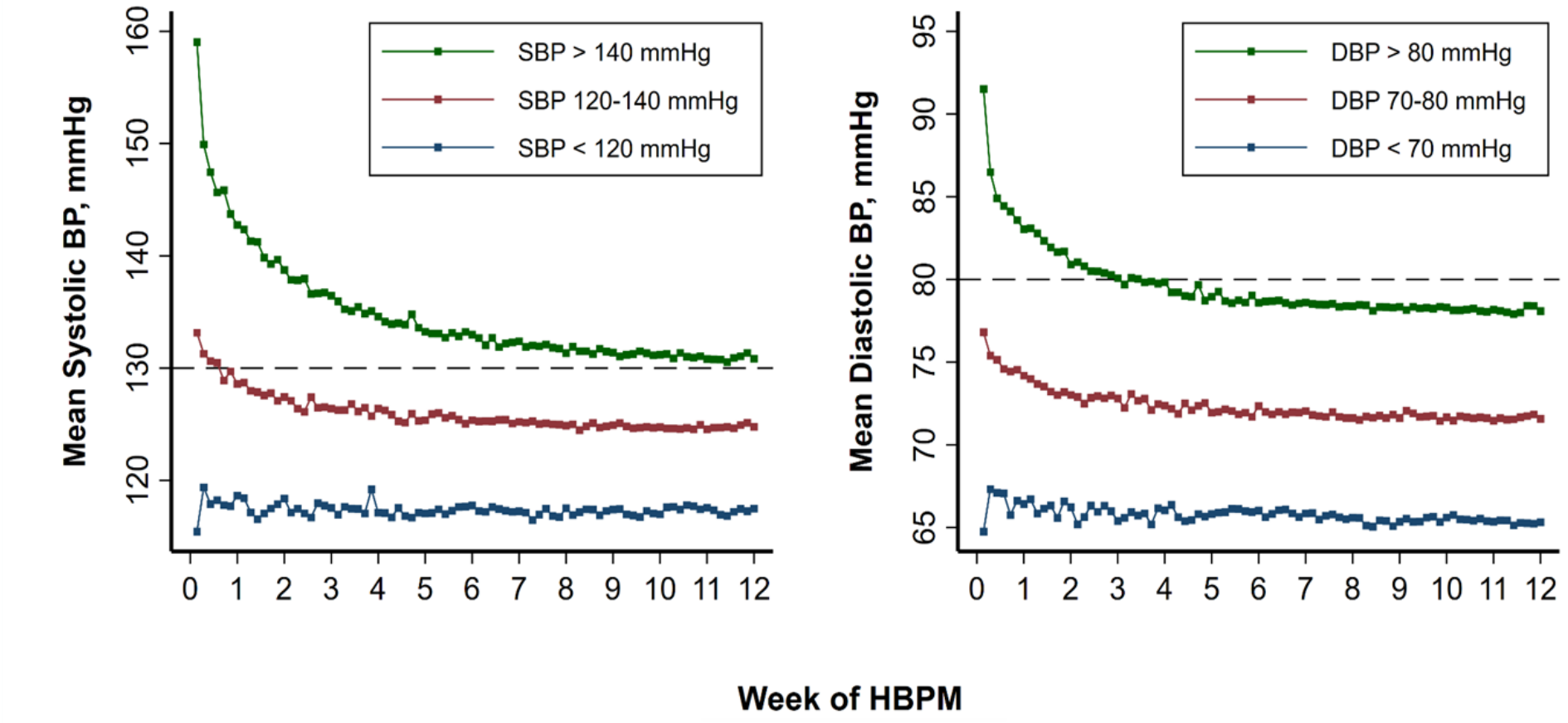


Figure 5-3 Home BP during three months of intensive monitoring and guided treatment, by categories of mean systolic and diastolic BP on the first day of monitoring

Blood pressure (BP); home BP monitoring (HBPM). The dashed horizontal line indicates the target BP. For patients who completed fewer than three months of monitoring, the mean of all readings on their final day of monitoring was used thereafter.

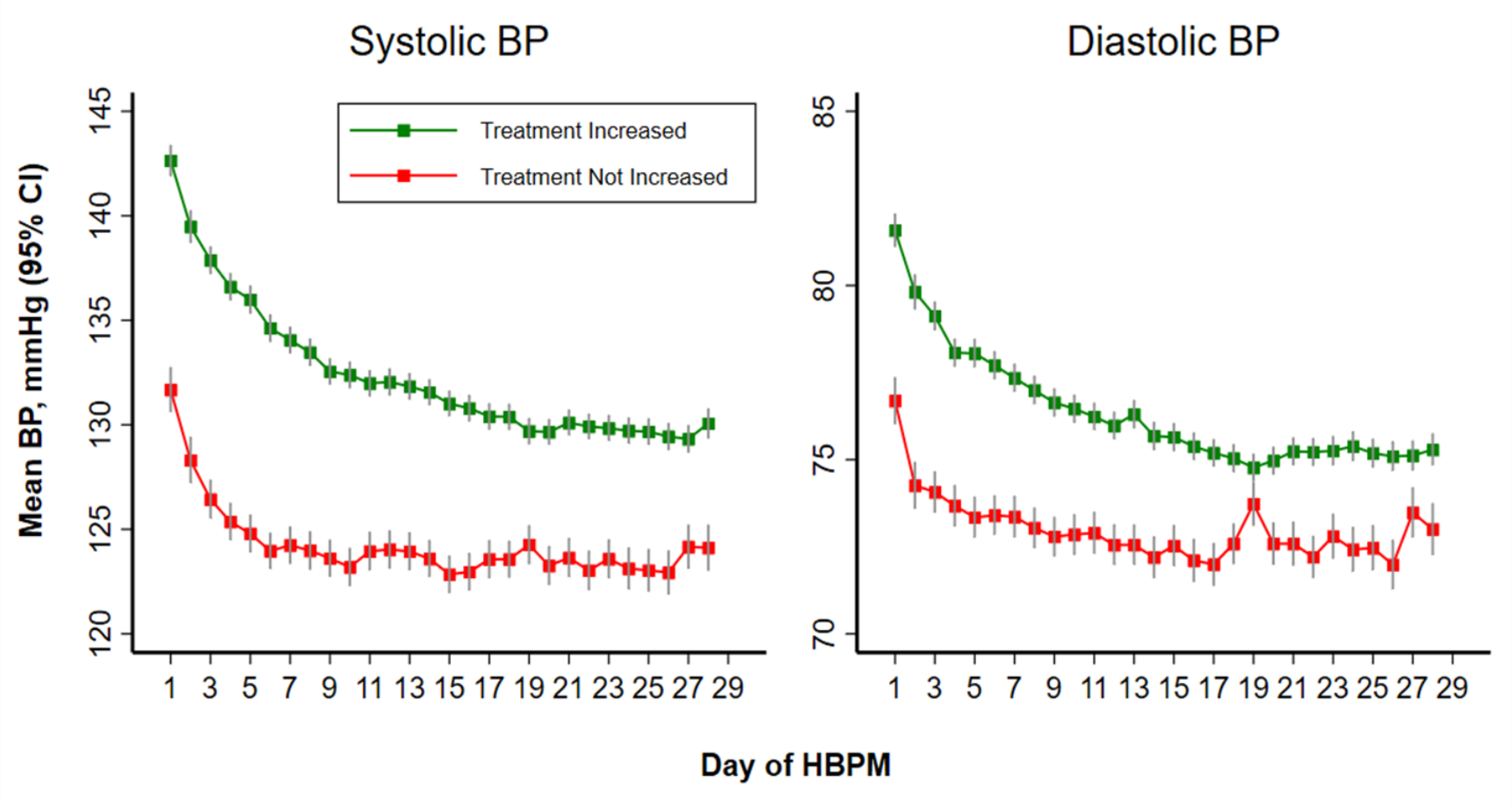


Figure 5-4 Home BP during one month of intensive monitoring and guided treatment, stratified by a net antihypertensive dosage increase during this time

Blood pressure (BP); home BP monitoring (HBPM). Antihypertensive treatment was defined as any medication specifically prescribed for reducing blood pressure between baseline and one-month follow-up

.

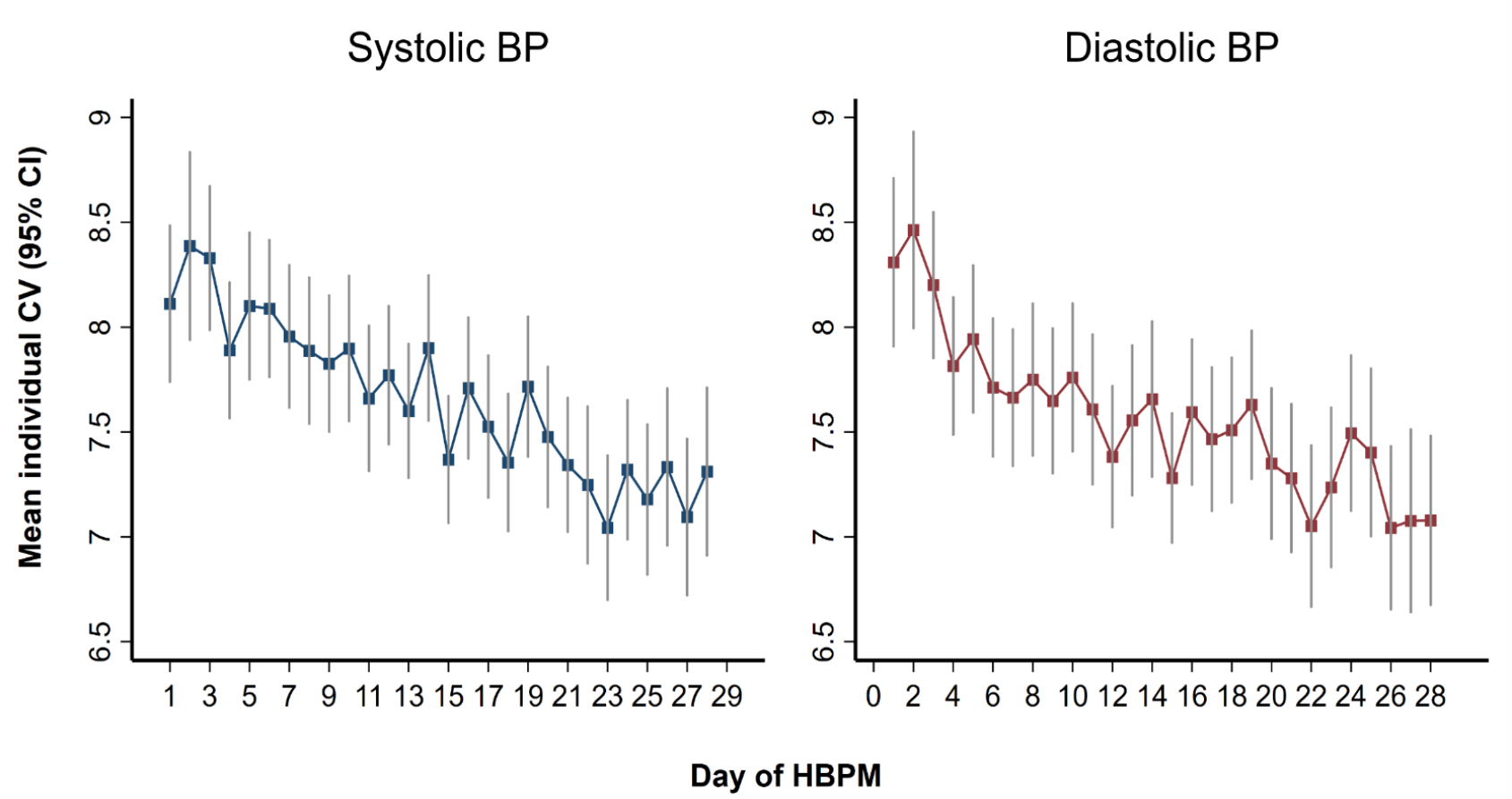


Figure 5-5 Mean daily individual coefficient of variation (%) of blood pressure during one month of intensive HBPM and guided treatment

Blood pressure (BP); home BP monitoring (HBPM); coefficient of variation (CV).

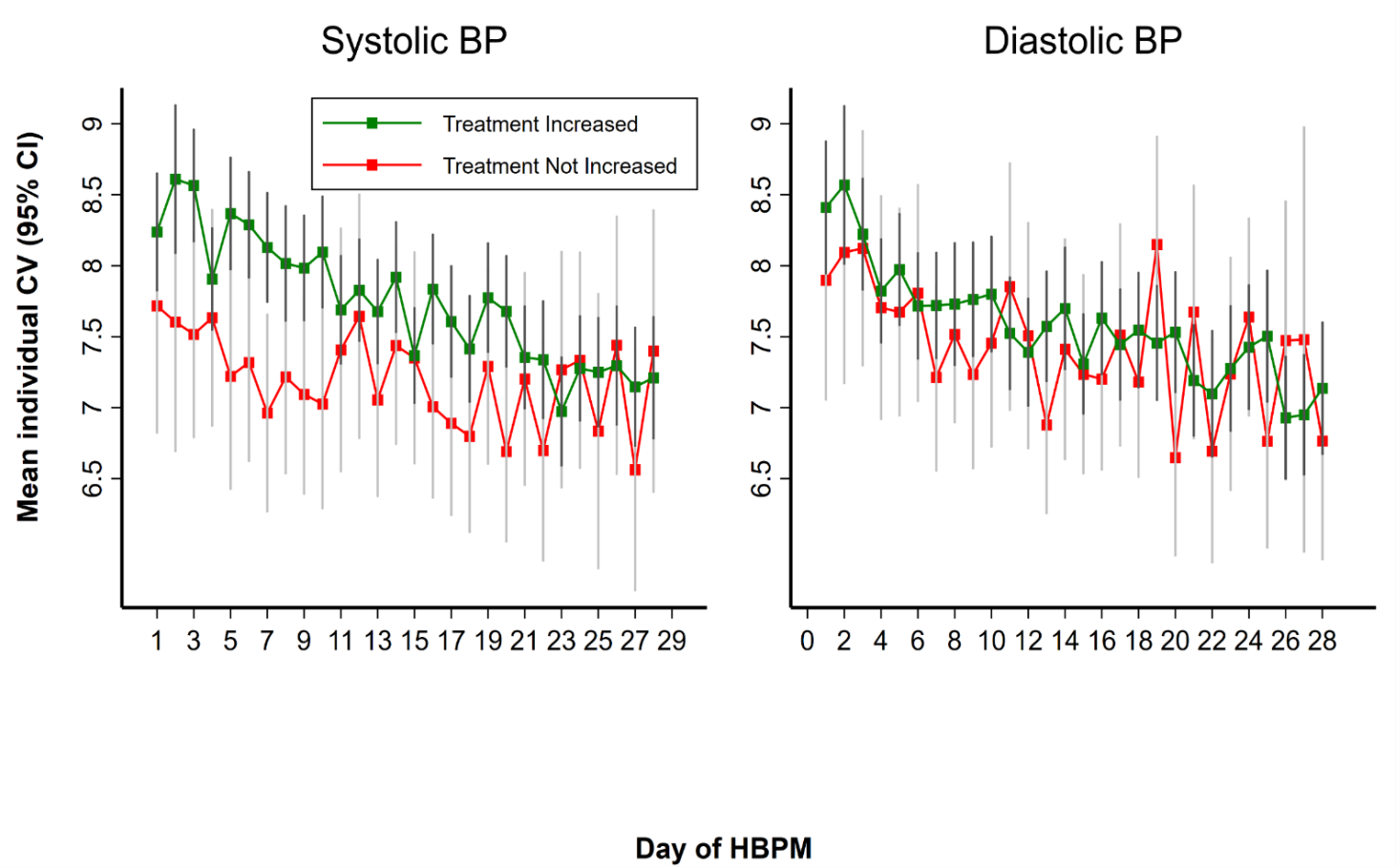


Figure 5-6 Mean daily individual coefficient of variation (%) of blood pressure during one month of intensive HBPM and guided treatment, stratified by a net antihypertensive dosage increase during this period

Blood pressure (BP); home BP monitoring (HBPM); coefficient of variation (CV). Antihypertensive treatment was defined as any medication specifically prescribed for reducing blood pressure between baseline and one-month follow-up.

HOME BLOOD PRESSURE MONITORING AUDIT

We would be very grateful if you could help us by answering some short questions about your experience using the home blood pressure monitor. Please tick the box that most closely matches your level of agreement with each of the following statements. Please give only one answer per line.

		Definitely agree	Moderately agree	Neither agree nor disagree	Moderately disagree	Definitely disagree
1	I liked the fact that the regular readings would provide better information about my blood pressure	☐	☐	☐	☐	☐
2	It reassured me to know that the equipment would transmit my readings directly to the hospital	☐	☐	☐	☐	☐
3	It was helpful to have a telephone number that I could call to discuss my blood pressure readings and treatment	☐	☐	☐	☐	☐
Measuring my blood pressure at home:						
4	was uncomfortable	☐	☐	☐	☐	☐
5	was too time consuming	☐	☐	☐	☐	☐
6	made me anxious	☐	☐	☐	☐	☐
7	I found it very difficult to remember to do it regularly	☐	☐	☐	☐	☐

Please rate your overall satisfaction with monitoring your blood pressure at home by marking a cross on the following line

0 25 50 75 100

Extremely dissatisfied **Extremely satisfied**

Has anyone helped you to fill in the questionnaire? (Please circle) **YES** or **NO**

Thank you very much for taking the time to complete this questionnaire.
Please return it to us in the attached prepaid envelope.
If you would like to make any additional comments please use the space provided overleaf

Figure 5-7 Telemetric home blood pressure monitoring-guided management programme patient satisfaction questionnaire

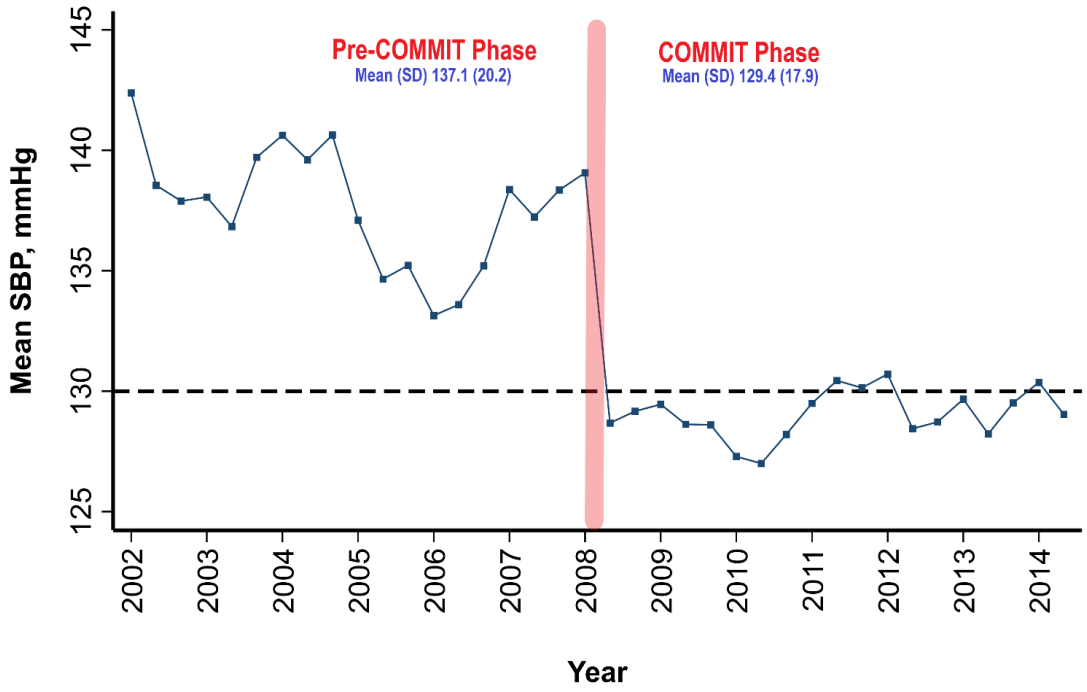


Figure 5-8 One-year follow-up clinic systolic blood pressure of OXVASC patients during the pre-COMMIT study period (6 years) and the first 6 years of the COMMIT study

Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT); systolic blood pressure (SBP). Available one-year follow-up clinic BP data: n=797 in COMMIT cohort, n=510 in the pre-COMMIT cohort. A uniformly weighted moving average of one-year follow-up SBP is presented, calculated separately before and after April 2008, by using 4-monthly time points with three lagged terms and including the current observation for each time point. Mean SBP is plotted according to the date of recruitment of each participant, not the one-year follow-up date. A standard average plot, without a cut-point in 2008, is presented in Figure 5-9. The dashed line indicates the COMMIT study target SBP (130 mmHg).

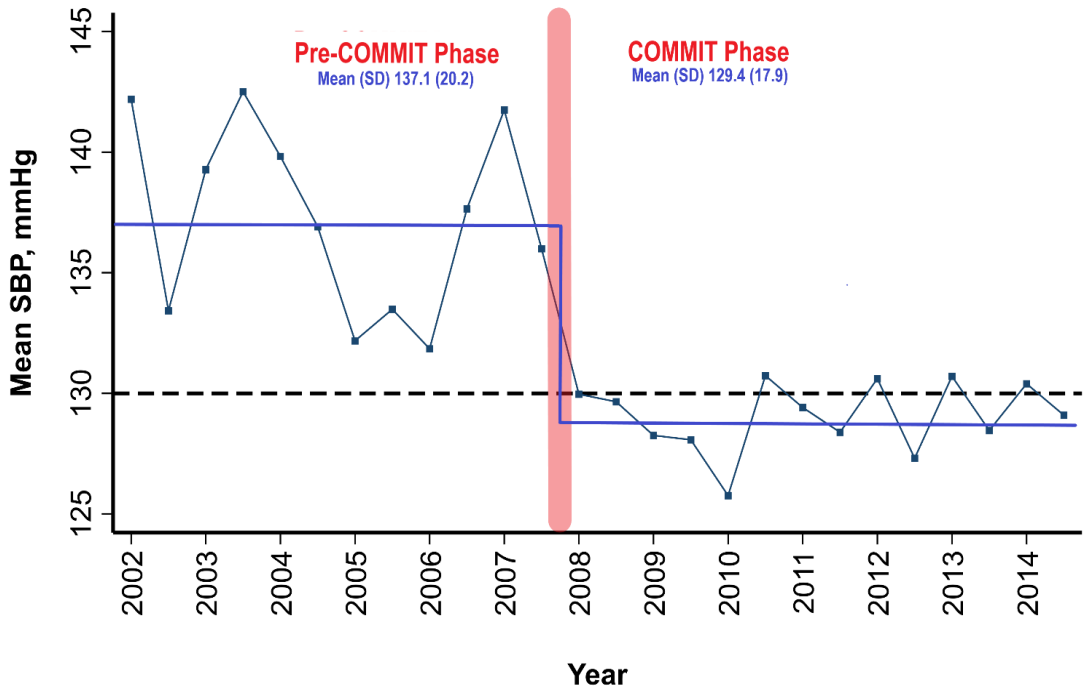


Figure 5-9 One-year follow-up clinic systolic blood pressure of OXVASC patients during the pre-COMMIT study period (6 years) and the first 6 years of the COMMIT study, standard average

Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT); systolic blood pressure (SBP). Available one-year follow-up clinic BP data: n=797 in COMMIT cohort, n=510 in the pre-COMMIT cohort. 6-monthly mean one-year follow-up SBP is shown, according to the date of recruitment of each participant, not the follow-up date. The blue line indicates the mean SBP in each phase. The dashed line indicates the COMMIT study target SBP (130 mmHg).

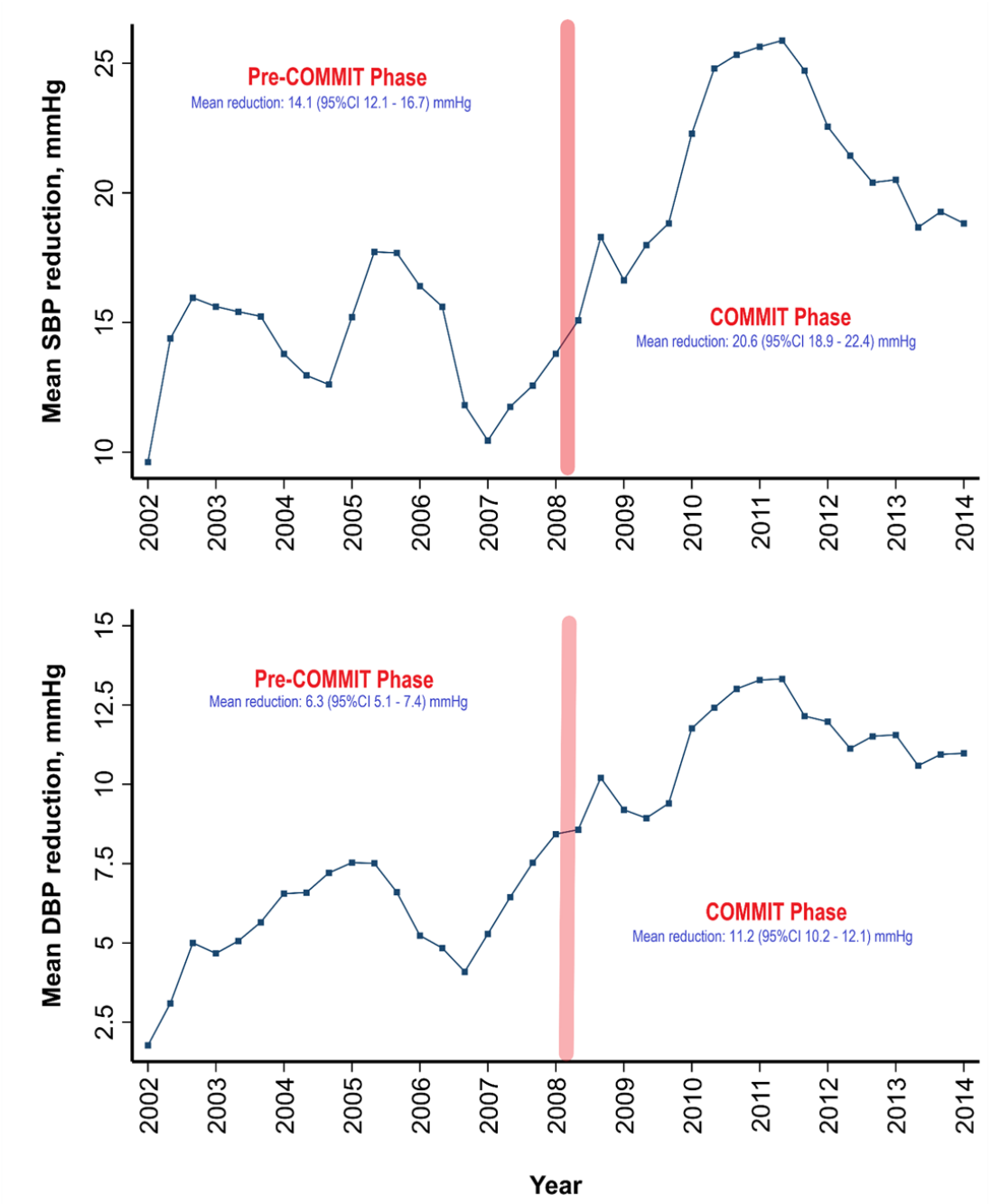


Figure 5-10 Reduction in blood pressure from baseline to one-year follow-up in OXVASC patients during the pre-COMMIT study period (6 years) and during the first 6 years of the COMMIT study

Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT); systolic blood pressure (SBP); diastolic blood pressure (DBP). Available baseline and one-year follow-up clinic BP data: n=797 in the COMMIT cohort, n=486 in the pre-COMMIT cohort. A uniformly weighted moving average of one-year follow-up BP is presented, calculated separately before and after April 2008, by using 4-monthly time points with four lagged terms and including the current observation for each time point. Mean BP is plotted according to the date of recruitment of each participant, not the one-year follow-up date.

Chapter 6: PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage (PROHIBIT-ICH): an interim report of a pilot randomised trial of home telemetry-guided treatment

6.1 Abstract **230**
6.2 Introduction **232**
6.3 Methods **234**
6.3.1 Study design and participants 234
6.3.2 Approvals 235
6.3.3 Randomisation 235
6.3.4 Procedures and intervention 235
6.3.5 Outcomes 238
6.3.6 Statistical analysis 239
6.4 Results **240**
6.5 Discussion **243**
6.6 Tables **246**
6.7 Figures **254**

6.1 Abstract

Background: Intracerebral haemorrhage (ICH) has the worst outcomes of all stroke subtypes, but advances in the prevention of ICH have not paralleled those of ischaemic stroke therapeutics in recent decades, and rates of recurrence remain high. Blood pressure is the most important risk factor for recurrence, and blood pressure-lowering treatment is associated with even greater reductions in risk of recurrent stroke in ICH than is observed for ischaemic stroke. In light of evidence supporting the use of telemetric home blood pressure monitoring (HBPM) to optimise blood pressure control after ischaemic stroke, and in the absence of trials targeting long-term blood pressure reduction after ICH, the PROHIBIT-ICH trial aimed to assess the BP-lowering efficacy and safety of HBPM-guided intensive blood pressure treatment in patients with spontaneous ICH, compared with usual care.

Methods: This study was a parallel, open-label, randomised controlled trial done in 16 UK hospitals, and included imaging-confirmed ICH survivors with blood pressure higher than 130/80 mmHg, who were willing to undergo home and ambulatory blood pressure monitoring. Participants were randomly assigned (1:1) to three months of HBPM-guided antihypertensive therapy with a target blood pressure of <120/80 mmHg (intervention) or usual care (control). The primary outcome was the change in assessment blood pressure from baseline to three-month follow-up in the intervention arm compared to the control arm.

Results: 59 participants from ten hospital research sites (range 1-11 per site) have been randomised to date, with five (8.5%) having been lost to follow-up during, two in the intervention arm and three in the control arm, and primary outcome data were available for 49 (83.1%) participants for this analysis. By the three-month follow-up, there was a significantly greater reduction in assessment blood pressure in the intervention group (20.4/8.6 [SD 21.4/10.6] mmHg) than in the control group (7.1/0.5 [17.5/8.9] mmHg, p=0.021/p=0.006). A more modest blood pressure reduction was found for three-month

awake ABPM assessment (14.9/6.5 [18.3/8.5] vs 3.7/0.0 [17.1/11.6] mmHg, p=0.050/0.054). Participants in the intervention group had a mean full-dose equivalent increase in BP-lowering drugs of 1.1 (SD 0.9) versus 0.3 (SD 0.5) drugs in the control group between baseline and three-month follow-up (p=0.0001). Adverse events during follow-up, however, were more frequent in the intervention group (18/29 [62.1%]) compared to the control group (6/30 [20.0%], p=0.001).

Conclusion: In these interim analyses, a programme of intensive HBPM-guided blood pressure control after ICH resulted in more frequent antihypertensive prescribing and lower follow-up assessment blood pressure compared with usual care, but at the expense of a higher burden of medication-related side effects.

6.2 Introduction

Spontaneous intracerebral haemorrhage (ICH) refers to non-traumatic bleeding in the brain parenchyma and is the deadliest form of stroke. The high one-month case fatality rate of ~40% and poor long-term outcome make ICH a major contributor to global morbidity and mortality.[102, 103] Although ICH accounts for a minority of stroke worldwide (10-30%), it is associated with a greater burden of disability-adjusted life years than ischaemic stroke, as ICH tends to affect people at earlier (working) ages[106] and has a high incidence in low- and middle-income countries.[337] Despite dramatic drops in ischaemic stroke mortality rates,[337] there has been limited improvement in case fatality from ICH in the last few decades[102, 338, 339] and the majority of survivors are left with severe disability, making ICH a persistent challenge for stroke research.[102, 105, 340]

Survivors are at high risk of recurrent ICH and other serious cerebrovascular and cardiovascular events, with annual rates of up to 10%,[105] and recurrent strokes result in higher mortality and disability than the first occurrence.[107] Observational data suggest that blood pressure is very high in the acute phase after ICH, significantly higher than that after ischaemic stroke.[34] High blood pressure in acute ICH is associated with haematoma expansion and poor clinical outcome,[111, 112] but uncertainty persists around whether blood pressure should be treated aggressively in the acute phase.[115-122] In the longer term, however, there appears to be a strong association between hypertension and ICH recurrence for both non-lobar and lobar bleeds,[110] and relative risk reduction for ICH was as twice as high as that for ischaemic stroke in the PROGRESS trial.[35]

Sustained post-acute blood pressure management, therefore, holds the most potential to improve long-term prognosis and recurrence, but there have been no dedicated trials targeting long-term blood pressure reduction after ICH. There are also concerns that intensive blood pressure lowering might have an adverse impact in older populations by reducing cerebral perfusion, causing cerebral ischaemia, progression of cognitive impairment, and falls.[125] Thus, although intensive blood pressure lowering is a very

promising secondary prevention intervention in ICH, the optimum long term target blood pressure remains uncertain. After showing that telemetric home blood pressure monitoring (HBPM) is can be used to optimise blood pressure control after TIA and minor stroke (Chapter 5:), I devised a multicentre, randomised controlled trial to assess whether the use of centralised telemetric HBPM to guide intensive blood pressure treatment in patients with spontaneous ICH is associated with a reduction in three-month blood pressure compared with standard care.

6.3 Methods

6.3.1 Study design and participants

PROHIBIT-ICH is a pilot, multicentre, open-label, randomised controlled trial, which is currently enrolling in 16 sites in the UK. I outline the methods in detail in the trial protocol (Appendix 2.1), but in this chapter, I will focus only on the methodology pertaining to the blood pressure outcomes of the trial.

Potentially eligible participants were identified by members of the care team from the hospital sites (acute stroke units or high dependency units), from outpatient clinics (stroke clinics, neurology clinics, geriatric clinics, and neurosurgical clinics), and at primary care sites, or from searches of clinical and research databases of patients who have had a previous ICH at any time, including databases of participants included in previous clinical trials. They were given an information leaflet and a letter of invitation by clinical staff at the site and had at least 24 hours to consider the information before being telephoned or approached by a member of the research/clinical team to discuss the study, explain the information sheet, and to assess eligibility.

Inclusion criteria were imaging-confirmed spontaneous ICH without evidence of a structural or macrovascular cause, age ≥ 30 years, inadequate blood pressure control (the opinion of the treating physician, and measured systolic blood pressure ≥ 130 mmHg), and the participant's ability to complete HBPM either unassisted or with the help of a carer. A protocol amendment was submitted in January 2021 to remove the requirement for a baseline MRI scan for trial entry (Appendix 2.1). If potentially-eligible participants were already prescribed BP-lowering medications, they were deemed ineligible if they were taking more than two different agents at the time of consent, and had to be free from a diagnosis of dementia, severe disability (modified Rankin score ≥ 3), and flow-restricting intracranial/extracranial large arterial stenosis on imaging.

6.3.2 Approvals

Ethical approval was granted from the London Camden & Kings Cross Research ethics committee (reference 18/LO/0866). All participants gave written informed consent, and a trial steering group supervised the trial. The trial is registered with ISRCTN, number ISRCTN23416732. ClinicalTrials.gov Identifier: NCT03863665.

6.3.3 Randomisation

Eligible and willing participants were invited to a baseline study visit, where informed consent was taken, baseline demographic data and measurements were collected, an MRI brain scan was performed, blood samples were drawn, and a 24-hour ambulatory blood pressure monitor was fitted. Randomisation was conducted between April 2019 and October 2021 (interim analysis) using a secure web-based system. A 1:1 group assignment ratio to intensive HBPM-guided blood pressure lowering (intervention group) or standard care (control group) was used, with stratification by ICH location (lobar versus non-lobar). Recruitment was suspended between March 20th and July 8th 2020 because of restrictions to all non-COVID-19 related research during a national lockdown. Neither the research team nor participants were blinded to group allocation. The blood pressure outcome measures (three-month follow-up clinic blood pressure, and mean daytime blood pressure on three-month 24-hour ABPM) were automated measures obtained by a research nurse who was not otherwise involved in the patient's care.

6.3.4 Procedures and intervention

A flowchart of trial procedures is presented in Figure 6-1. Participants randomly allocated to standard care were not informed of the results of their baseline 24-hour ABPM, nor were these communicated to their GP, unless mean daytime blood pressure was sufficiently different to the patient's known recent daytime blood pressure (based on recorded inpatient and baseline blood pressure measurements) to justify informing based on clinical need. Thereafter, blood pressure was managed at the discretion of their GP or stroke physician.

ABPM was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by trained study personnel. I provided instructional videos and written guides to participants (Appendix 2.20) if these devices needed to be fitted at home for virtual follow-up assessments. Blood pressure was measured at 30-minute intervals during the day (07:00 to 23:00) and 60-minute intervals at night. Participants were asked to refrain from excessive activity during recordings and were asked to keep a diary of their day, which was used for the determination of awake versus asleep mean blood pressure values.

Participants assigned to the intervention arm were fitted for the correct sized blood pressure cuff and received an A&D UA-767 BT Bluetooth-enabled, fully-calibrated, telemetric blood pressure monitor. They received training on how to use this device at the baseline visit and were also directed to online instructional videos (Appendix 2.20) and written guides (as used for the TRIDENT HBPM sub-study, Appendix 3.13).

The telemetric HBPM device allowed me to closely monitor the participant's blood pressure to direct treatment to achieve the predefined blood pressure target of <120/80 mm Hg, by the three-month follow-up visit. Participants were instructed to complete blood pressure readings three times daily (early morning, early afternoon and evening), with three readings on each occasion taken over ten minutes in the seated position, and using the non-dominant arm, unless there was severe hemiparesis. Measurements were automatically transmitted in real-time by Bluetooth to a Raspberry Pi microcomputer hub, for secure transmission via a cellular network to a server hosting a password-protected website for review and download (OBS Medical, Abingdon, UK). Along with the assistance of research nurses and therapists, I was responsible for checking all blood pressure data daily, and directly advised patients by telephone on starting or adjusting blood pressure medication according to a standard protocol based on the latest British Hypertension Society guideline, to ensure that blood pressure was lowered to the intervention arm target. For the treatment-naïve participant, first-line treatment (in

the absence of contraindications) was usually combination therapy with perindopril arginine 5mg and indapamide MR 1.5mg per day, or amlodipine 5mg, increased to 10mg if needed. Subsequent treatment was decided on a patient-specific basis, taking into account previous treatment trials and treatment responses. I notified the participant's GP of any proposed medication changes, and the GP provided prescriptions to participants.

If the target blood pressure was consistently achieved after a minimum of one month of monitoring, telemetric HBPM devices were either collected and conventional monitors issued in their place, or connectivity was deactivated so the devices functioned as conventional HBPM monitors. This was usually done at the three-month follow-up visit unless extenuating circumstances resulted in a need for prolonged monitoring and further treatment to achieve the blood pressure target. Participants were then advised to use the conventional home BP monitors weekly (Appendix 2.14) at their discretion to allow them to assess their blood pressure and contact their GP with any concerns about high/low readings. The responsibility for blood pressure treatment returned to the GP after the end of the intensive telemetric HBPM period, but I remained available for advice if participants contacted me during that time.

A protocol amendment was submitted to permit a delay for up to 12 additional months for participants to attend their final follow-up visit, because of COVID-19-related trial interruptions. GP letters were sent at three-month and 12-24 month follow-up including the participant's clinic blood pressure readings. When an in-person follow-up visit was not possible due to COVID-19 restrictions, telephone-based follow-up was permitted after being approved in a protocol amendment. In this instance, two test readings on the ABPM machine, performed by the patient or their carer for this purpose at the time of assessment, were used instead of the two clinic readings at three-month and/or 12-24-month follow-up. If the participant refused to undergo ABPM or was not capable of fitting the machine at home, two readings on a conventional home blood pressure monitor

were permitted to be taken by the patient during the time of the telephone assessment. Cognitive assessment in this scenario was performed using a 22-point Telephone Montreal Cognitive Assessment.

6.3.5 Outcomes

The primary outcome of the BP-monitoring part of the PROHIBIT-ICH trial was the change in assessment blood pressure from baseline to three-month follow-up in the intervention arm compared to the control arm.

Secondary blood pressure efficacy outcomes included:

(i) the magnitude of difference in mean daytime blood pressure measured on three-month ABPM in the intervention arm versus the control arm compared with baseline ABPM;

(ii) the magnitude of difference in mean daytime blood pressure measured on 12-month ABPM in the intervention arm versus the control arm compared with baseline ABPM;

(iii) the number of BP-lowering drugs at three-month and 12-24-month follow-up visits.

Additional outcomes comprised clinical endpoints (recurrent vascular events and cognition), feasibility endpoints (predefined criteria: <30% dropout from the intervention arm before one month; participant approval of the monitoring process in ≥70% of those randomised to the intervention arm), and safety endpoints (serious adverse events related to reducing blood pressure in the intervention arm, cognitive function change since baseline, and a composite of all recurrent major cerebrovascular and cardiovascular events). In this chapter, I will only report the preliminary blood pressure efficacy and safety endpoints.

6.3.6 Statistical analysis

It was estimated that 112 participants (56 per group, before allowing for attrition) would be required to detect a mean difference in systolic blood pressure of 10 mm Hg between the intervention and control arms (and standard deviations of 10 mm Hg and 15 mm Hg, respectively) at three-month follow-up.

Analysis was performed according to the intention to treat principle. The difference in change from baseline blood pressure between randomised groups at three-month follow-up was compared using paired t-tests. Proportions of adverse events and recurrent events between randomised groups were compared using Fisher's exact test. Randomised groups were compared for the mean number of BP-lowering drugs at three-month and one-year follow-up visits using t-tests and paired t-tests (for comparisons with baseline treatment).

The anticipated study sample size was not reached for this interim analysis; therefore, subgroup analyses were not performed and results were interpreted in the light of the resulting limited power for all outcome analyses. All analyses were performed using Stata version 16.1.

6.4 Results

Of 6972 people assessed for eligibility on hospital wards, clinics, and previous trial screening logs, 6913 (99.2%) were excluded by the research team for not meeting the inclusion criteria (5820, 84.2%), declined to participate (558, 8.1%), or died before being approached or providing consent (535, 7.7%). 59 participants from ten hospital research sites (range 1-11 per site) entered the trial (Figure 6-2).

The trial profile is shown in Figure 6-3; five (8.5%) randomised participants were lost to follow-up during, two in the intervention arm and three in the control arm, of whom four withdrew and one died due to recurrent ICH (control arm). Primary outcome data were available for 49 (83.1%) participants; seven participants had not yet attended their three-month follow-up assessment by the time of writing of this interim analysis, and three participants withdrew before the three-month follow-up.

Baseline characteristics of participants are shown in Table 6-1; overall, these were well matched between groups, aside from higher baseline blood pressure in the intervention arm (only significant for diastolic blood pressure on awake ABPM), which was taken into account by the pre-specified use of paired analysis of the primary outcome. The mean age was 66.4 (SD 13.3) years, and 41 (69.5%) participants were male. 32 (54.2%) of qualifying events were lobar ICH, and the median interval from the date of ICH to randomisation was 34 (IQR 8-116) days.

The mean of the two sitting clinic readings at baseline was 149.1/86.9 (SD 16.7/12.1) mmHg, and 48 (81.4%) of participants were prescribed antihypertensive treatment at the time of the baseline visit (mean [SD] number of agents 1.3 [0.8]). There were no important differences in baseline characteristics between participants who had a three-month assessment blood pressure recording for the primary outcome, versus those who did not (Table 6-1).

By the three-month follow-up, there was a significantly greater reduction in assessment blood pressure in the intervention group (20.4/8.6 [SD 21.4/10.6] mmHg) than in the control group (7.1/0.5 [SD 17.5/8.9] mmHg, p=0.021/p=0.006, Table 6-2). This result was maintained to 12-24-month follow-up for systolic blood pressure (25.0 [SD 19.8] mmHg reduction versus 10.8 [7.1] mmHg, p=0.053), albeit not statistically significant due to the small sample size, and not for diastolic blood pressure (8.7 [SD 14.3] versus 11.4 [13.1] mmHg, p=0.89). A more modest blood pressure reduction was found for three-month awake ABPM assessment (14.9/6.5 [SD 18.3/8.5] vs 3.7/0.0 [17.1/11.6] mmHg, p=0.050/0.054). There was no significant difference in three-month assessment BP, however, between the intervention (131.2/77.9 [SD 15.7/8.3] mmHg) and control groups (131.2/83.4 [SD 16.3/14.8] mmHg, p=0.21/p=0.12).

Greater reductions in blood pressure in the intervention group versus the control group corresponded to more frequent increases in antihypertensive medications. Participants in the intervention group were prescribed a mean of 2.1 (SD 1.0) BP-lowering drugs by three-month follow-up, compared to 1.7 (0.7) in the control group (Table 6-3). This equated to a mean increase of 0.9 (1.0) versus 0.3 (0.6) drugs from baseline in the intervention versus the control group (p=0.016), or a 1.1 (0.9) versus 0.3 (0.5) increase (p=0.0001) when the number of drugs was adjusted for the number of full-dose equivalent medications (the conversion schema for every drug used in the trial is outlined in Table 6-4). In the subset of patients for whom 12/24-month follow-up data were available, the difference in the increase of the dose-adjusted number of drugs from baseline persisted to this follow-up (1.2 [0.8] versus 0.2 [0.4], p=0.004).

Adverse events during follow-up were more frequent in the intervention group (18/29 [62.1%]) compared to the control group (6/30 [20.0%], p=0.001). There was one recurrent ICH in each group, and that ICH was fatal in the participant in the control group (Table 6-5). When restricting adverse events to common side effects of BP-lowering drugs (dizziness/faintness/fatigue, lower limb oedema, dry cough, postural

hypotension/falls, and electrolyte disturbances), these were 3.8 (95% CI 1.2-15.5) times more likely to occur in the intervention versus the control group (p=0.019). Feasibility issues regarding HBPM and ABPM at each follow-up that arose in this trial are outlined in Table 6-6 and Table 6-7.

6.5 Discussion

This blood pressure analysis of the currently-recruiting PROHIBIT-ICH trial, the first dedicated trial either of HBPM or long-term blood pressure lowering in ICH, has shown that the use of telemetric HBPM with guided antihypertensive therapy to achieve a more stringent blood pressure target in ICH survivors results in greater reductions in blood pressure by three-month follow-up than usual care, and such differences appear to persist beyond one year. Moreover, participants in this trial who underwent guided HBPM were more frequently treated with antihypertensive agents during this period than those who received usual care. However, the pre-specified blood pressure target (mean blood pressure <120/80 mm Hg) was not achieved on average in the intervention group, and there was a higher burden of adverse events compared with those assigned to usual care. Furthermore, this is an underpowered interim analysis, so the findings must be interpreted with caution.

HBPM has previously been shown to improve blood pressure control when combined with systematic antihypertensive medication titration in primary care. A UK randomised controlled trial of blood pressure home self-monitoring (with or without telemetric monitoring) versus usual clinic readings to guide medication titration in individuals with poorly controlled hypertension in primary care demonstrated significantly lower systolic blood pressure in the telemetric monitoring group (-4.7 mm Hg [95% CI -7 to -2.4]) than in the usual care group after 12 months,[227] consistent with the findings of an earlier, smaller UK trial of telemonitoring, using 6-month ABPM as the primary outcome.[341] However, no such BP-lowering benefit has been observed in studies that included patients with a history of stroke.[238, 239, 331]

In Chapter 5:, I outlined how centrally managed, telemetric HBPM-guided, BP-lowering after TIA or minor stroke was feasible, safe, acceptable to patients, and achieved sustained blood pressure control to guideline targets. These interim results provide randomised evidence that further support the BP-lowering efficacy of HBPM-guided

antihypertensive treatment in high-risk patients after stroke, and in particular after ICH, where the impact of reducing blood pressure on recurrent vascular events is likely to be even greater.[35]

Although the between-group assessment systolic blood pressure difference at three-month follow-up (5.9 mmHg) was lower than anticipated (10 mmHg) in my power calculations, baseline imbalance of systolic blood pressure between groups resulted in more impressive blood pressure reductions from baseline to three-month follow-up in the intervention group. Indeed, the reduction in clinic systolic blood pressure of 20 mmHg between baseline and three-month follow-up in this trial is greater than that observed in the intervention arm of any of the trials comparing HBPM after stroke to usual care (systolic blood pressure reduction range 1.7-10.2 mmHg),[239, 290, 331] and was similar to the blood pressure reduction in clinic blood pressure achieved between baseline and three-month follow-up in TIA and minor stroke in the COMMIT study (24.3 mmHg), as outlined in Chapter 5:. The discrepancy between the results of PROHIBIT-ICH and previous trials might relate to higher baseline blood pressure in ICH that is more amenable to greater reductions with treatment, and/or a more intensive monitoring and treatment strategy, similar to that performed in the COMMIT study. However, treatment to target (<120 mmHg) in this trial was limited by adverse events in over 60% of the patients in the intervention group, many of them directly related to BP-lowering treatment. I intend to assess cognitive data and other clinical and safety outcomes, and their association with the extent of blood pressure reduction, on trial completion.

Strengths of this study include the wide entry criteria for baseline blood pressure and extent of disability, which, along with the fact that many participants were elderly and 25% were from ethnic minorities, ensures the generalisability of the findings to current post-acute ICH clinical practice. In addition, the trial intervention was simple and pragmatic; the use of a real-time blood pressure telemonitoring system that was easy to use provided valid and reliable blood pressure data, while overcoming the problems of

incomplete/imprecise recordings in conventional HBPM,[220-222] and the intervention (centrally-guided blood pressure treatment recommendations to GPs) was achievable even in a multi-site setting. The use of ambulatory blood pressure monitoring for secondary blood pressure outcome measures, as opposed to reliance on clinic blood pressure alone as found in comparable trials,[227, 239] was another strength. The main limitation of this interim analysis is that it is underpowered for all outcomes. This also precluded any subgroup analyses for this report. Recruitment to the trial has been slower than anticipated and further hindered by a long recruitment suspension due to COVID-19. Clinical trials in ICH face unique challenges and often encounter recruitment difficulties; a less common and more severe on average condition results in a sizeable proportion of patients being ineligible,[342, 343] and the low recruitment rate among almost 7000 screened patients in PROHIBIT-ICH was mostly attributable to ineligibility.

In conclusion, in Chapter 5: I have identified telemetric home monitoring as a promising strategy to facilitate HBPM and optimise medication to better control blood pressure after TIA and minor stroke, and this interim report of a randomised controlled trial provides tentative evidence supporting the feasibility and efficacy of this strategy in more severely impaired patients with ICH, as well as on transferability to multiple centres beyond the previous research setting in Oxfordshire. Further recruitment and collection of safety, feasibility, BP-lowering efficacy, and imaging data over the next year will afford more power to these analyses and will allow me to address the question of whether using HBPM to achieve intensive blood pressure control after ICH is associated with improved outcomes.

6.6 Tables

Table 6-1 Baseline characteristics

	All participants			Participants with clinic BP at 3-month follow-up		
	Usual care (n=30)	**Intervention (n=29)**	**p-value**	**Usual care (n=25)**	**Intervention (n=24)**	**p-value**
Demographics						
Male sex, n (%)	20 (67%)	21 (72%)	0.63	16 (64%)	17 (71%)	0.61
Age, mean (SD)	67.7 (14.6)	65.1 (11.8)	0.46	70.08 (13.3)	66.3 (12.2)	0.3
Ethnicity, n (%)						
White	22 (73%)	22 (75%)	0.61	19 (76%)	20 (83%)	0.54
Black	3 (10%)	4 (14%)		2 (8%)	0 (0%)	
Asian	4 (13%)	0 (0%)		4 (16%)	2 (8%)	
Other	1 (3%)	3 (11%)		0 (0%)	2 (8%)	
ICH characteristics						
Location						
Lobar	14 (47%)	18 (62%)	0.24	12 (48%)	13 (54%)	0.67
Non-lobar	16 (53%)	11 (38%)		13 (52%)	11 (46%)	
Cerebellar	*2 (13%)*	*2 (18%)*	*0.68*	*1 (8%)*	*2 (18%)*	*0.44*
Days from ICH to randomisation, mean (SD)	108 (222)	65 (146)	0.38	119 (241)	72 (159)	0.43
Modified Rankin score, mean (SD)						
Pre-ICH	1.2 (0.7)	1.1 (0.4)	0.45	1.3 (0.7)	1.1 (0.5)	0.45
Baseline	2.6 (1.0)	2.1 (1.0)	**0.04**	2.6 (1.0)	2.2 (1.0)	0.21
Medical history						
Prior hypertension	19 (66%)	14 (48%)	0.18	17 (68%)	12 (50%)	0.2
Diabetes mellitus	4 (14%)	1 (4%)	0.17	3 (12%)	0 (0%)	0.086
Atrial fibrillation	2 (7%)	3 (10%)	0.64	2 (8%)	3 (13%)	0.6
Hypercholesterolaemia	11 (38%)	6 (21%)	0.24	9 (36%)	5 (21%)	0.33
Dementia/cognitive impairment	0 (0%)	1 (3%)	0.31	0 (0%)	1 (4%)	0.3
Epilepsy/seizures prior to ICH	1 (3%)	1 (3%)	0.99	1 (4%)	0 (0%)	0.32
Myocardial infarction / peripheral vascular disease / ischaemic stroke	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Medication history						
Antiplatelet therapy pre-ICH	5 (17%)	4 (14%)	0.72	5 (20%)	3 (13%)	0.48
Anticoagulant therapy pre-ICH	4 (14%)	3 (10%)	0.69	4 (16%)	3 (13%)	0.73
Antihypertensive therapy pre-ICH	25 (86%)	23 (79%)	0.49	21 (84%)	19 (79%)	0.66
History of intolerance to antihypertensive drugs	1 (3%)	5 (17%)	0.08	1 (4%)	5 (21%)	0.07

Lifestyle factors						
Smoking						
Current	1 (3%)	3 (10%)		0 (0%)	2 (8.3%)	
Former	13 (45%)	7 (24%)	0.19	12 (48%)	5 (21%)	0.07
Never	15 (52%)	19 (66%)		13 (52%)	17 (71%)	
Alcohol: current drinker	16 (55%)	18 (64%)	0.48	13 (52%)	17 (74%)	0.12
Alcohol: units per week, mean (SD)	7.9 (15.6)	5.1 (8.3)	0.39	8.7 (16.8)	5.7 (8.9)	0.44
Recreational drug use (cannabis)	3 (10%)	0 (0%)	0.08	3 (12%)	0 (0%)	0.09
Baseline BP mmHg, mean (SD)						
Clinic, systolic	145.9 (18.6)	152.2 (14.2)	0.16	144.2 (18.6)	151.6 (14.8)	0.13
Clinic, diastolic	85.6 (15.6)	88.1 (8.9)	0.43	83.9 (13.1)	86.5 (8.3)	0.41
ABPM awake, systolic	145.0 (15.1)	153.1 (19.6)	0.1	143.2 (13.9)	151.6 (19.9)	0.11
ABPM awake, diastolic	82.1 (11.1)	89.5 (12.7)	**0.03**	80.1 (9.4)	87.8 (11.4)	**0.02**

Ambulatory blood pressure monitoring (ABPM); standard deviation (SD); blood pressure (BP)

Table 6-2 Mean blood pressure at baseline, 3-month, and 12-24-month follow-up

	Baseline	3-month follow-up	12-month follow-up	Baseline to 3-month reduction	p-value, intervention versus control	Baseline to 12-24-month reduction	p-value, intervention versus control
Clinic assessment							
n	*59*	*49*	*20*	*49*		*20*	
Systolic blood pressure, mmHg, mean (SD)							
Intervention group	152.2 (14.2)	131.2 (15.7)	131.9 (12.8)	20.4 (21.4)	**0.021**	25.0 (19.8)	0.053
Control group	145.9 (18.6)	137.1 (16.3)	133.3 (19.2)	7.1 (17.5)		8.7 (14.3)	
Diastolic blood pressure, mmHg, mean (SD)							
Intervention group	88.1 (8.9)	77.9 (8.3)	77.3 (4.6)	8.6 (10.6)	**0.006**	10.8 (7.1)	0.89
Control group	85.6 (15.6)	83.4 (14.8)	75.8 (12.2)	0.5 (8.9)		11.4 (13.1)	
Awake ABPM assessment							
n	*51*	*44*	*22*	*41*		*21*	
Systolic blood pressure, mmHg, mean (SD)							
Intervention group	153.1 (19.6)	135.4 (13.1)	135.2 (11.2)	14.9 (18.3)	**0.05**	21.4 (23.3)	**0.041**
Control group	145.0 (15.1)	140.4 (13.3)	138.6 (20.0)	3.7 (17.1)		3.7 (10.7)	
Diastolic blood pressure, mmHg, mean (SD)							
Intervention group	89.5 (12.7)	81.0 (7.3)	79.3 (5.3)	6.5 (8.5)	0.054	10.8 (11.2)	**0.007**
Control group	82.1 (11.1)	80.1 (9.4)	82.3 (9.6)	0.0 (11.6)		-1.6 (7.1)	

Ambulatory blood pressure monitoring (ABPM); standard deviation (SD); blood pressure (BP). Analyses of BP reductions are restricted to those participants with complete data for both investigations.

Table 6-3 Blood pressure medication use at baseline, 3-month, and 12-24-month follow-up

	Baseline	3-month follow-up	12-month follow-up	Baseline to 3-month increase	p-value, intervention versus control	Baseline to 12-24-month increase	p-value, intervention versus control
Clinic assessment							
n	*58*	*50*	*20*	*50*		*20*	
Number of antihypertensive medications (mean, SD)							
Intervention group	1.2 (0.8)	2.1 (1.0)	2.5 (0.9)	0.9 (1.0)	**0.016**	1.1 (0.9)	**0.011**
Control group	1.4 (0.8)	1.7 (0.7)	1.6 (0.9)	0.3 (0.6)		0.1 (0.4)	
Dose-adjusted number of antihypertensive medications (mean, SD)							
Intervention group	0.9 (0.7)	2.1 (1.2)	2.3 (1.2)	1.1 (0.9)	**0.0001**	1.2 (0.8)	**0.004**
Control group	1.1 (0.8)	1.3 (0.7)	1.3 (1.0)	0.3 (0.5)		0.2 (0.4)	

Standard deviation (SD); blood pressure (BP). Analyses of BP reductions are restricted to those participants with complete data for both investigations. The dose-adjustment formula is provided in Table 4.

Table 6-4 Full dose equivalent adjustment table for included participants

	Dose equivalent								
Drug class, dose (mg)	**0.125**	**0.25**	**0.5**	**0.6**	**0.75**	**1**	**1.25**	**1.5**	**2**
Angiotensin-converting enzyme inhibitors									
Lisinopril		5	10		15	20		40	80
Ramipril		2.5	5		0.75	10			
Perindopril erbumine		2	4			8			
Enalapril		5	10			20			
Angiotensin receptor antagonists									
Valsartan		40	80		160	240			320
Losartan			50			100			
Candesartan		8	16		24	32			
Calcium channel antagonists									
Amlodipine		2.5	5		7.5	10			
Lercanidipine			10			20			
Nifedipine (formulation dependent)		20	40/45	60		80/90	120		
Diltiazem (formulation dependent)				200	240	240/300			
Diuretics									
Indapamide						2.5			
Bendroflumethiazide						2.5			5
Furosemide			20			40			80
Bumetainde						1			
Beta receptor antagonists									
Bisoprolol	1.25	2.5	5			10			
Alpha receptor antagonists									
Doxazocin			2			4	6	8	16

Table 6-5 Adverse events during follow-up

	Intervention group		Control group	
	n	**%**	**n**	**%**
Dizziness / faintness / fatigue	10	50.0%	1	12.5%
Lower limb oedema	*2*	10.0%	2	25.0%
Dry cough	2	10.0%	1	12.5%
Urinary frequency	2	10.0%	0	0.0%
Recurrent ICH / death	1	5.0%	1	12.5%
Headache	1	5.0%	1	12.5%
Diarrhoea	1	5.0%	1	12.5%
Loss of vision	1	5.0%	0	0.0%
Pruritus	0	0.0%	1	12.5%
Falls	0	0.0%	0	0.0%
Electrolyte disturbance	0	0.0%	0	0.0%
Total	20	100	8	100
Total number of patients with at least 1 adverse event	*18/29*	*62.10%*	*06/30*	*20.00%*

Table 6-6 Feasibility issues regarding home BP monitoring

Issue encountered during PROHIBIT-ICH	Number of participants in the intervention arm (%)	Action taken
HBPM telemetric kit technical issues/failure	10 (34.4%)	(i) Advised relocation of kit in participant's home / connect via Ethernet cable
		(ii) New hub device shipped to the participant
		(iii) Wrong size/type of BP cuff given to the participant in error by site, new equipment shipped
Poor adherence to monitoring / delayed commencement of monitoring / other individuals using the participant's monitor	5 (17.2%)	(i) Frequent phone calls to encourage adherence / explain the procedure again
Delays in securing contact with the participant's GP by phone and/or delays in patient appointments to receive an updated prescription	6 (20.7%)	(i) Participant sought an appointment with an alternative GP at the practice or locum GP
		(ii) Sought email addresses for GPs from practice administrators
Pharmacy stock issues of amlodipine causing delays in starting treatment	2 (6.9%)	(i) Encourage participants to attend alternative pharmacies
Nationwide shortage of nifedipine requiring an alternative formulation to be prescribed and a temporary dose reduction	1 (3.4%)	(i) Trial site hospital pharmacy contacted for emergency supply
		(ii) Avoid new prescriptions of nifedipine
Nationwide shortage of valsartan	1 (3.4%)	(i) Sought supply from other pharmacies
		(ii) Switched prescription to losartan
		(iii) Avoid new prescriptions of valsartan
Medication side effects prompting self-discontinuation of treatment	4 (13.8%)	(i) Highlighted the need for participants to contact the Oxford BP monitoring centre before discontinuing treatment
Medications reduced by GP or local site investigator	2 (6.8%)	(i) Participant advised to contact the Oxford BP monitoring centre when changes are made by other prescribers during the trial period
Lapses in telemetric BP monitoring due to trips overseas	2 (3.4%)	(i) Participants encouraged to use the BP monitor (without the telemetric hub) when abroad where possible

Table 6-7 Feasibility issues regarding 24-hour ambulatory BP monitoring

Assessment	Number of participants	Reason for missing data in PROHIBIT-ICH
Baseline	3	The participant did not tolerate monitoring on the first attempt (removed monitor after insufficient readings taken)
	3	Monitor not set to 'automatic' mode (only test reading registered), or switched off at internal battery. 2nd monitor was sent to the patient, but taken off prematurely or refused.
	2	Refused 1st attempt ABPM
	1	Withdrew before baseline ABPM
3-month follow-up	4	Refused follow-up ABPM (hourly readings on HBPM used in lieu in one participant, as per protocol amendment)
	2	Withdrew before 3-month ABPM
	1	Virtual 3-month follow-up due to COVID-19, and patient unable to fit monitor themselves
12-month follow-up	2	Withdrew before 12-month ABPM
	2	Refused follow-up ABPM

Blood pressure (BP); ambulatory BP monitoring (ABPM).

6.7 Figures

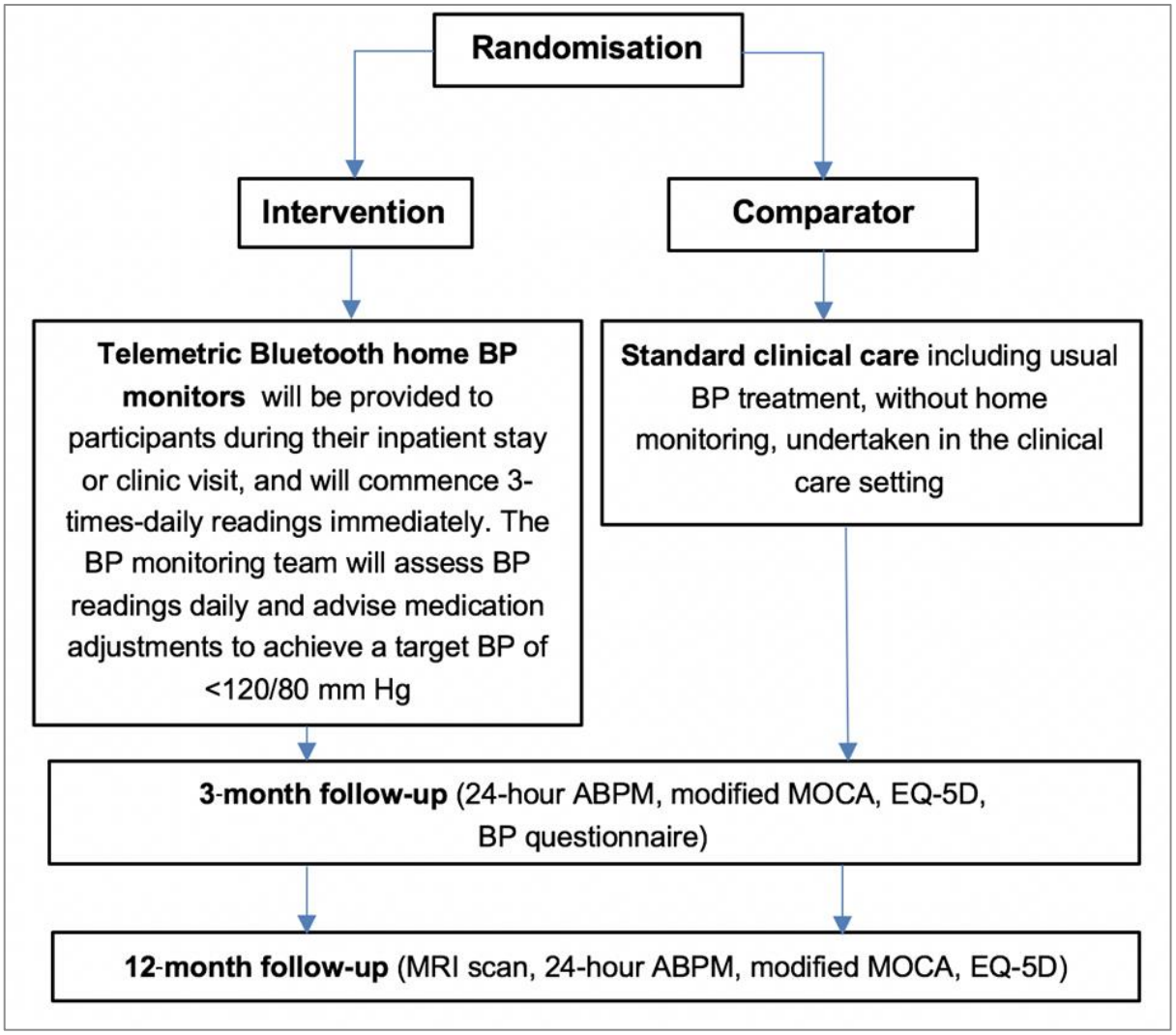


Figure 6-1 PROHIBIT-ICH trial procedure

Blood pressure (BP); ambulatory blood pressure monitoring (ABPM); Montreal cognitive assessment (MoCA); EuroQol standardised measure of health-related quality of life (EQ-5D).



Figure 6-2 PROHIBIT-ICH trial sites and recruitment

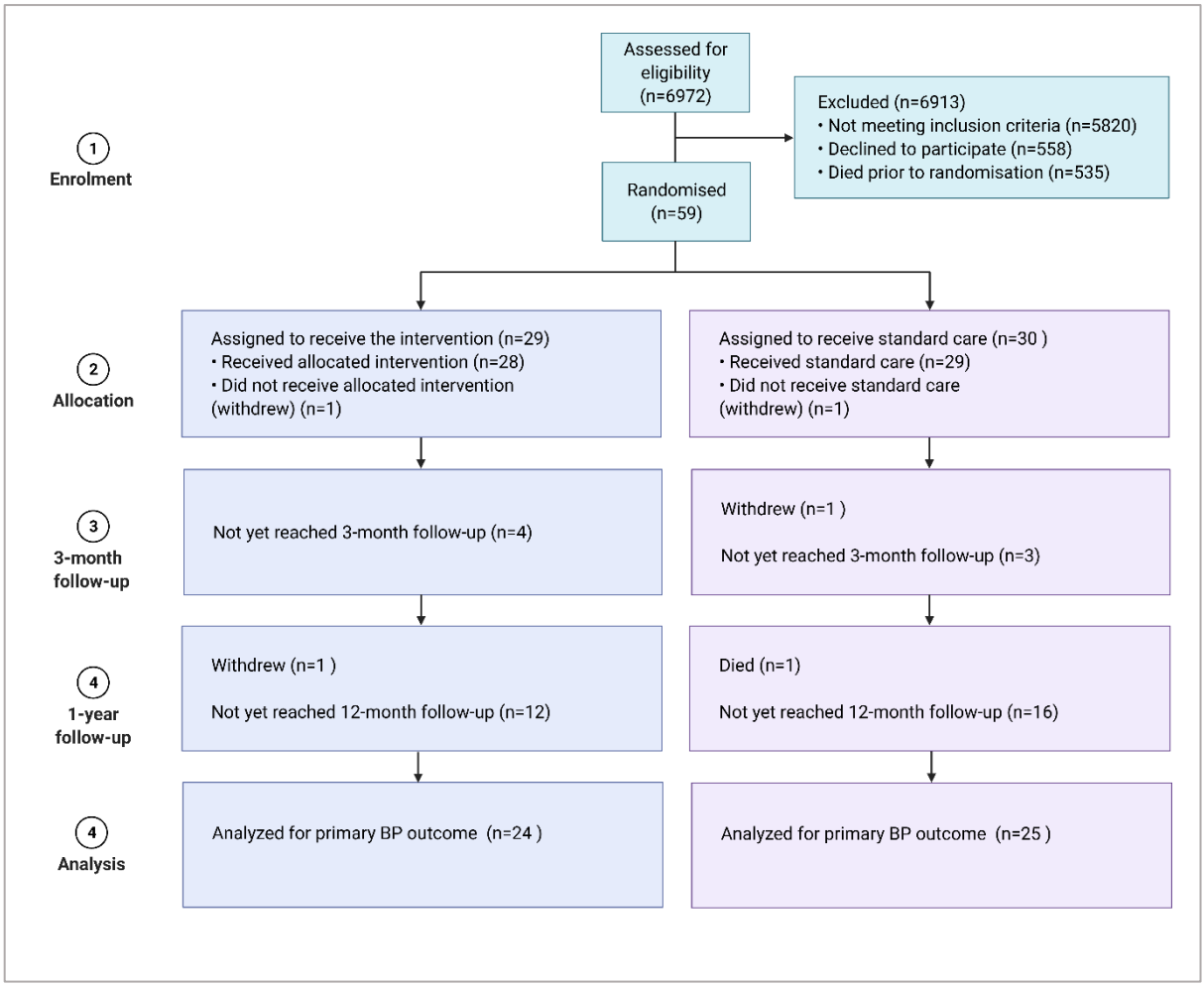


Figure 6-3 PROHIBIT-ICH interim trial profile

Chapter 7: Durability of telemonitoring-guided blood pressure control after TIA and stroke: long-term treatment adherence and recurrent vascular events (Centrally Observed home telemetric Monitoring of blood pressure to Manage Initial Treatment (COMMIT) study)

7.1 Abstract 258
7.2 Introduction 260
7.3 Methods 262
7.3.1 Study design and participants 262
7.3.2 Procedures 262
7.3.3 Statistical analysis 264
7.4 Results 267
7.5 Discussion 274
7.6 Tables 280
7.7 Figures 293

7.1 Abstract

Background: Blood pressure-lowering medications reduce the risk of recurrent vascular events after transient ischaemic attack (TIA) and stroke. However, rates of discontinuation of these medications are high in the months and years following cerebrovascular events. There is a considerable risk of recurrent stroke despite advances in secondary prevention treatment, but it is uncertain to what extent, if any, that poor medication adherence accounts for this. I aimed to assess the association of long-term adherence to blood pressure-lowering drugs with vascular risk after TIA and minor stroke, in a population with initial intensive home blood pressure monitoring (HBPM)-guided control.

Methods: Consecutive eligible patients with acute TIA or minor stroke in a population-based study (Oxford Vascular Study) underwent a programme of telemetric HBPM-guided antihypertensive therapy, with a target blood pressure of <130/80 mmHg, for at least one month or until target blood pressure was achieved. 24-hour ambulatory blood pressure monitoring (ABPM) was performed at one-month and one-year follow-up, and clinic blood pressure was measured up to ten-year follow-up. Secondary prevention medication adherence was assessed by patient interview and GP prescribing records at regular follow-up intervals. Discontinuing or decreasing antihypertensive therapy was related to the risk of recurrent major vascular events (MVE) on ten-year follow-up, with comparative adherence to lipid-lowering and antithrombotic agents used to mitigate healthy user bias.

Results: Of 1626 patients who completed the intensive HBPM-guided blood pressure-lowering treatment programme, 1618 (99.5%, mean/SD age=69.8/13.1) had sufficient follow-up data. Target blood pressure was sustained to one-year follow-up (daytime ABPM mean 129.2/74.1 mmHg). However, of 1435 (88.7%) patients taking blood pressure-lowering treatment by the end of the HBPM period, 496 (34.6%) had their antihypertensive treatment permanently reduced/stopped, and follow-up blood pressure

was substantially higher in these patients versus those who remained on an equivalent dose throughout (systolic blood pressure at ten-year follow-up 144.5 vs 134.7 mmHg, p=0.011 adjusted for age, sex, and baseline systolic blood pressure). Of 177 recurrent MVE in patients treated for hypertension, 89 (50.3%) occurred in those whose medication dose was reduced/stopped during 8279 person-years of follow-up, and 80 (89.9%) of these medication decreases occurred in the same or preceding follow-up interval as that of the recurrent MVE. Decreasing/stopping antihypertensive therapy after the HBPM period in patients who remained adherent to both antithrombotic and lipid-lowering treatment was associated with a 3.01 (95% CI 1.98-4.62, p<0.0001) times greater risk of MVE, adjusted for vascular risk factors, with the strongest associations observed for patients who were hypertensive (blood pressure ≥135/85 mmHg) on baseline three-day HBPM (HR 4.11, 2.46-6.85, p<0.0001). Overall, 42.8 (25.0-59.4)% of the risk of MVE in hypertensive patients adherent to all other secondary prevention medications was attributable to reducing or stopping blood pressure-lowering treatment.

Conclusion: After accounting for healthy user bias and assuming causality, over 40% of recurrent vascular events after TIA and minor stroke were attributable to poor adherence to blood pressure medications in patients with hypertension. An early intensive HBPM-guided treatment programme after TIA/stroke is unlikely to be sufficient to manage long-term blood pressure control alone, and some form of longer-term monitoring is advisable after cerebrovascular events to ensure continued adherence and to reduce the residual risk of recurrent events.

7.2 Introduction

Following a regimen of secondary prevention medications and lifestyle changes after transient ischaemic attack (TIA) and stroke should result in around an 80% relative risk reduction of recurrent events.[20] Despite this, the residual risk remains high, with almost a third of all strokes occurring in those with a prior event,[8, 9] and a particularly high risk is observed in those with inadequate blood pressure control.[19]

The main obstacle to reducing hypertension-associated morbidity is not a lack of effective treatments, but inadequate initiation of treatment and poor adherence to prescribed medications.[344, 345] Indeed, up to a third of people discontinue or reduce their antihypertensive treatment after TIA/stroke.[14, 18, 243] Most published research on the factors determining poor adherence after TIA/stroke focuses on patient- and drug-specific influences, with post-stroke cognitive impairment, disability, medication side-effects, and patient beliefs about treatment all being implicated.[245] However, institutional factors also play a role,[246] and it has been suggested that the majority of so-called 'nonadherence' to secondary prevention medications might be purposeful discontinuation on the advice of health care providers after discharge from hospital.[243] This poses the question: to what extent, if any, is a decrease or discontinuation of antihypertensive treatment after TIA/stroke contributing to residual risk?

This question would be impractical and ethically impossible to address in a randomised controlled trial and requires investigation in a population with a high burden of vascular events and high rates of intensively controlled hypertension. Observational studies reporting the effects of poor treatment adherence on the risk of adverse outcomes are, however, subject to 'healthy user' bias, i.e. adherence is a surrogate marker for typically unmeasured health-related behaviours that mediate risk.[346, 347] Therefore, I examined adherence to blood pressure-lowering medications and long-term risk of recurrent vascular events, minimising bias by accounting for adherence to other secondary prevention medications, in a population-based study of initial telemetric-home blood

pressure monitoring (HBPM) guided intensive blood pressure control after TIA and minor stroke.

7.3 Methods

7.3.1 Study design and participants

The Oxford Vascular Study (OXVASC) is a longitudinal, population-based cohort study of the incidence and outcome of all acute vascular events in a defined population of 92,728 individuals, registered with around 100 general practitioners in nine primary care practices in Oxfordshire, UK.[264, 298] OXVASC was approved by the Oxfordshire research ethics committee, including the HBPM substudy (OREC A: 05/Q1604/70). Written, informed consent or assent from relatives was obtained for all participants for study interview and follow-up, including ongoing review of primary care and hospital records and death certificate data.

7.3.2 Procedures

Consecutive patients with TIA or non-disabling stroke were prospectively recruited to this blood pressure-monitoring study between April 1st 2008 and March 31st 2019 from OXVASC. Case ascertainment of TIA/stroke was done using multiple overlapping methods and is near-complete for events reaching medical attention.[265, 299] These methods included a rapid access daily clinic to which general practitioners and the local emergency department referred individuals with suspected cerebrovascular events, daily searches of emergency departments, relevant hospital wards, eye hospital attendances, radiographic or vascular surgical investigations or procedures, and monthly searches of primary care practice diagnostic codes and referrals to acute and community hospitals.

All consenting patients underwent a standardised medical history and examination, ECG, and blood tests. Patients underwent a stroke protocol MRI brain scan and contrast-enhanced MRA (or CT brain scan and either a carotid Doppler ultrasound or CT-angiogram when MR imaging was contraindicated), an echocardiogram, and five

days of ambulatory cardiac monitoring. All patients were assessed by a study physician and reviewed by the senior study neurologist (Professor Peter Rothwell).

Patients were followed up face-to-face at one, three, six, 12, 60, and 120 months. Secondary prevention medication adherence was assessed at each follow-up by non-judgemental dialogue with patients and their families, and electronic hospital and primary care prescribing records were assessed. Recurrent cardiovascular events were ascertained at each follow-up and by multiple methods of ascertainment.[265, 299]

Clinic blood pressure was measured at baseline and each follow-up clinic visit in the non-dominant arm by trained personnel, with two measurements made five minutes apart in the sitting position, after five minutes of rest. Patients were provided with a Bluetooth-enabled, regularly-calibrated, telemetric blood pressure monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT, on the day of the baseline clinic assessment. After appropriate training on the day, they were asked to perform three home blood pressure readings over ten minutes, three times daily (after waking, midday, and evening).

Measurements were automatically transmitted by Bluetooth to a Raspberry Pi microcomputer hub, for secure transmission via a cellular network to a server hosting a password-protected website for review and download (OBS Medical, Abingdon, UK). Patients continued monitoring for at least one month, or until all possible efforts had been made to achieve target blood pressure thereafter.

The day before the one-month and one-year follow-up visits, ABPM was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by trained study personnel. Blood pressure was measured at 30-minute intervals during the day (07:00 to 23:00) and 60-minute intervals at night. Patients were asked to refrain from excessive activity during recordings and were asked to keep a diary of their day.

Hypertension was treated according to current guidelines,[95] initially based on baseline clinic readings and then according to HBPM, aiming for a target blood pressure <130/80 mmHg. Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a combination of perindopril arginine 5mg and indapamide 1.25mg, followed by amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion. Patients were generally advised to take their antihypertensive medication in the morning. Education was provided during the monitoring period to guide the patient on how to interpret their blood pressure readings.

At the end of the telemetric HBPM period, a conventional blood pressure monitor was provided to each recipient, and they were asked to record once weekly blood pressure readings during the first year of follow-up to guide their blood pressure control and to present to the OXVASC study team or their GP should they have concerns about their readings.

7.3.3 Statistical analysis

Clinic blood pressure at baseline and follow-up was calculated as the mean of the two sitting measurements during the assessment. HBPM readings for each participant were downloaded from the encrypted website and manually assessed to remove those with erroneous measures or incorrect date/time stamps (n=87, <0.1%). Recordings with systolic blood pressure <50 mmHg (n=3), diastolic blood pressure (diastolic blood pressure) >140 mmHg if pulse pressure <40 mmHg (n=5), and any pulse pressure <10 mmHg (n=6) were excluded.

The first three days of HBPM at baseline and the last 7 days of HBPM for each participant were used to assess mean blood pressure changes over the monitoring period, both to minimise effects of blood pressure treatment at baseline clinic and to equalise any diminution in the number of daily readings among participants at the end of the HBPM programme.

Mean daytime blood pressure on ABPM at one-month and one-year follow-up was derived after exclusion of artefactual measurements according to predefined criteria,[312] analogous to those used for HBPM.

Prior hypertension was defined as a diagnosis reported by the patient, prior antihypertensive treatment, or hypertension listed on the primary care list of diagnoses. Hypertension was defined at each time-point as mean blood pressure ≥140/90 mmHg for clinic readings, and ≥135/85 mmHg for HBPM and daytime ABPM, according to European guidelines.[59]

Reduction or withdrawal of major secondary prevention medications (antihypertensive, lipid-lowering, and antithrombotic drugs) after the HBPM period and before any recurrent vascular events, where present, were included in analyses if they were clinically significant and permanent during follow-up (i.e. temporary minor dose reductions or drug switches to another agent/class with comparable efficacy were not included). Discontinuation of antithrombotic treatment was only recorded if both antiplatelet and anticoagulant treatment were discontinued; for example, switching from an antiplatelet drug to an anticoagulant due to the detection of atrial fibrillation during follow-up was not coded as a treatment decrease.

Means, medians, and proportions of baseline characteristics were stratified according to decrease or discontinuation of secondary prevention medications during follow-up and compared using t-tests, Wilcoxon rank-sum tests, and chi-square tests, respectively. Logistic regression models and paired t-tests were used to determine the associations of reductions in secondary-prevention medications with hypertension characterised on the first three and last seven days of HBPM, mean follow-up blood pressure measured in clinic, or on ABPM, adjusted for age, sex, and vascular risk factors (history of hypertension, diabetes mellitus, smoking status, and any previous cardiovascular, peripheral vascular, or cerebrovascular events).

The risk of major vascular events (MVE: cardiovascular death, stroke, myocardial infarction, acute peripheral vascular events) was determined by Cox regression for reductions in antihypertensive medications during follow-up as a time-varying covariate, with adjustment for age, sex, and vascular risk factors. Follow-up systolic blood pressure was subsequently added to models to test if the association was mediated by a lapse in long-term blood pressure control, either measured on daytime ABPM for analyses restricted to the first two years of follow-up, or on clinic assessment for the entire study period, and fitted as a time-varying covariate.

The time at risk commenced from the end of the intensive HBPM monitoring period for each participant. Exposure time to reductions in preventive medications was defined as commencing at the mid-point of each follow-up interval, so that time discrepancies would be balanced on average, and sensitivity analyses were performed with exposure time commencing at the start and the end of each follow-up interval.

Models were stratified by hypertension status on HBPM, treatment intensification during HBPM, and achieved blood pressure reductions, and patients never treated with secondary prevention medications were excluded from survival analyses. Additional models compared antihypertensive treatment reductions to those of lipid-lowering and antithrombotic agents, or restricted inclusion to those with persistent adherence to other secondary prevention medications, to minimise any impact of a healthy user effect.

The fraction of MVE attributable to reductions in blood pressure-lowering medications, assuming causality by restricting to those participants who remained adherent to other secondary preventions, was estimated by *Pd*(hazard ratio−1)/hazard ratio*, where *Pd* represents the proportion of all MVE in the relevant population, and 95% confidence intervals were calculated by combining the 97.5% confidence intervals of both the prevalence and hazard ratio (Bonferroni inequality method).[348, 349] Missing data are reported and were not imputed. All analyses were performed using Stata version 16.1.

7.4 Results

Of 1833 patients with TIA or minor stroke attending the OXVASC clinic during the study period, 51 (2.8%) refused to take part in the blood pressure-monitoring study, and 126 (6.9%) were excluded due to early death, acute intercurrent illness, severe dementia, excessive physical disability, or residence outside of the study area (Figure 7-1). 1656 (90.3%) consented to home telemetric blood pressure monitoring, of whom 1626 (98.2%) continued measuring until at least their one-month follow-up clinic assessment. 736 (44.4%) of patients were maintained on telemetric HBPM beyond six weeks, and 236 (14.3%) up to or beyond three months due to intermissions in monitoring or delays in achieving target blood pressure control.

Of 30 (1.8%) patients who discontinued HBPM before their one-month follow-up, 13 withdrew from the study, nine were unable to tolerate HBPM for one month, four had acute intercurrent illness precluding blood pressure measurement, three died, and one was a resident in a nursing home in which assistance for HBPM was not available. Of 1626 patients who completed the intensive blood pressure monitoring programme, eight (<0.5%) were lost to follow-up, and 1618 (99.5%) had sufficient follow-up data to determine adherence to secondary prevention medication, so were included in the analysis cohort (Figure 7-1).

Median follow-up was 5.0 years (IQR 2.4-7.5), with 8279 total patient-years. Mean age at baseline clinic was 69.8 (SD 13.1) years, and 51.6% of participants were men (Table 7-1). 1609 (97.2%) attended their scheduled one-month follow-up assessment, of whom 1382 (85.9%) agreed to be fitted for 24-hour ABPM and tolerated monitoring. 1327 (80.1%) attended their one-year follow-up assessment, of whom 962 (72.5%) agreed to be fitted for repeat 24-hour ABPM and tolerated monitoring.

Of 802 (48.4%) participants not taking antihypertensive treatment at baseline, 537 (67.0%) were prescribed at least one agent before the one-month follow-up clinic, such

that 1340 (80.9%) of patients were treated. Overall, 1108 (66.9%) patients had their antihypertensive medications changed (i.e. either started, new agents prescribed, dosage alterations, or stopped) between their initial clinic assessment and one-month follow-up, of which 1044 (94.2%) was a net dosage increase and 64 (5.8%) was a net dosage decrease. By three-month follow-up, 1158/1344 (86.2%) patients assessed were taking antihypertensive treatment, and this proportion was relatively stable by six-month follow-up (1139/1355, 84.1%, Figure 7-2).

Mean blood pressure decreased across the period of telemetric HBPM-guided treatment (Figure 7-3), with significant reductions in clinic blood pressure between baseline and three-month assessments (24.2/11.9 mmHg, $p<0.0001$). Intensive blood pressure control (<130/80 mmHg) was achieved regardless of the measurement modality: three-month follow-up clinic mean (SD) 127.1/73.0 (16.5/10.7); last week of HBPM 125.8/73.5 (12.0/8.9); one-month daytime ABPM 129.2/73.8 (12.8/8.1), 12-month daytime ABPM 129.5/74.3 (13.3/8.0) mmHg.

Despite rapid blood pressure control to target, only 3.4% (56/1626) of patients fell during the first month of HBPM-guided treatment, of which no falls resulted in significant trauma. Nine (16.1%) falls were associated with treatment-induced hypotension. Two of these patients with hypotension-related falls required a reduction in antihypertensive medication, and there were a further 13 medication changes due to other possible hypotension-related symptoms (postural dizziness, presyncopal symptoms, general fatigue). Between one- and three-month follow-up, there were a further 48 falls. Six (12.5%) were associated with hypotension, of which three resulted in medication changes, and there were eight further reductions due to possible hypotension-related symptoms.

Overall, of 1435 (88.7%) patients taking antihypertensive treatment by the end of the intensive HBPM-guided treatment period, 496 (34.6%) had their treatment dose reduced permanently during extended follow-up, prior to any recurrent major vascular events,

where relevant, of whom 181 (36.5%) discontinued all antihypertensive agents. The initiator of treatment reduction and the rationale for the decision were unknown in the majority of cases, but among those for whom information was available, medication side-effects (38.5%), hypotension/falls (24.0%), and co-morbidity (21.9%) were the most common reasons, with reductions performed by the patient's GP in the majority (49.6%) of cases (Table 7-2). Among those participants for whom data were available on the reasons for stopping all blood pressure-lowering drugs, 44.2% was a decision of the patient themselves, and 32.7% was instigated by their GP. Of 1446 (89.4%) patients taking lipid-lowering agents by the end of the intensive HBPM-guided treatment period, 325 (22.5%) had their dose permanently reduced during follow-up, of whom 228 (70.2%) discontinued entirely. Of 1316 patients taking antithrombotic treatment, 54 (4.1%) stopped all agents permanently during follow-up, of whom two (3.7%) discontinued their anticoagulation treatment due to haemorrhage.

The majority of secondary prevention medication treatment dose reduction or discontinuation occurred beyond the one-year follow-up (Figure 7-4). Patients who decreased any secondary prevention medications during follow-up were marginally older than those who remained fully adherent to secondary prevention treatment (mean [SD] 70.8 [12.6] vs 69.2 [13.2] years, p=0.014), and were more likely to have a history of hypertension or antihypertensive treatment (67.1% vs 59.8%, p=0.003), but were otherwise similar (Table 7-3).

Of 474 patients who were taking secondary prevention therapy by the end of the intensive monitoring period and decreased either their dose of antihypertensive or lipid-lowering/antithrombotic treatment after one-month follow-up, but not both, those who decreased antihypertensives (n=307, 64.8%) were more likely to be older (72.7 [11.3] vs 70.0 [11.7] years, p=0.016) and diabetic (17.6% vs 10.8%, p=0.048) than those who decreased either lipid-lowering or antithrombotic treatment (n=167, 35.2%), but were otherwise similar (Table 7-4**,** Figure 7-5).

Overall, there were 200 recurrent major vascular events (MVE) after the period of intensive HBPM-guided treatment, of which 177 (88.5%) occurred in patients prescribed antihypertensive treatment by the end of this period. Of these, 89 (50.3%) MVE occurred in those whose antihypertensive medication dose was decreased before the recurrent vascular event (OR 2.00, 95%CI 1.44-2.78, p<0.0001, adjusted for age, sex, and vascular risk factors). 80 (89.9%) of the blood pressure-lowering medication reductions in those with recurrent MVE occurred in the same or preceding follow-up interval as that of the event (Table 7-5**,** Figure 7-6). Among 74 recurrent MVE in patients who decreased either their dose of antihypertensive or lipid-lowering/antithrombotic treatment after one-month follow-up, but not both, 62 (83.8%) occurred in those with blood-pressure-lowering drug reductions (OR 2.84, 95%CI 1.45-5.57, p=0.002, adjusted for age, sex, and vascular risk factors).

Reduction of antihypertensive treatment after the intensive monitoring period was strongly associated with hypertension on the first three days of HBPM (mean blood pressure ≥135/85 mmHg) in those with recurrent MVE (OR 4.08, 1.99-8.38, p<0.0001, adjusted for age, sex, prior hypertension, and other vascular risk factors, Table 7-6**,** Figure 7-7). This association was attenuated when hypertension was defined according to the last week of HBPM for each participant, where blood pressure was generally well-controlled aside from early adherence issues or medication side-effects/comorbidities precluding treatment (adjusted OR 1.37, 0.68-2.75, p=0.375, Table 7-6). There was also a strong association between hypertension and reduction of antihypertensive treatment (relative to reduction of lipid-lowering/antithrombotic treatment) in those with recurrent MVE (OR 7.36, 1.38-39.11, p<0.0001).

In patients without recurrent MVE during follow-up, however, there was no significant association between hypertension on first three-day HBPM and antihypertensive treatment reduction versus persistence (adjusted OR 0.97, 0.76-1.25, p=0.693), nor with

antihypertensive treatment versus lipid-lowering/antithrombotic treatment reduction (adjusted OR 0.97, 0.76-1.25, p=0.693).

The risk of MVE associated with reductions of antihypertensive medications during follow-up in time-dependent analyses is shown in Table 7-7. A reduction of antihypertensive medication dosage during follow-up, defined as occurring in the mid-point of each follow-up interval, was associated with a 2.77 (95%CI 1.96-3.91, p<0.0001) times higher risk of subsequent MVE, adjusted for age, sex, prior hypertension or treatment, and other vascular risk factors. This association was driven by patients reliably characterised as hypertensive by baseline three-day HBPM (HR 3.86, 2.55-5.85, p<0.0001, Figure 7-8), especially those who had their blood pressure-lowering treatment decreased and achieved a reduction in systolic blood pressure of ≥ 25 mmHg (HR 9.73, 3.36-40.14, p=0.002, Figure 7-9).

A similar association between antihypertensive dose reduction and the risk of MVE was observed in those who remained fully adherent to both lipid-lowering and antithrombotic drugs during the same follow-up period (HR 3.01, 1.98-4.62, p<0.0001, Table 7-7), and the strongest associations in this group were found for patients who were hypertensive on baseline HBPM (HR 4.11, 2.46-6.85, p<0.0001, Figure 7-10**,** Figure 7-11), and those who had a net blood pressure-lowering treatment intensification during the monitoring period (HR 3.44, 2.06-5.75, p<0.0001, Table 7-7). Additionally, patients who had their blood pressure-lowering treatment reduced had a 2.44 (1.45-4.10) times greater risk of MVE than those who had either their lipid-lowering or antithrombotic drugs, or both, reduced (Table 7-7).

When calculated as a population-attributable fraction, and assuming a causal association, 42.8% (95%CI 25.0 - 59.4%) of the risk of MVE in hypertensive patients adherent to all other secondary prevention medications was attributable to reducing or stopping blood pressure-lowering treatment.

A dose reduction in lipid-lowering agents was not significantly associated with an increased risk of recurrent MVE (HR 1.27, 0.85-1.89, p=0.249), but the strongest risk associations were seen for patients who permanently discontinued both antihypertensive and lipid-lowering treatment during follow-up versus those who continued to take both classes of medication (HR 3.00, 1.73-5.20, p<0.0001).

Despite sustained blood pressure control to target during the intensive monitoring period, long-term blood pressure control in survivors appeared to diminish over time, beyond expected blood pressure changes with increasing age: mean (SD) 12-month clinic blood pressure 130.1/73.7 (17.6/10.6), five-year clinic blood pressure 132.6/75.1 (20.2/11/0); ten-year clinic blood pressure 138.0/74.3 (22.3/11.6) mmHg. Blood pressure was significantly higher at follow-up in patients whose antihypertensive treatment was reduced before the blood pressure assessment in question compared to those who remained fully adherent, when measured both in clinic and on ABPM (the latter was only performed at one-year follow-up), and with and without adjustment for age, sex, and baseline blood pressure (Table 7-8). Moreover, the lapse in blood pressure control between the three-month follow-up and five-year follow-up assessments was substantially greater in those whose treatment was reduced or stopped compared to those who remained on the same net dosage (blood pressure increase of 11.2/4.8 mmHg vs 4.8/1.2 mmHg, p=0.001/0.003 adjusted for age, sex, baseline blood pressure).

To ascertain whether the association of decrease or discontinuation of antihypertensive medications with recurrent vascular events was indeed mediated through poor blood pressure control, analyses were restricted to the first two years of follow-up, where blood pressure was accurately characterised using ABPM, and where any survival or age-related effects on blood pressure during longer-term follow-up would be minimised. A reduction of blood pressure-lowering medications between the end of the intensive HBPM period and one-year follow-up was associated with an increased risk of recurrent

vascular events during the subsequent year compared to persistent adherence during this period (HR 2.92, 95%CI 1.52 – 5.63, p=0.001, adjusted for age, sex, vascular risk factors, and mean daytime systolic blood pressure on one-month ABPM). This association was substantially attenuated after adjustment for mean daytime systolic blood pressure on one-year ABPM (adjusted HR 1.03, 0.21 – 5.08, p=0.97, Table 7-9).

However, when performing the same analysis for the whole of the follow-up period, and adjusting using follow-up clinic systolic blood pressure as a time-varying covariate, the strength of the association remained unchanged, regardless of the commencement of follow-up time (Table 7-9).

Sensitivity analyses fitting the reduction in antihypertensive medication as a time-varying covariate to different points during follow-up intervals revealed similar results, with the weakest associations predictably observed when any reduction was conservatively allocated to the end of each interval (effectively reducing person-time for all analyses, Table 7-10).

7.5 Discussion

Over a third of patients reduced or discontinued their antihypertensive treatment during an average of five years follow-up after TIA or minor stroke, despite a programme of intensive HBPM-guided blood pressure treatment incorporating primary care physician involvement and patient education that achieved guideline targets of blood pressure control with minimal adverse events. The risk of recurrent vascular events was three times higher in participants whose blood pressure-lowering treatment was reduced versus those who remained adherent, in the presence of poorer long-term blood pressure control in those with poor adherence, even after adjusting for potential differences in these populations and restricting to patients who remained adherent to other secondary prevention medications.

This study addresses an important research question that cannot be readily answered in the setting of a randomised trial. Although there have been trials of medication withdrawal in other settings, such as for antidepressant drugs when potential enrolees felt well enough to consider stopping,[350] or for diuretics in older people without manifest hypertension or heart failure,[351, 352] dedicated trials of discontinuation of antihypertensive drugs are scarce.[353] Most are limited to wash-out phases in hypertension trials,[352, 354] or short-term dose reduction trials in otherwise healthy older people who were considered appropriate for mediation reduction.[353, 355] A low number of event rates impedes any definite conclusions about the risks of treatment discontinuation, and a recent Cochrane review of six trials has called for more research on populations with the greatest uncertainty regarding the balance of the risks of discontinuation versus the potential benefits of avoiding adverse events of blood pressure-lowering medications, especially older age-groups.[353] The exclusion of high-risk participants and the short follow-up in existing trials of medication deprescribing are both necessary for ethical reasons; the risk:benefit ratio of antihypertensive withdrawal in secondary prevention settings would be expected to be skewed in favour of persistent treatment in those at high risk of

recurrent vascular events, and the short-term effects of treatment withdrawal must be established before it would be appropriate to conduct a trial with longer follow-up. A few observational studies have examined withdrawal of antihypertensive treatment in older people over longer follow-up, but mostly excluded those with previous vascular events, so are not generalisable to a secondary prevention setting.[354]

My study, however, was well placed to investigate the effects of blood pressure-lowering medication withdrawal on vascular risk. The OXVASC population would be unsuitable for recruitment to most trials, but the high recurrent vascular event rate in this older, high-risk, TIA/stroke cohort affords much more power to risk estimations. In addition, there is a need to control the risk factor in question to reveal any potential harm of recrudescence. Inadequate prior hypertension treatment in previous studies is a possible explanation as to why most did not detect any association of risk with treatment withdrawal, and those which did report blood pressure over time found relatively modest incremental changes after treatment discontinuation.[353-355] In contrast, and as outlined in Chapter 5:, the population in the COMMIT study achieved levels of blood pressure control superior to those attained in normal clinical practice during the monitoring period, so the impact of treatment discontinuation will have been greater.

A criticism of observational studies that ascribe risk of adverse outcomes to poor treatment adherence is that much or all of the association might be due to healthy user bias.[346, 347] There are several factors in my study, however, which support a causal relationship between blood pressure-lowering treatment reductions and risk of recurrent major vascular events. First, the strength of the associations I observed for decreases in antihypertensive medications, a three times greater risk of major vascular events compared to persistence with treatment in those who remained adherent to other secondary prevention agents, and over double the risk compared to decreasing other agents, both adjusted for all measurable confounders, are unlikely to be entirely accounted for by unmeasured differences in those who remained adherent to

antihypertensive treatment. In fact, because of the methodology of this study, differences in unmeasured characteristics would have had to exist not just between those who adhered and those who didn't adhere to antihypertensive treatment, but between those who adhered to antihypertensive treatment versus those who adhered to lipid-lowering and antithrombotic treatment. Such differences are unlikely to exist, as previous studies in stroke populations have shown that adherence patterns to antihypertensive drugs mirror those of statins.[356] If anything, the magnitude of the effect in my study is greater than what would be expected from the 20-30% relative risk reductions observed in meta-analyses of trials of antihypertensive therapy versus placebo in populations with prior stroke.[11, 27] This might be due to an additive effect of some residual healthy user bias, but could also be due to an underrepresentation of the benefit of antihypertensive drugs in these secondary prevention trials. Earlier hypertension trials, which recruited people with severe hypertension who discontinued all previous medications before being randomised to a new agent or placebo, observed larger effect sizes as treatments were arguably being measured against a high risk of treatment discontinuation.[357] Reverse causality, whereby recurrent events might influence prior treatment discontinuation, is another possible explanation for the large observed associations in my study, but this should have been minimised by restricting analyses to participants who remained fully adherent to other agents. Second, the temporality of the relationship between antihypertensive discontinuation and recurrent vascular events in my study supports the presence of a causal association. 90% of the blood pressure-lowering medication reductions in those with recurrent MVE occurred in the same or preceding follow-up interval as that of the event, and associations were stronger when medication reduction was fitted as a time-varying covariate. Third, the findings were consistent whether patients who had their antihypertensive drugs decreased were compared to those who remained adherent, or to those who decreased other agents, as well as after adjustment for all measurable confounders. The association was not restricted to the subset of the population that stopped all

medications, for example, due to intercurrent illness, which might be expected if the risk was entirely mediated via reverse causation, and was observed even when restricting to those who remained fully adherent to lipid-lowering and antithrombotic treatment. Finally, the association is plausible, as it was observed only in participants who had a history of well-characterised hypertension using HBPM at baseline (and not hypertension on HBPM at the end of the monitoring period, where blood pressure was well controlled). Moreover, the association was completely attenuated after adjusting for follow-up blood pressure on ABPM over two-year follow-up, which suggests that achieved blood pressure is on the causal pathway.

A potential concern, however, is that I did not observe a meaningful reduction in the effect size after controlling for follow-up *clinic* blood pressure as a time-varying covariate over the whole follow-up period. This lack of effect mediation by follow-up clinic blood pressure has also been observed in a single study in a primary prevention setting and led the authors to conclude that the entirety of the association is mediated through a healthy user effect.[346] The apparently contradictory findings in my study can be reconciled in two ways. First, better characterisation of blood pressure on ABPM may facilitate more accurate detection of lapses in blood pressure control due to poor adherence, which might be masked due to inflated readings on clinic blood pressure assessment in patients with good home blood pressure control (as outlined in Chapter 2: Chapter 3: and Chapter 4:. Second, adjusting for follow-up blood pressure as a single time-varying covariate means that only the fraction of the information coded in the variable that corresponds to time points distal to medication reductions will contribute to its model-adjusting effects. This is further complicated by the fact that reductions in blood pressure-lowering medications that occurred shortly after a follow-up visit (for example if an OXVASC clinic review letter prompted a GP assessment to review current medications) might have triggered a recurrent vascular event prior to a subsequent follow-up visit, so an increase in blood pressure would not be detected. This issue will not have arisen in the model performed

over two years of follow-up, where all medication reductions occurred before one-year ABPM.

The main strengths of my study include the stringently controlled blood pressure in the months after cerebrovascular events as a result of the telemetric HBPM-guided treatment programme, the large number of patients and outcome events, and the long follow-up compared to previous observational studies and trials.[353, 354, 357, 358]

However, my analyses had several limitations. First, the acquisition of information on treatment discontinuation and withdrawal was potentially subject to information bias, as patients with recurrent events are more likely to have had additional encounters between follow-up visits where more detail on prescribed medications and adherence might have been provided. However, I used the pre-established OXVASC follow-up intervals to ascertain definite medication changes, irrespective of recurrent events. Moreover, any such discrepancy in data acquisition would also be present for lipid-lowering and antithrombotic drugs, so analyses comparing reduction of blood pressure-lowering drugs to discontinuation of these agents should not be affected by this potential source of bias. Second, reductions in antihypertensive drugs are theoretically more likely to be recorded than those of lipid-lowering or antithrombotic drugs, since combination therapy is more likely. This might explain the higher relative rates of antihypertensive versus lipid-lowering/antithrombotics medication lowering in my study compared with other studies of medication adherence after TIA/stroke.[14, 18, 243] However, a more sensitive definition of antihypertensive medication reduction, i.e. one that includes any treatment decrease, is necessary when multiple agents are usually required to achieve adequate control,[59, 95] and comparable results were found for complete treatment discontinuation in my study. Third, I did not have access to prescription fulfilment records for this study. As a result, rates of nonadherence might have been higher than those documented based on patient interview and GP prescription records. This also precluded establishing the exact timing of medication withdrawal. Finally, the initiator and reasons for treatment discontinuation

were not available in the majority of cases, preventing definite conclusions on whether treatment withdrawal was primarily due to purposeful deprescribing or poor adherence.

In conclusion, after accounting for healthy user bias and assuming causality, over 40% of the risk of recurrent vascular events in people with initially well-controlled hypertension after TIA and stroke is attributable to reductions to antihypertensive treatment during long-term follow-up. Rather than pursuing a continued research focus on new drugs with marginal risk-reducing benefits, long-term blood pressure monitoring after TIA/stroke and addressing long-term adherence to existing agents might be rewarded with bigger reductions in residual risk of recurrent vascular events.

7.6 Tables

Table 7-1 Characteristics and blood pressure of patients, by decreases in BP-lowering, lipid-lowering, and antithrombotic drugs after the intensive BP-monitoring period

Patient characteristics	Whole cohort	BP-lowering drugs decreased after the intensive monitoring period	Lipid-lowering drugs decreased after the intensive monitoring period
n/total prescribed each class by the end of the intensive BP monitoring period (%)	*n=1618*	*496/1435 (34.6%)*	*105/1560 (6.7%)*
Male sex, n (%)	835 (51.6%)	251 (50.6%)	53 (50.5%)
Age, mean (SD)	69.8 (13.1)	71.7 (12.3)	67.3 (15.4)
Event type, n (%)			
Stroke	638 (39.4%)	198 (39.9%)	35 (33.3%)
TIA	980 (60.6%)	298 (60.1%)	70 (66.7%)
Medical history prior to event, n (%)			
Hypertension (prior history/treatment)	1012 (62.6%)	351 (70.8%)	60 (57.1%)
Angina	186 (11.5%)	67 (13.5%)	6 (5.7%)
Diabetes mellitus	213 (13.2%)	78 (15.7%)	11 (10.5%)
Hyperlipidaemia	515 (31.8%)	158 (31.9%)	34 (32.4%)
Myocardial infarction	48 (3.0%)	15 (3.0%)	3 (2.9%)
Atrial fibrillation	189 (11.7%)	61 (12.3%)	6 (5.7%)
Heart failure	66 (4.1%)	21 (4.2%)	5 (4.8%)
Peripheral vascular disease	52 (3.2%)	20 (4.0%)	0 (0%)
Prior stroke	90 (5.6%)	32 (6.5%)	2 (1.9%)
Prior TIA	236 (14.6%)	81 (16.3%)	13 (12.4%)
Lifestyle factors (self-reported)			
Current smoker, n (%)	243 (15.0%)	86 (17.3%)	13 (12.4%)
Ever-smoker, n (%)	832 (51.4%)	267 (53.8%)	58 (55.2%)
Antihypertensive use, n (%)			
Baseline	832 (51.4%)	292 (58.9%)	49 (46.7%)
One-month follow-up	1340 (80.9%)	496 (100%)	84 (80.0%)
Baseline BP mmHg, mean (SD)			
Clinic, systolic	151.3 (22.9)	153.8 (23.2)	150.0 (21.4)
Clinic, diastolic	85.0 (13.3)	85.0 (13.2)	83.5 (12.6)
HBPM first 3 days of monitoring, systolic*	135.6 (16.1)	138.1 (15.8)	134.5 (14.8)
HBPM first 3 days of monitoring, diastolic	79.0 (10.3)	79.7 (10.6)	79.7 (10.0)

One-month follow-up BP mmHg, mean (SD)			
Clinic, systolic¶	132.2 (18.5)	132.3 (19.2)	130.2 (15.5)
Clinic, diastolic	75.5 (11.1)	74.7 (11.7)	74.6 (9.7)
HBPM 3 days prior to one-month clinic, systolic¥	127.3 (12.7)	128.8 (12.4)	127.7 (12.0)
HBPM 3 days prior to one-month clinic, diastolic	74.3 (9.2)	74.4 (9.5)	74.8 (8.4)
ABPM daytime, systolic§	129.3 (12.8)	128.7 (13.6)	128.6 (11.9)
ABPM daytime, diastolic	73.8 (8.1)	73.0 (8.7)	74.0 (8.9)
One-year follow-up BP mmHg, mean (SD)			
Clinic, systolic¶¶	130.1 (17.6)	130.6 (18.5)	129.2 (18.5)
Clinic, diastolic	73.6 (10.6)	73.3 (11.2)	72.7 (10.4)
ABPM daytime, systolic§§	129.3 (13.4)	128.6 (14.2)	126.2 (13.5)
ABPM daytime, diastolic	74.1 (7.9)	73.5 (8.2)	72.5 (8.4)

Home blood pressure monitoring (HBPM); ambulatory blood pressure monitoring (ABPM); standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP)). * Baseline HBPM n=1614; ¶ one-month clinic BP n=1600; ¥ one-month HBPM n=1596; § one-month ABPM n=1379; ¶¶ one-year clinic BP n=1282; §§ one-year ABPM n=960.

Table 7-2 Initiator and rationale for antihypertensive medication discontinuation/reduction after the intensive BP monitoring period

Time of decrease	Who decreased/stopped BP-lowering medications?					
	Patient	GP	Hospital	OXVASC	Unknown	**Total**
1m-3m FU	5	4	2	6	10	27
3m-6m FU	2	12	0	2	32	48
6m-12m FU	14	14	1	3	104	136
12m-5yr FU	12	22	7	0	187	228
>5yr FU	2	9	6	0	40	57
Total	35	61	16	11	373	496

Time of decrease	Who stopped all BP-lowering medications?					
	Patient	GP	Hospital	OXVASC	Unknown	**Total**
1m-3m FU	4	2	2	1	2	11
3m-6m FU	1	3	0	0	12	16
6m-12m FU	8	2	0	2	45	57
12m-5yr FU	8	4	4	0	56	72
>5yr FU	2	6	3	0	14	25
Total	23	17	9	3	129	181

Time of decrease	Why was the dose of BP-lowering medications decreased?					
	Side-effects	Hypotension/falls	Adherence	Co-morbidity	Unknown	**Total**
1m-3m FU	8	3	2	3	11	27
3m-6m FU	6	2	2	1	37	48
6m-12m FU	10	6	7	2	111	136
12m-5yr FU	11	7	3	8	199	228
>5yr FU	2	5	1	7	42	57
Total	37	23	15	21	400	496

Blood pressure (BP); follow-up (FU); Oxford Vascular Study team (OXVASC).

Table 7-3 Characteristics of patients prescribed secondary prevention medications by the end of the intensive BP monitoring period, by decreases in any of these drugs during follow-up

Patient characteristics ***n (% cohort prescribed treatment)***	**Cohort prescribed secondary prevention medications** ***1606 (100%)***	**Any secondary prevention medications decreased after the intensive monitoring period** ***696 (43.3%)***	**Secondary prevention medications not decreased after the intensive monitoring period** ***910 (56.7%)***	**p-value**
Male sex, n (%)	829 (51.6%)	353 (50.7%)	476 (52.3%)	0.528
Age, mean (SD)	69.9 (13.0)	70.8 (12.6)	69.2 (13.2)	**0.014**
Event type, n(%)				
Stroke	635 (39.5%)	279 (40.1%)	356 (39.1%)	0.695
TIA	971 (60.5%)	417 (59.9%)	554 (60.9%)	
Medical history prior to event, n (%)				
Hypertension (prior history/treatment)	1011 (63.0%)	467 (67.1%)	544 (59.8%)	**0.003**
Angina	186 (11.6%)	85 (12.2%)	101 (11.1%)	0.489
Diabetes mellitus	213 (13.3%)	96 (13.8%)	117 (12.9%)	0.584
Hyperlipidaemia	515 (32.1%)	216 (31.0%)	299 (32.9%)	0.438
Myocardial infarction	48 (3.0%)	20 (2.9%)	28 (3.1%)	0.813
Atrial fibrillation	189 (11.8%)	90 (12.9%)	99 (10.9%)	0.206
Heart failure	66 (4.1%)	34 (4.9%)	32 (3.5%)	0.171
Peripheral vascular disease	52 (3.2%)	22 (3.2%)	30 (3.3%)	0.879
Prior stroke	90 (5.6%)	41 (5.9%)	49 (5.4%)	0.662
Prior TIA	235 (14.6%)	110 (15.8%)	125 (13.7%)	0.245
Lifestyle factors (self-reported)				
Current smoker, n (%)	243 (15.1%)	111 (16.0%)	132 (14.5%)	0.424
Ever-smoker, n (%)	865 (53.9%)	374 (53.7%)	491 (54.0%)	0.930

Antihypertensive use, n (%)				
Baseline	831 (51.7%)	386 (55.5%)	445 (48.9%)	**0.009**
One-month follow-up	1311 (81.6%)	605 (86.9%)	706 (77.6%)	**<0.0001**
Baseline BP mmHg, mean (SD)				
Clinic, systolic	151.4 (22.9)	153.0 (23.7)	150.2 (22.2)	**0.016**
Clinic, diastolic	85.0 (13.3)	84.8 (13.1)	85.2 (13.5)	0.508

Standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP).

Table 7-4 Characteristics of patients with decreases in BP-lowering versus lipid-lowering/antithrombotic drugs, but not both, after the intensive BP-monitoring period

Patient characteristics ***n (% 474: decreased either, but not both classes)***	**Decreased BP-lowering drugs but not lipid-lowering/antithrombotic drugs** ***307 (64.8%)***	**Decreased Lipid-lowering/antithrombotic drugs but not BP-lowering drugs** ***167 (35.2%)***	**p-value**
Male sex, n (%)	153 (49.8%)	87 (52.1%)	0.638
Age, mean (SD)	72.7 (11.3)	70.0 (11.7)	**0.016**
Event type, n(%)			
Stroke	67 (40.1%)	123 (40.1%)	0.991
TIA	100 (59.9%)	184 (59.9%)	
Medical history prior to event, n (%)			
Hypertension (prior history/treatment)	231 (75.2%)	116 (69.5%)	0.174
Angina	52 (16.9%)	16 (9.6%)	**0.029**
Diabetes mellitus	54 (17.6%)	18 (10.8%)	**0.048**
Hyperlipidaemia	111 (36.2%)	54 (32.3%)	0.404
Myocardial infarction	8 (2.6%)	5 (3.0%)	0.805
Atrial fibrillation	42 (13.7%)	27 (16.2%)	0.463
Heart failure	15 (4.5%)	13 (7.8%)	0.201
Peripheral vascular disease	14 (4.6%)	2 (1.2%)	0.053
Prior stroke	22 (7.2%)	9 (5.4%)	0.455
Prior TIA	110 (15.8%)	125 (13.7%)	0.245
	46 (15.0%)	23 (13.8%)	0.721
Lifestyle factors (self-reported)			
Current smoker, n (%)	46 (15.0%)	20 (12.0%)	0.366
Ever-smoker, n (%)	158 (51.5%)	91 (54.5%)	0.529
Antihypertensive use, n (%)			
Baseline	195 (63.5%)	94 (56.3%)	0.123
One-month follow-up	286 (93.2%)	147 (88.0%)	0.057
Baseline BP mmHg, mean (SD)			
Clinic, systolic	154.6 (23.8)	154.2 (24.5)	0.864
Clinic, diastolic	85.0 (13.8)	85.2 (13.0)	0.897

Standard deviation (SD); transient ischaemic attack (TIA); interquartile range (IQR); blood pressure (BP).

Table 7-5 Recurrent major vascular events and secondary prevention medication reduction/withdrawal by follow-up interval

	Medication withdrawal in the same interval as MVE			*Medication withdrawal in the same or preceding interval as MVE*			*Medication withdrawal in the same or preceding interval as MVE, excluding those with events beyond one year after the start of the subsequent interval*		
	n	**Total***	**%**	**n**	**Total**	**%**	**n**	**Total**	**%**
Net decrease in BP-lowering treatment after the intense monitoring period	44	89	49.4%	80	89	89.9%	58	89	65.2%
Stopped all BP-lowering treatment after the intense monitoring period	12	23	52.2%	20	23	87.0%	17	23	73.9%
Net decrease in lipid-lowering treatment after the intense monitoring period	12	35	34.3%	28	35	80.0%	20	35	57.1%
Stopped lipid-lowering treatment after the intense monitoring period	7	24	29.2%	19	24	79.2%	10	24	41.7%
Stopped antithrombotic treatment after the intense monitoring period	6	9	66.7%	7	9	77.8%	7	9	77.8%

*Denominator is the total number of patients who had a dose decrease/stopped a secondary prevention drug and had a subsequent recurrent event

Table 7-6 Associations of secondary prevention medication discontinuation with accurately-characterised hypertension at baseline and the end of the HBPM period, stratified by recurrent major vascular events

	Recurrent MVE			No recurrent MVE		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Association of BP-lowering treatment decrease with hypertension on first 3 days HBPM (excluding those never treated)	4.08	1.99 - 8.38	**<0.0001**	0.97	0.76 - 1.25	0.693
Association of BP-lowering treatment decrease vs lipid-lowering/antithrombotic treatment with hypertension on first 3 days HBPM (excluding those never treated / those who decreased both)	7.36	1.38 - 39.11	**0.019**	1.14	0.74 - 1.76	0.546
Association of BP-lowering treatment decrease with hypertension on last 7 days HBPM (excluding those never treated)	1.37	0.68 - 2.75	0.375	1.04	0.78 - 1.38	0.787
Association of BP-lowering treatment decrease vs lipid-lowering/antithrombotic treatment with hypertension on last 7 days HBPM (excluding those never treated / those who decreased both)	0.54	0.10 - 2.96	0.476	0.74	0.46 - 1.18	0.208

Odds ratio (OR); confidence interval (CI); home blood pressure monitoring (HBPM). Models are adjusted for age, sex, vascular risk factors (history of hypertension, diabetes mellitus, current smoking, history of smoking), and history of vascular disease (angina, myocardial infarction, peripheral vascular disease, TIA, stroke). The BP threshold for hypertension on HBPM is BP ≥135/85 mmHg.

Table 7-7 Risk of recurrent major vascular events associated with reduction in secondary prevention medications

Medication Decrease	Events, n	HR	95% CI	p-value
Antihypertensive medications				
Dose reduction/stopped	177	2.77	(1.96 - 3.91)	**<0.0001**
Hypertension on 3-day HBPM	119	3.86	(2.55 - 5.85)	**<0.0001**
Normotension on 3-day HBPM	58	1.21	(0.61 - 2.40)	0.581
BP-lowering treatment net increase during HBPM	117	2.82	(1.86 - 4.29)	**<0.0001**
Achieved reduction in systolic BP on HBPM ≥ 25 mmHg	*20*	*9.73*	*(2.36 - 40.14)*	***0.002***
Achieved reduction in systolic BP on HBPM < 25 mmHg	*97*	*2.37*	*(1.49 - 3.77)*	***<0.0001***
BP-lowering treatment no net increase during HBPM	60	2.61	(1.38 - 4.96)	**0.003**
Stopped all, excluding dose reductions	111	2.37	(1.37 - 4.11)	**0.002**
Lipid-lowering agents				
Dose reduction/stopped	183	1.27	(0.85 - 1.89)	0.249
Stopped all, excluding dose reductions	172	1.32	(0.83 - 2.10)	0.242
Antihypertensives and lipid-lowering agents				
Dose reduction/stopped	95	3.00	(1.73 - 5.20)	**<0.0001**
Antithrombotic agents				
Stopped all	195	1.77	(0.81 - 3.88)	0.152
Antihypertensives versus lipid-lowering/antithrombotic drugs				
Dose reduction/stopped	74	2.44	(1.45 - 4.10)	**0.001**

Antihypertensives, but persistent adherence to both lipid-lowering and antithrombotic agents				
Dose reduction/stopped	128	3.01	(1.98 - 4.62)	**<0.0001**
Hypertension on 3-day HBPM	83	4.11	(2.46 - 6.85)	**<0.0001**
Normotension on 3-day HBPM	45	1.34	(0.57 - 3.13)	0.499
BP-lowering treatment net increase during HBPM	84	3.44	(2.06 - 5.75)	**<0.0001**
Achieved reduction in systolic BP on HBPM ≥ 25 mmHg	*18*	*6.91*	*(1.70 - 28.05)*	***0.007***
Achieved reduction in systolic BP on HBPM < 25 mmHg	*66*	*2.78*	*(1.52 - 5.08)*	***0.001***
BP-lowering treatment no net increase during HBPM	44	2.05	(0.92 - 4.60)	0.080

Hazard ratio (HR); confidence interval (CI); home blood pressure monitoring (HBPM). The threshold for hypertension on 3-day HBPM is BP ≥135/85 mmHg, and the achieved reduction in systolic BP on HBPM is the difference between the mean of the first 3 days and the last 7 days of readings. Reduction of secondary prevention medications is fitted as a time-varying covariate in each model, with exposure time occurring at the mid-point of each follow-up interval. Models are adjusted for age, sex, vascular risk factors (history of hypertension, diabetes mellitus, current smoking, history of smoking), and history of vascular disease (angina, myocardial infarction, peripheral vascular disease, TIA, stroke). Those never treated with the secondary prevention medication in question were excluded from the analysis.

Table 7-8 Follow-up blood pressure by reduction in antihypertensive medications

Follow-up blood pressure, mean/mean difference (mmHg)	n	Antihypertensive medication decrease prior to follow-up BP assessment	Persistent adherence to antihypertensive medication prior to follow-up BP assessment	p-value	p-value, adjusted for age, sex, and baseline BP
12-month follow-up					
Clinic systolic	1151	135.6	130.1	**0.0006**	**<0.0001**
Clinic diastolic	1151	76.1	73.2	**0.003**	**<0.0001**
3-month to 12-month follow-up clinic systolic BP increase	1077	8.6	2.1	**0.0001**	**<0.0001**
3-month to 12-month follow-up clinic diastolic BP increase	1077	4.5	0.0	**<0.0001**	**<0.0001**
Daytime ABPM systolic	856	134.7	129.2	**0.0003**	**0.001**
Daytime ABPM diastolic	856	75.9	73.8	**0.018**	**<0.0001**
1-month to 12-month daytime ABPM systolic BP increase	815	4.6	0.1	**0.003**	**0.004**
1-month to 12-month daytime ABPM diastolic BP increase	815	2.7	0.2	**0.006**	**0.005**
5-year follow-up					
Clinic systolic	585	136.1	130.1	**0.026**	**0.028**
Clinic diastolic	585	76.4	74.3	**0.034**	**0.003**
3-month to 5-year follow-up clinic systolic BP increase	549	11.2	4.8	**0.0009**	**0.001**
3-month to 5-year follow-up clinic diastolic BP increase	549	4.3	1.2	**0.003**	**0.003**
10-year follow-up					
Clinic systolic	119	144.5	134.7	**0.017**	**0.011**
Clinic diastolic	119	75.4	73.2	0.321	0.291
3-month to 10-year follow-up clinic systolic BP increase	113	21.3	10.6	**0.009**	**0.007**
3-month to 10-year follow-up clinic diastolic BP increase	113	3.6	-1.3	**0.041**	**0.039**

Blood pressure (BP); ambulatory blood pressure monitoring (ABPM). Those never treated with antihypertensive medications were excluded from analyses, and those with treatment discontinuation at later time points than the time of follow-up BP assessment were treated as being adherent.

Table 7-9 Risk of recurrent vascular events associated with reduction in antihypertensive medications after the intensive monitoring period, in sequentially-adjusted models

	First 2 years of follow-up			Full follow-up period		
Model	HR	95% CI	p-value	HR	95% CI	p-value
Unadjusted	0.96	(0.61 - 1.51)	0.873	1.60	(1.20 - 2.17)	**0.001**
Adjusted for age, sex	0.94	(0.60 - 1.48)	0.799	1.55	(1.16 - 2.09)	**0.004**
+ Vascular risk factors	0.86	(0.54 - 1.36)	0.522	1.45	(1.08 - 1.96)	**0.014**
+ Baseline systolic BP*	0.73	(0.43 - 1.24)	0.244	1.45	(1.08 - 1.96)	**0.014**
+ Medication reduction fitted as a time-varying covariate according to the middle of each follow-up interval	2.92	(1.52 - 5.63)	**0.001**	2.77	(1.96 - 3.91)	**<0.0001**
+ Follow-up systolic BP* fitted as a time-varying covariate	1.03	(0.21 - 5.08)	0.970	2.79	(1.89 - 4.10)	**<0.0001**

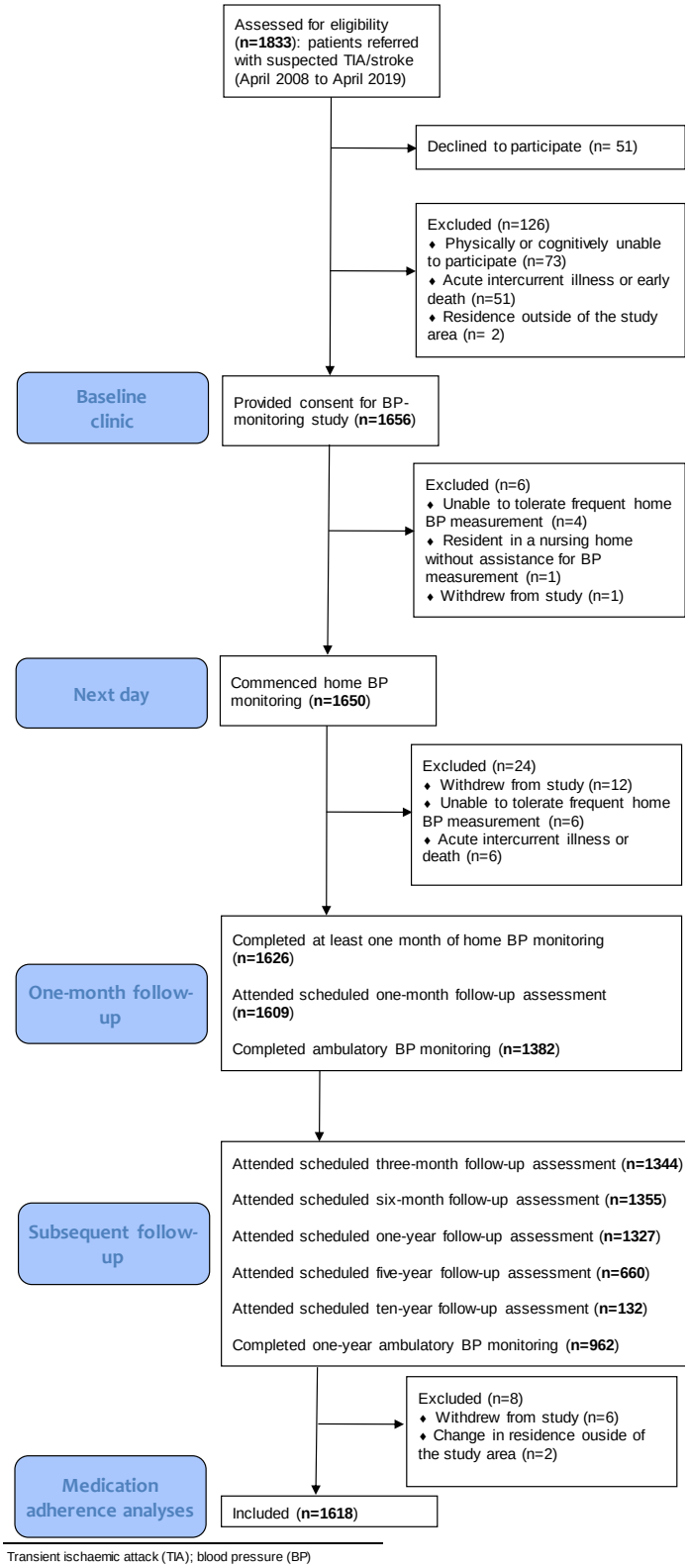
Blood pressure (BP); confidence interval (CI). * Adjustment by one-month/one-year daytime ambulatory BP monitoring for analyses in the first two years of follow-up, adjustment by baseline/follow-up clinic BP thereafter

Table 7-10 Risk of recurrent vascular events associated with reduction in antihypertensive medications after the intensive monitoring period, by timing of medication reduction fitted as a time-varying covariate to different points during each follow-up interval

	First 2 years of follow-up			Full follow-up period, 1-month entry			Full follow-up period, 3-month entry		
Model	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Medication reduction fitted as a time-varying covariate according to the end of each follow-up interval	2.22	(1.01 - 4.89)	**0.048**	2.25	(1.54 - 3.28)	**<0.0001**	2.24	(1.54 - 3.27)	**<0.0001**
Medication reduction fitted as a time-varying covariate according to the start of each follow-up interval	2.86	(1.58 - 5.20)	**0.001**	2.75	(1.98 - 3.82)	**<0.0001**	2.71	(1.95 - 3.78)	**<0.0001**
Medication reduction fitted as a time-varying covariate according to the middle of each follow-up interval	2.92	(1.52 - 5.63)	**0.001**	2.77	(1.96 - 3.91)	**<0.0001**	2.78	(1.97 - 3.93	**<0.0001**

Confidence interval (CI). Models are adjusted for age, sex, vascular risk factors, and baseline blood pressure (based on ambulatory monitoring for the first 2 years analysis and on clinic recordings thereafter.

7.7 Figures



Transient ischaemic attack (TIA); blood pressure (BP)

Figure 7-1 Flowchart of study inclusion and exclusion

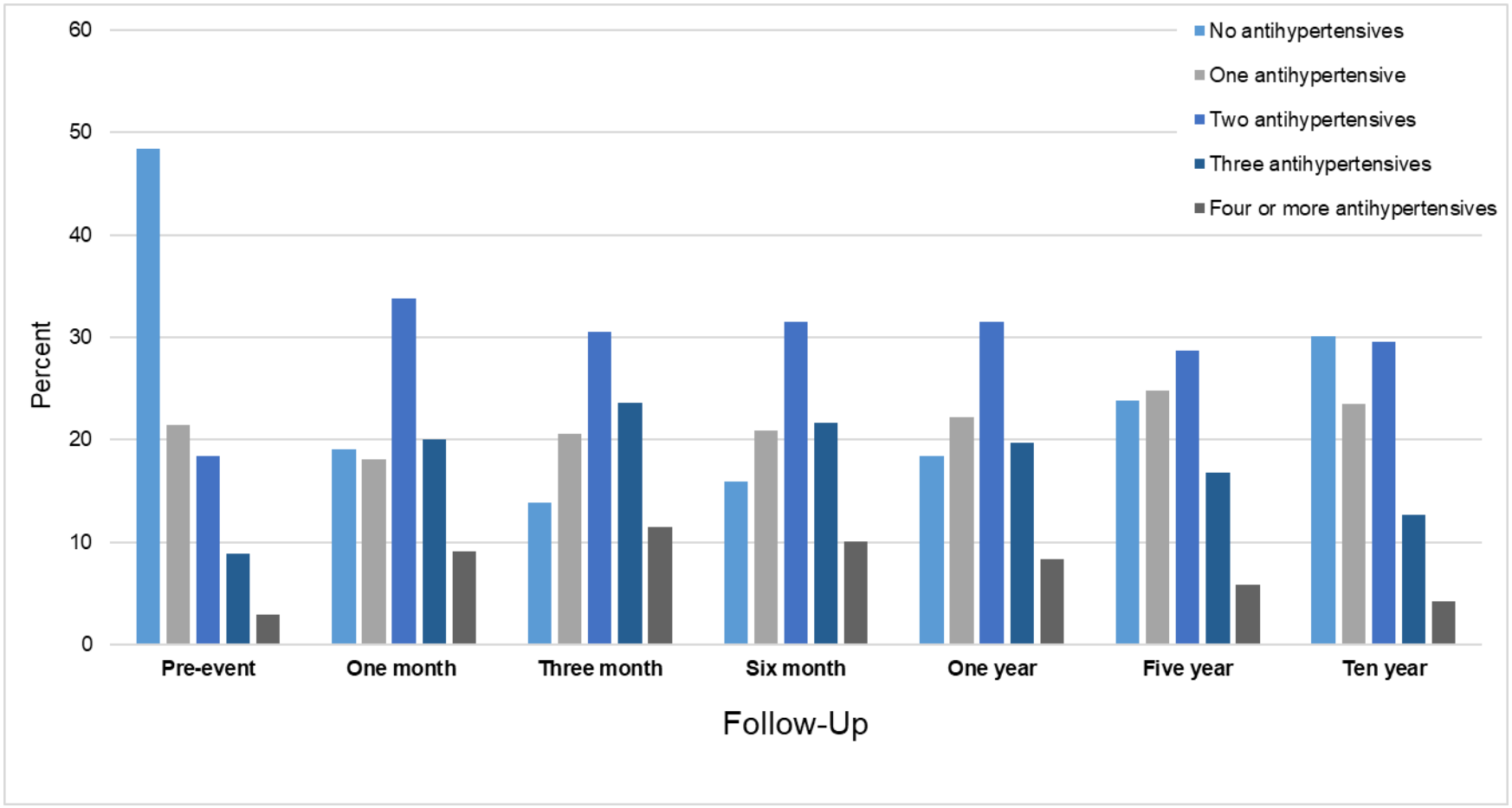


Figure 7-2 Change in antihypertensive use during and following the intensive HBPM-guided treatment phase

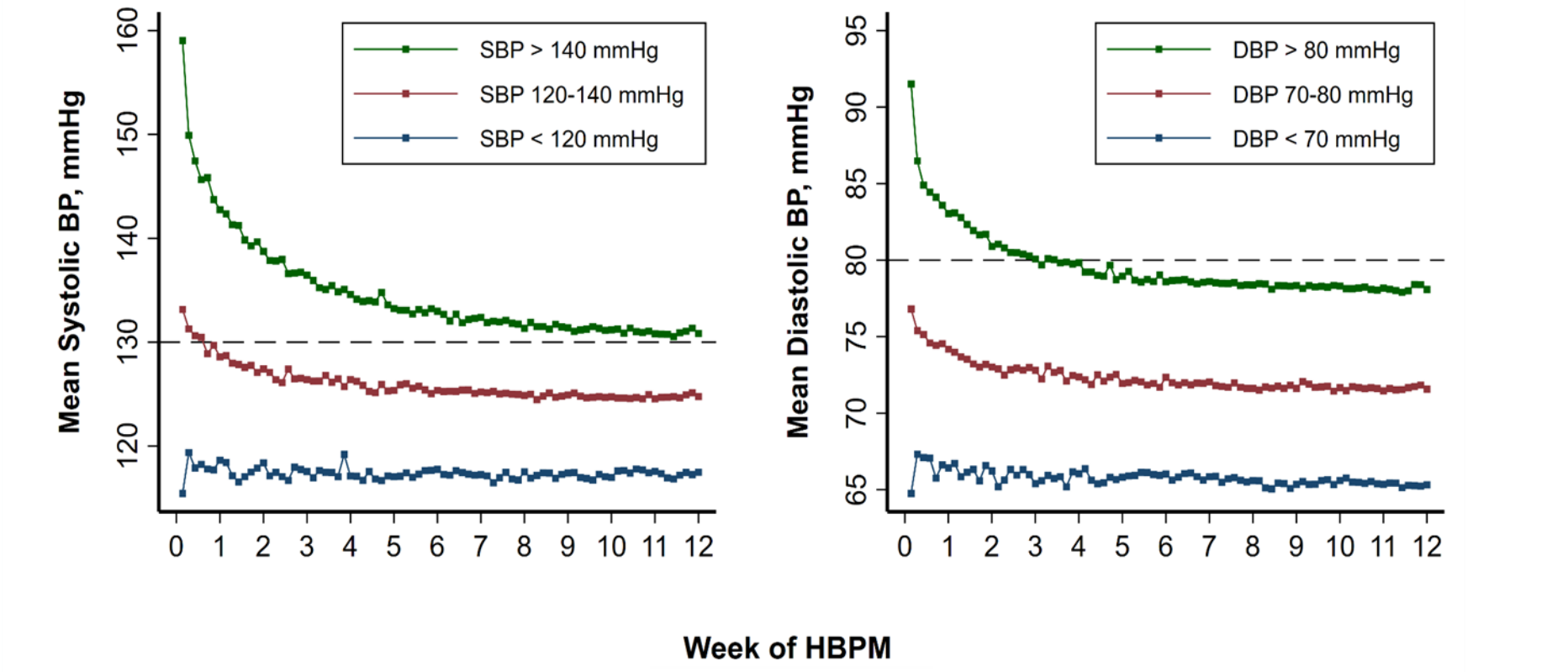


Figure 7-3 Home BP over three months of intensive monitoring and guided treatment, by categories of mean systolic and diastolic BP on the first day of monitoring

Blood pressure (BP); home BP monitoring (HBPM). The dashed horizontal line indicates the target BP. For patients who completed fewer than three months of monitoring, the mean of all readings on their final day of monitoring was used thereafter

.

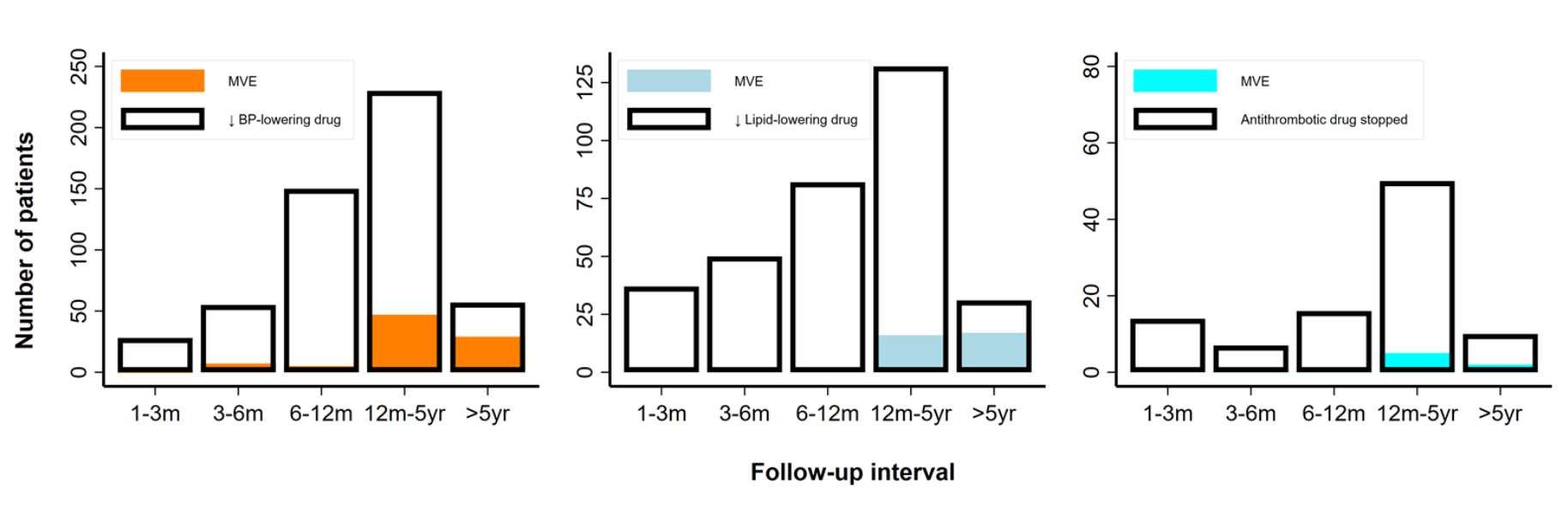


Figure 7-4 Timing of discontinuation of secondary prevention medications after the intensive monitoring period, and timing of recurrent major vascular events in all patients who discontinued treatment

Major vascular events (MVE); blood pressure (BP). The shaded portion in each bar is the proportion of patients who has recurrent major vascular events during follow-up that occurred after discontinuation of treatment.

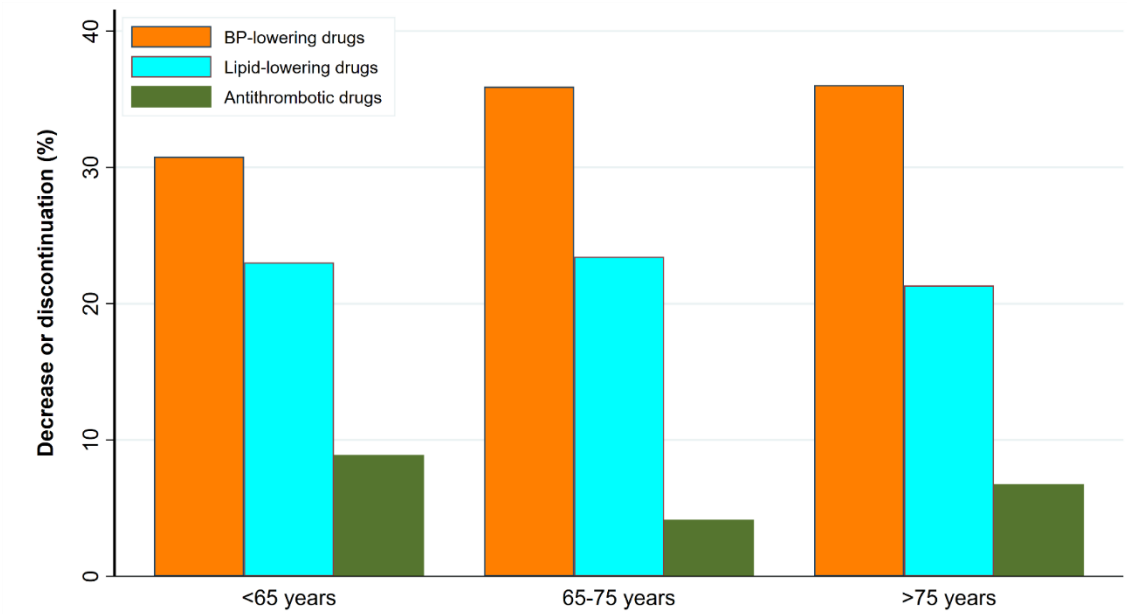


Figure 7-5 Discontinuation of secondary prevention medications after the intensive monitoring period, by age category

Participants are categorised by age category at baseline

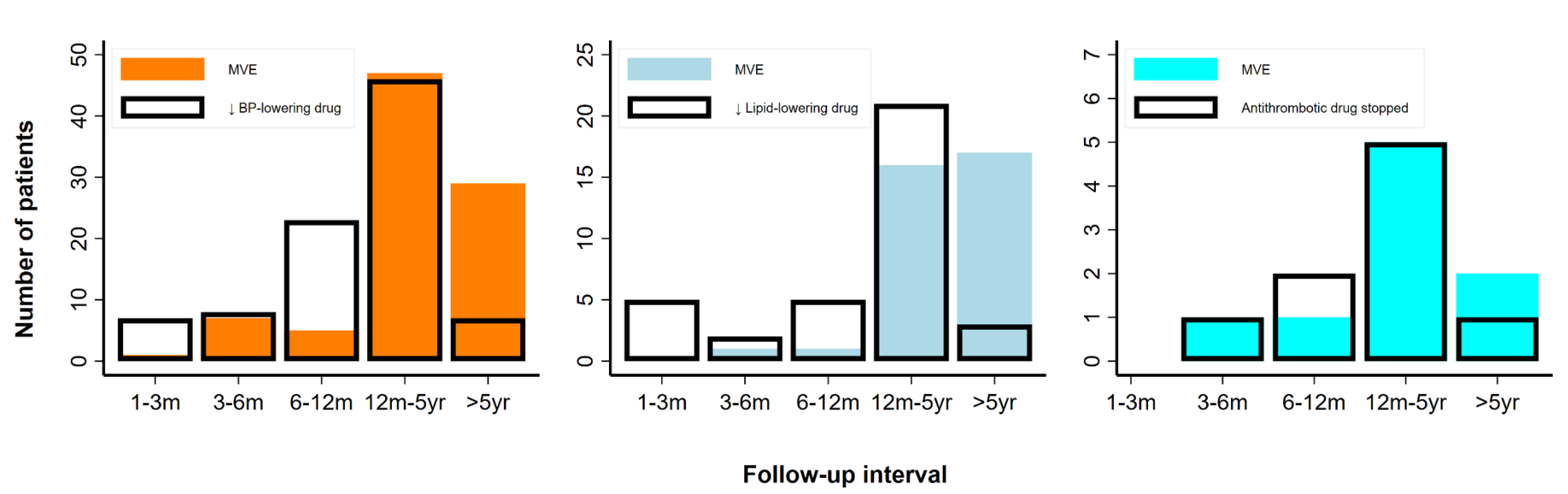


Figure 7-6 Timing of discontinuation of secondary prevention medications after the intensive monitoring period, relative to the timing of recurrent major vascular events during follow-up

Major vascular events (MVE); blood pressure (BP). Analyses are restricted to those participants who discontinued the secondary prevention medication in question before a recurrent major vascular event.

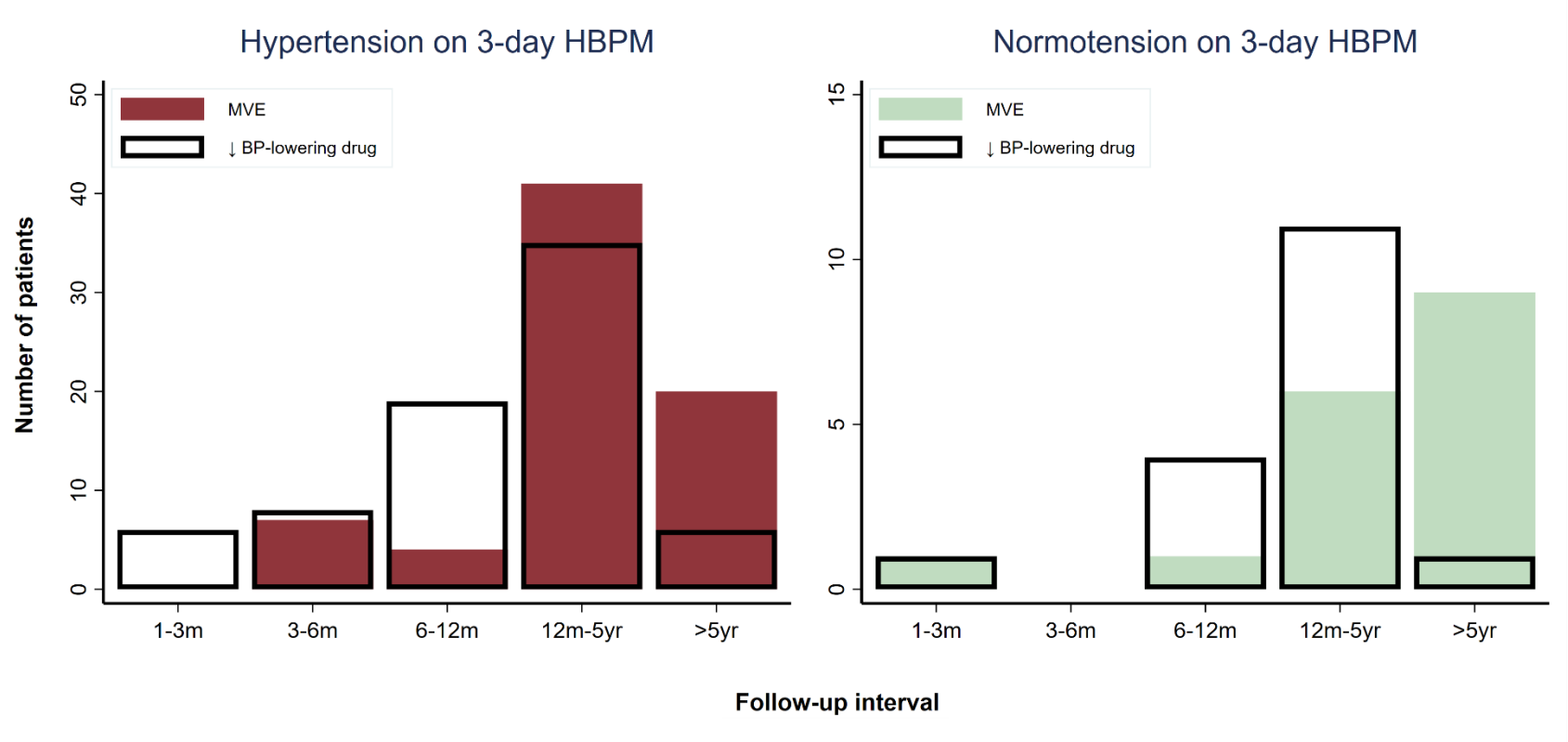


Figure 7-7 Timing of discontinuation of antihypertensive medication after the intensive monitoring period relative to the timing of recurrent major vascular events during follow-up, by hypertension on 3-day home blood pressure monitoring

Major vascular events (MVE); blood pressure (BP); home BP monitoring (HBPM). Analyses were restricted to those participants who both discontinued antihypertensive medications before a recurrent major vascular event. The threshold for hypertension on 3-day HBPM is BP ≥135/85 mmHg.

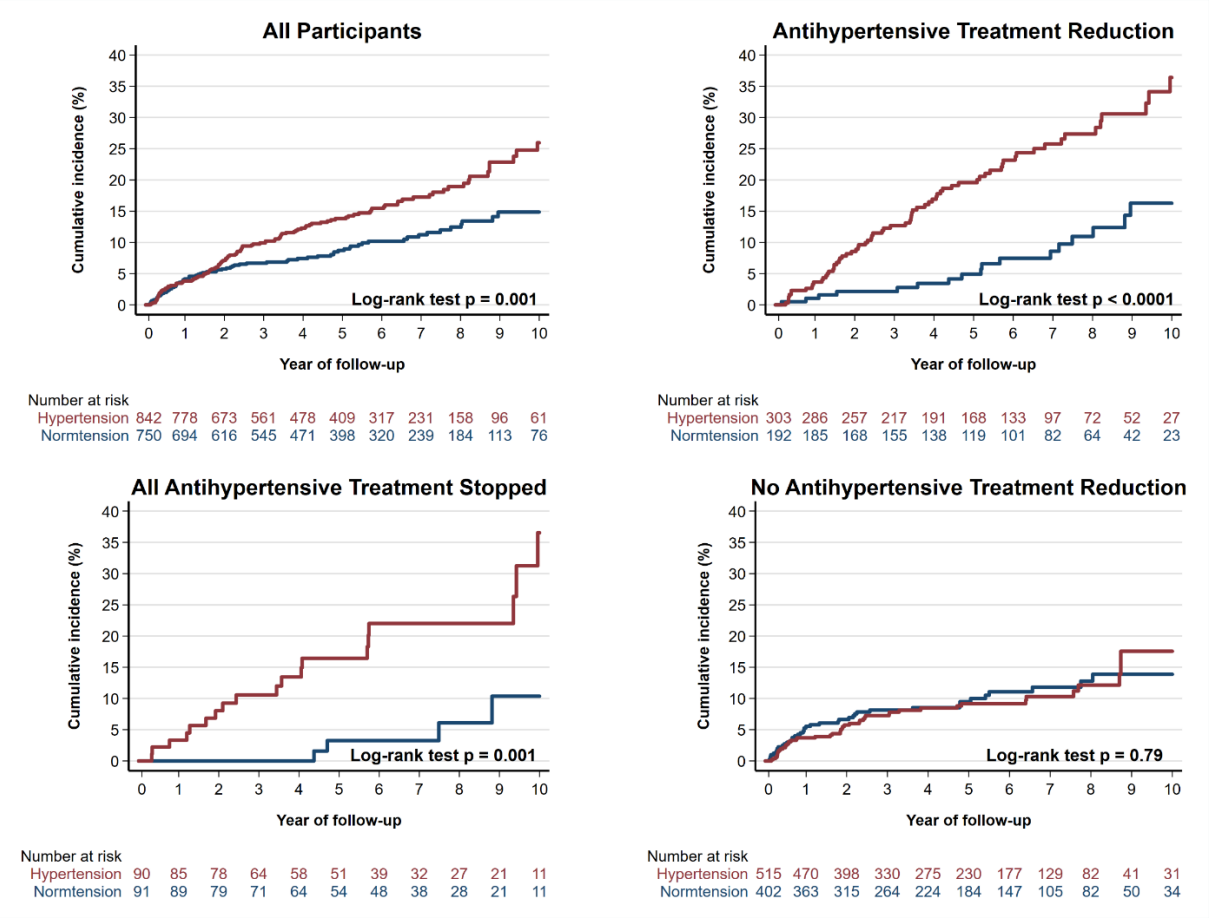


Figure 7-8 Risk of recurrent major vascular events after the intensive monitoring period by hypertension on baseline 3-day HBPM, according to antihypertensive medication reduction during follow-up

Home blood pressure monitoring (HBPM). Only treatment discontinuation before MVE was included, and those never treated with antihypertensive medications were excluded from the analysis. The threshold for hypertension on 3-day HBPM is BP ≥135/85 mmHg.

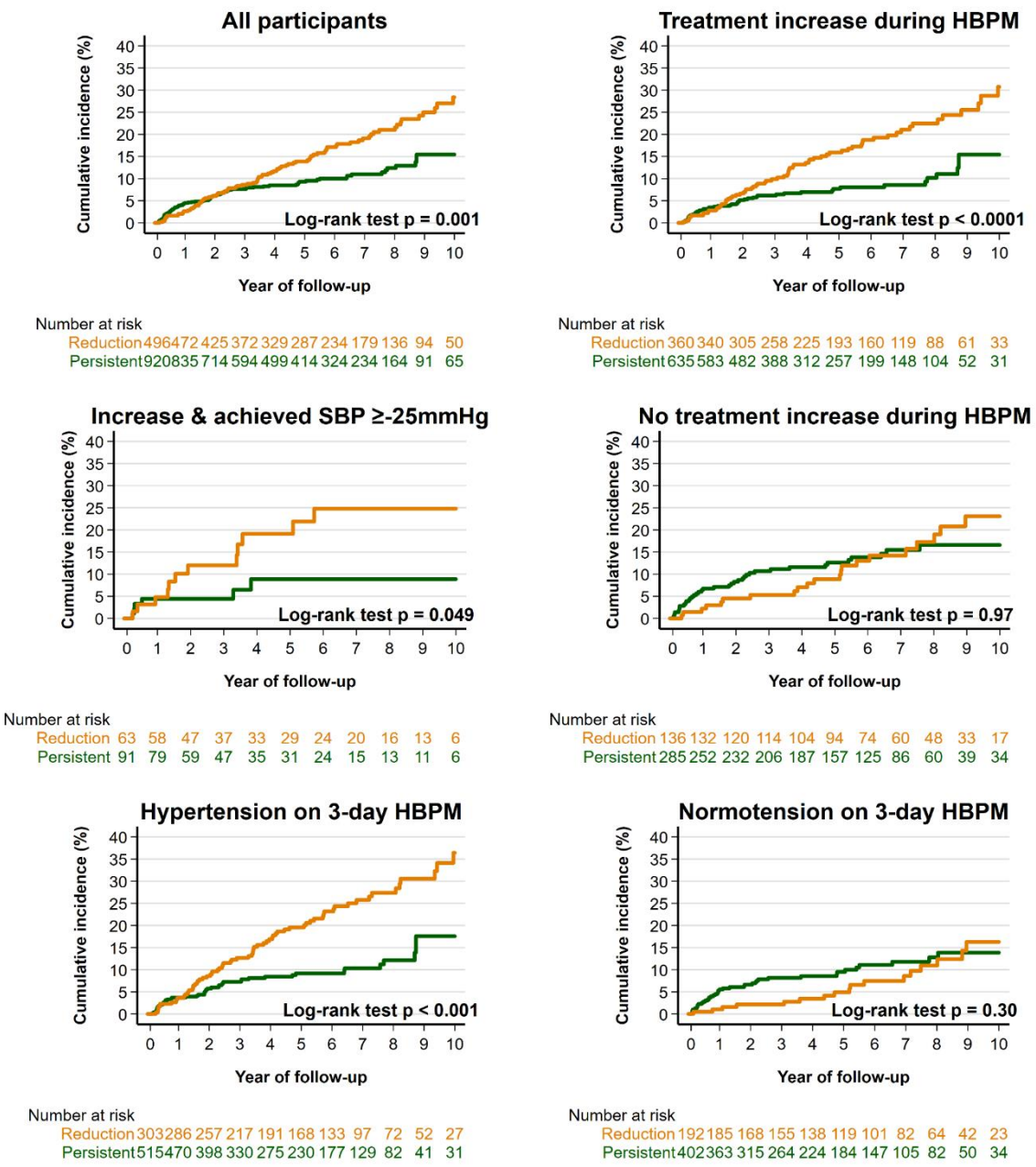


Figure 7-9 Risk of recurrent major vascular events after the intensive monitoring period by antihypertensive medication dose reduction/discontinuation versus persistence with the initial prescribed dose (or dose increase) during follow-up

Home blood pressure monitoring (HBPM); systolic blood pressure (SBP). Only treatment discontinuation before MVE was included, and those never treated with antihypertensive medications were excluded from the analysis. Treatment increase during HBPM was defined as a net increase in the adjusted dosage of medications between commencement and completion of HBPM. The threshold for hypertension on 3-day HBPM is BP ≥135/85 mmHg, and the achieved reduction in systolic BP on HBPM is the difference between the mean of the first 3 days and the last 7 days of readings.

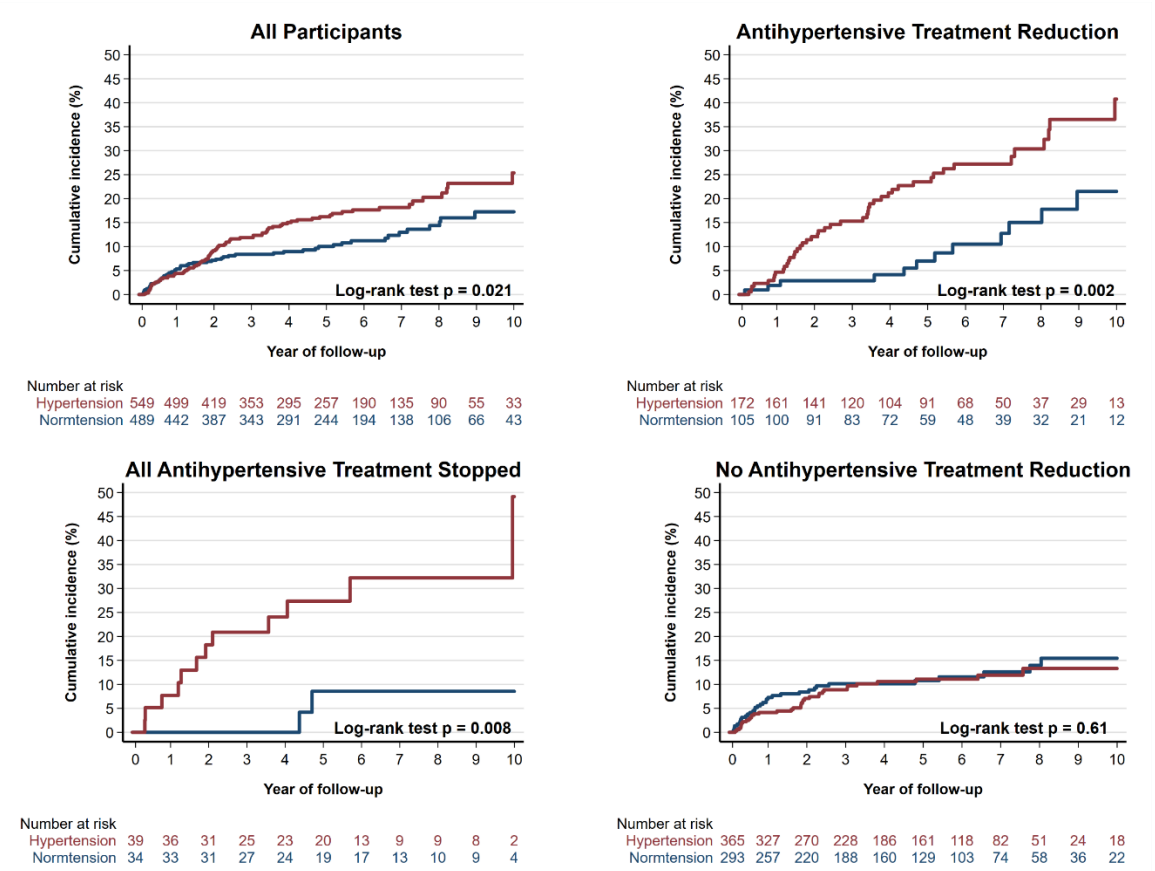


Figure 7-10 Risk of recurrent major vascular events after the intensive monitoring period by hypertension on baseline 3-day HBPM, according to antihypertensive medication reduction in patients who remained fully adherent to lipid-lowering and antithrombotic drugs

Home blood pressure monitoring (HBPM). Only treatment discontinuation before MVE was included, and those never treated with antihypertensive medications were excluded from the analysis. The threshold for hypertension on 3-day HBPM is BP ≥135/85 mmHg.

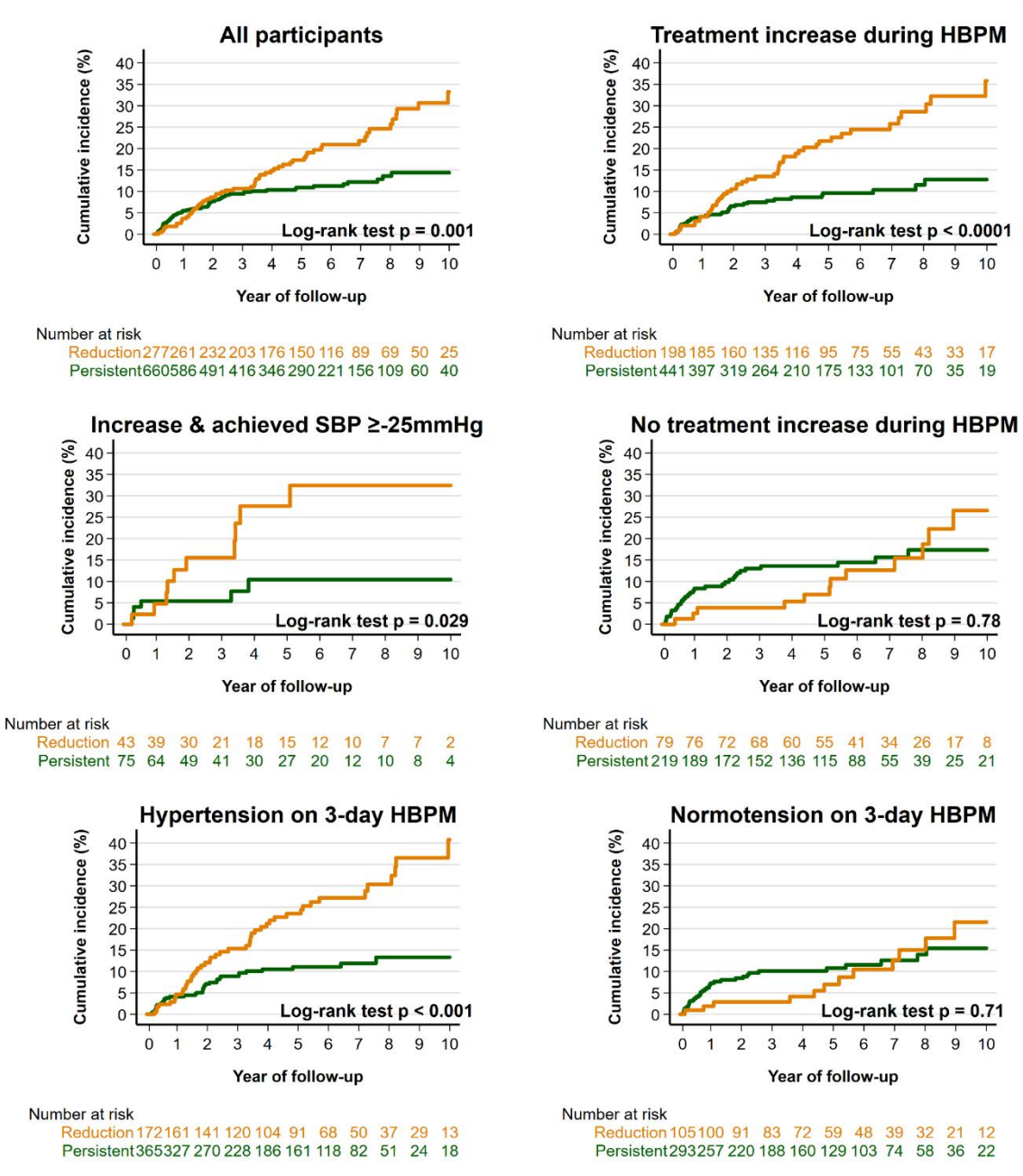


Figure 7-11 Risk of recurrent major vascular events after the intensive monitoring period by antihypertensive medication dose reduction/discontinuation versus persistence with the initial prescribed dose (or dose increase), in patients who remained fully adherent to lipid-lowering and antithrombotic drugs

Home blood pressure monitoring (HBPM); systolic blood pressure (SBP). Only treatment discontinuation before MVE was included, and those never treated with antihypertensive medications were excluded from the analysis. Treatment increase during HBPM was defined as a net increase in the adjusted dosage of medications between commencement and completion of HBPM. The threshold for hypertension on 3-day HBPM is BP ≥135/85 mmHg, and the achieved reduction in systolic BP on HBPM is the difference between the mean of the first 3 days and the last 7 days of readings.

Chapter 8: Conclusions and future directions

8.1 Introduction 305
8.2 Key findings and implications for clinical practice 306
8.3 Future research directions 308
8.3.1 Acute phase blood pressure after TIA and minor stroke 308
8.3.2 Clinical outcomes in COMMIT and PROHIBIT-ICH 310
8.3.3 Target blood pressure in stroke secondary prevention; evidence for a J-curve……311
8.4 Figures 316

8.1 Introduction

Reducing blood pressure is the single most effective strategy for long-term stroke prevention, but uncertainty still surrounds the issue of blood pressure lowering after cerebrovascular events. The work presented in this thesis helps to address some important unanswered research questions about blood pressure measurement and control in this population, in order to assist clinical decision making about commencing and maintaining antihypertensive treatment, and ultimately to improve secondary prevention care.

Although the trial analyses in this thesis are underpowered, I am involved in ongoing data collection and will publish the final results after the trial is concluded. Additionally, now that I have shown that poor adherence to antihypertensive treatment might account for a large proportion of the residual risk of vascular events after TIA and stroke, more data are required to better understand the reasons for treatment discontinuation, and this is something that I intend to work on in the coming years. There are also some observations that came about from the research in this thesis that warrant further study, which I will outline in this chapter.

8.2 Key findings and implications for clinical practice

Controlling blood pressure after TIA and stroke proves a major challenge due to concerns about potential harm from too intensive blood pressure lowering, high rates of treatment discontinuation, and unreliable quantification of blood pressure and long-term response to treatment, with lingering uncertainty due to a relative paucity of large randomised trials in this setting.[359, 360] Some of the findings of this thesis should help to address, or at least help guide future targeted research to address some of this uncertainty.

First, I have shown that over a third of apparent hypertension in clinic after TIA and minor stroke is transient and has little prognostic importance, and over a quarter of apparent normotension in clinic is misdiagnosed high-risk hypertension. Therefore, clinic assessment of blood pressure immediately after TIA and minor stroke should not be relied upon to guide treatment decisions. It is likely preferable to delay initiation of treatment by a few days in most cases, as is already the recommended practice for major ischaemic stroke,[59, 95] until blood pressure is better characterised, for example by performing a few days of home blood pressure monitoring.

Second, I have shown that home and ambulatory blood pressure monitoring are probably not interchangeable methods of blood pressure measurement in a secondary prevention cohort, echoing the findings of a smaller existing study.[278] Home blood pressure monitoring had the strongest predictive value of any modality, but night-time blood pressure is also of additive prognostic importance, so newer home monitoring technologies that support nocturnal recordings might hold the most promise for future clinical practice.

Third, a programme of intensive blood pressure control guided by home telemetric monitoring achieved larger blood pressure reductions than usual care in a pilot randomised trial and was not associated with excess major adverse events in a larger

observational cohort. However, long-term treatment adherence waned, and this was associated with both a deterioration in blood pressure control and an increased risk of recurrent vascular events.

NHS England has committed to increased use of home blood pressure monitoring in primary care, with a particular focus on people with a history of TIA and stroke.[320] Based on my findings, this is likely to improve blood pressure control if combined with guided prescription of blood pressure-lowering medications. However, any such programme should be equipped to provide long-term monitoring beyond one year, to ensure long-term mediation adherence.

8.3 Future research directions

8.3.1 Acute phase blood pressure after TIA and minor stroke

In Chapter 2:, I found that almost 40% of apparent hypertension measured in clinic after TIA and minor stroke resolved spontaneously (even in the absence of treatment commencement) when blood pressure was measured over the coming days at home. I hypothesised that this transient hypertension was either an artefact of blood pressure variability captured on clinic assessment, or a distinct entity, or a manifestation of both to varying degrees. My observations that premorbid blood pressure was not elevated in these individuals with transient post-event hypertension, and that pre-hospital measurements were similarly elevated, support its existence as a distinct entity to at least some degree. This poses the question of whether this transient hypertension is a consequence of the cerebrovascular event (either an autoregulation response or an amplified white-coat effect due to heightened anxiety) or the remnant of a premorbid surge in blood pressure that might have triggered the event.

The phenomenon of post-event hypertension is well recognised in major stroke. It has been consistently demonstrated in case-control studies that blood pressure in patients with acute major stroke is higher than in matched controls with other acute illnesses.[70, 71] The cause is unknown, however, and premorbid hypertension itself is associated with high post-stroke blood pressure.[70, 73, 74] A specific physiological reaction to the stroke has been postulated for major events, possibly due to disturbed cerebral autoregulation,[75] but it remains uncertain whether post-stroke hypertension is a specific response to cerebral injury or the remnant of a premorbid surge in blood pressure.

Professor Rothwell's group has previously found that in patients with major ischaemic stroke, the first acute-phase systolic blood pressure was much lower than after ICH, was little higher than premorbid levels, and decreased only slightly during the first 24 hours.[34] By contrast, the mean first systolic blood pressure after ICH was substantially higher than premorbid levels and fell substantially in the first 24 hours. In addition, ICH was

preceded by a steep increase in mean systolic blood pressure in the days and weeks before the event, while this was not observed for major ischaemic stroke. Given that acute rises in blood pressure can precipitate ICH,[361, 362] the above discrepancy in post-event hypertension might be accounted for, at least in part, by a recent premorbid blood pressure increase. Additional OXVASC research comparing premorbid blood pressure in lacunar versus non-lacunar TIA/ischaemic stroke has shown that mean premorbid blood pressure was substantially higher in the former, accounted for by higher mean blood pressure during the five years before the event and a rising trend toward higher blood pressure leading up to the event.[37]

I have begun, therefore, to seek further insights into the nature of post-stroke hypertension based on my observations in the COMMIT study, by extending these comparisons to include minor ischaemic stroke, TIA, and ocular ischaemia. These analyses on the wider OXVASC population are beyond the scope of this thesis and require more work, but I outline my provisional findings here as an indication of ongoing progress in addressing this research question.

I have performed initial analyses on data collated from 2438 OXVASC participants ascertained after stroke or TIA, in whom blood pressure recorded within 24 hours of incident TIA or stroke was available. Of these, 793 (32.5%) had measurements in the hyper-acute phase (within 90 minutes). 1359 (55.7%) were taking antihypertensive therapy. Mean first acute-phase systolic blood pressure was substantially higher after intracerebral haemorrhage than after major (NIHSS≥3) ischaemic stroke (180.7 vs 155.5 mmHg, $p<0.0001$), and was lower after major stroke than after TIA/minor stroke (155.5 vs 160.1 mmHg, $p=0.044$). Cardioembolic stroke, despite being the most severe, predicted 8.7 mmHg (95% CI 6.1–11.4, $p<0.0001$) lower post-event systolic blood pressure after adjusting for age, sex, antihypertensive medications, and event-to-blood pressure time compared with large artery disease/small vessel disease/undetermined aetiology. Mean first systolic blood pressure measured within 24 hours of major stroke

was not significantly higher than that for transient ocular ischaemic events (155.4 vs 153.2 mmHg; p=0.714).

To examine premorbid blood pressure, I extended the population to include 3293 participants in whom a blood pressure measurement was recorded within 7 days of incident TIA or ischaemic stroke. Of these, 793 (21.5%) had acute-phase (within 90 minutes) readings. 45,604 premorbid measurements were available, with a median of 16 (IQR 7-32) per person. The median time from the most recent premorbid blood pressure was 4.3 months (IQR 2.4-22.9). Compared with the most recent premorbid reading, the mean first post-event systolic blood pressure was significantly higher (155.2 vs 138.5 mmHg, p<0.0001, Figure 8-1). The increment from the most recent premorbid to the first acute-phase systolic blood pressure was significantly higher for TIA/minor stroke than for major (NIHSS≥3) stroke (24.9 vs 18.2 mm Hg, p=0.022) despite a similar median time interval (p=0.427), with the smallest increment seen for cardioembolic major stroke (16.1 mmHg). A trend towards higher increments to the first systolic blood pressure measured within 24 hours was seen for transient ocular ischaemic events versus major stroke (26.3 vs 17.6 mm Hg, p=0.266). Similar results were found for comparisons with mean premorbid blood pressure and diastolic blood pressure.

Overall, the post-event acute-phase blood pressure and the pre-morbid to acute-phase post-event BP increment appear to be *inversely* related to the severity of ischaemic events. This suggests that cerebral injury itself is not a major driver of post-event hypertension, but further work is required to elucidate the true cause and to definitively establish any causal role of transient surges in blood pressure in precipitating cerebrovascular events.

8.3.2 Clinical outcomes in COMMIT and PROHIBIT-ICH

The PROHIBIT-ICH trial (Chapter 6:) is not powered to detect vascular outcomes, and a low number of recurrent vascular events thus far precludes any quantitative comparisons. In Chapter 5:, I examined follow-up blood pressure in the OXVASC

population before and after the commencement of the COMMIT study. Rapid and sustained blood pressure control will certainly be associated with a reduction in recurrent vascular events, and the blood pressure reduction I achieved in the COMMIT study is likely to result in at least a 40% reduction in recurrent stroke risk.[7] However, it would be preferable to demonstrate this directly.

One such approach in an observational setting is to replicate the methodology of the EXPRESS study, a population-based sequential comparison, previously performed in the OXVASC cohort.[42] Provisional population-based analyses that I have performed suggest substantial reductions in the risk of recurrent vascular events in the OXVASC population after the commencement of the COMMIT study (Figure 8-2), but other interventions coincided with the introduction of HBPM-guided treatment, which I intend to examine in more detail.

8.3.3 Target blood pressure in stroke secondary prevention; evidence for a J-curve with intensive BP lowering

As outlined in Chapter 1:, while a linear association of blood pressure with vascular events may be true in the general population, this might not be the case for people with existing vascular disease. The potential existence of a 'J-curve' in the association of blood pressure with stroke, i.e. a plateau in the beneficial effect (or harmful effects) when blood pressure is lowered below a critical nadir, might limit the utility of aggressive blood pressure treatment.

The J-curve was first observed for the association of diastolic blood pressure with MI and death, mostly in people with coronary artery disease who were treated for hypertension.[363, 364] More numerous studies have been performed in people with treated hypertension irrespective of coronary artery disease, where a J-shaped association has also been reported for cardiac events.[365-372] This is biologically plausible because, in contrast to other organs, the heart is perfused mainly during diastole so might be

particularly vulnerable to reductions in diastolic blood pressure. For stroke, however, a J-curve has not typically been observed in studies that reported J-shaped associations for other cardiovascular outcomes in a primary prevention setting,[373] nor in patients with coronary artery disease,[370, 371, 374] although data are generally lacking and most were inadequately powered for stroke outcomes.[375] There are even fewer data in patients with a history of stroke, but a J-shaped association with recurrent stroke has been observed in a few observational studies after ischaemic stroke for both systolic[376] and diastolic blood pressure.[377, 378]

Findings have been mixed in post hoc observational analyses of the main trials of blood pressure lowering after stroke. Achieved systolic blood pressure <120 mmHg was associated with an increased risk of recurrent stroke in PRoFESS compared to those with systolic blood pressure 130-140 mmHg after adjustment for major confounders,[19] and in SPS3, there was an increased rate of recurrent vascular events below 124/67 mmHg.[379] In PROGRESS, on the other hand, the lowest risk of recurrent stroke was found in the lowest category of achieved systolic blood pressure (<120, median 112 mmHg), suggesting a linear relationship.[63] However, whilst trials are the best way to determine effects of treatment, they are subject to potential selection bias that can undermine the reliability of risk associations within treatment groups.

Methodological differences might also explain these discrepant findings. First, PROGRESS included index ICH events, for which risk of recurrence is more strongly associated with blood pressure and might not follow the same shape as ischaemic stroke.[63] Second, a considerable number were withdrawn due to hypotensive symptoms during a run-in period,[61, 380] so some of the patients most vulnerable to harm from intensive blood pressure lowering might not have been included in the analysis. Third, randomisation to PROGRESS was delayed by at least six weeks post-event (only after a period of ‘clinical stability’ of at least two weeks plus a four-week run-in period) and patients were eligible for inclusion up to five years after TIA/stroke, so timing might be

an important factor regarding any potential harm from intensive blood pressure lowering.[61] Indeed, in PRoFESS, the J-curve for recurrent stroke was most pronounced in the subacute phase,[19] and in a post hoc analysis of the International Stroke Trial data, where patients were randomised within two days of a qualifying stroke, there was a strong J-shaped association between baseline systolic blood pressure and early death, and a trend towards a J-shaped association with early recurrent stroke.[78]

There are a number of possible explanations for the observation of a J-shaped association between blood pressure and stroke recurrence, not all of which support its existence as a true causal association. First, cerebral perfusion might be more dependent on systemic blood pressure after cerebrovascular events or in chronic uncontrolled hypertension, thus aggressive lowering of blood pressure might truly increase the risk of cerebral ischaemia. The cerebrovascular bed depends more on systolic blood pressure than does coronary perfusion,[381, 382] which might explain some of the contrast between stroke and cardiac events in the earlier studies of the J-curve with diastolic blood pressure. In addition, the J-curve might only apply to certain stroke subtypes and is perhaps dependent on the timing of post-event blood pressure lowering, which might explain some of the heterogeneity in the observational findings outlined above. Analogous to increased risk of cardiac events in low diastolic blood pressure in the presence of severe coronary artery disease, an inverse association of systolic blood pressure with recurrent stroke risk was found among patients with severe bilateral carotid stenosis in the non-intervention arms of carotid endarterectomy trials, but was not seen in participants randomised to surgery.[65] A similar finding has been observed for blood pressure control to <140/90 mmHg in the setting of high-grade vertebrobasilar stenosis with where blood flow is restricted.[66] The clear association of low systolic blood pressure with recurrent stroke in SPS3[379] might also indicate a specific mechanism for a J-curve in cerebral SVD. Mean systolic blood pressure <110 mmHg in the months preceding a first-ever TIA/stroke in a population-based study was almost three times

more likely (p=0.04) for lacunar than non-lacunar events among people aged ≥65 years,[37] and extreme dipping of nocturnal blood pressure has been associated with a greater burden of silent lacunar infarcts in elderly Japanese people.[147] Second, the association of low diastolic blood pressure and stroke recurrence, when observed particularly in elderly individuals,[37, 377, 378] might reflect high pulse pressure due to arterial stiffness, which in itself is a powerful risk factor for stroke.[383-386] In addition, true diastolic blood pressure is likely to be even lower than is recorded in these individuals, due to a cuff artefact.[378, 387] Moreover, a large cerebral blood pressure gradient in older people with stiff arteries means that for a diastolic blood pressure of 75 mmHg at the brachial artery, pressure in small intracerebral branch vessels might be below 40 mmHg, frequently dropping below the threshold for adequate perfusion.[388] Third, the J-shape could be a manifestation of the epidemiological phenomenon of reverse causality, whereby residual confounding risk factors might be the cause of both low blood pressure and recurrent events.[389] This might explain, for example, why a stronger J-shaped association with baseline systolic blood pressure was observed for early death than early recurrent stroke in the International Stroke Trial.[78] If this were the only cause of the J-curve in observational studies of people with stroke, then although clinicians should consider moderating antihypertensive treatment in patients with identified comorbidities, it would be wrong to assume that intensive reduction of blood pressure after stroke should be avoided more generally. However, considering the totality of the evidence, it is unlikely that reverse causality accounts entirely for the J-curve. A J-shaped association appears to persist after adjustment for identified chronic conditions, including heart failure, and baseline blood pressure levels,[19] and was observed in a recent study after adjustment for blood pressure trajectory in the preceding years, suggesting that it is not merely an artefact of blood pressure decline.[315]

The ESH-CHL-SHOT trial (NCT01563731) was a promising opportunity to address the question of the ideal target blood pressure in a large-scale, international, randomised

trial of intensive blood pressure-lowering (to <125 mmHg) after TIA/stroke in older, higher risk, and more hypertensive patients than in SPRINT. Unfortunately, despite continued recruitment being encouraged even after publication of the results of SPRINT,[390] the study was terminated due to poor recruitment.[391]

The COMMIT study population, with intensively controlled blood pressure across a range of stroke subtypes and long-term follow-up for vascular events, represents an excellent opportunity to examine for the presence of a J-curve, and I intend to investigate this further. I have performed some preliminary analyses, which suggest the presence of a J-shaped association between blood pressure and recurrent vascular events. This appears to be more marked on nocturnal than daytime blood pressure in categorical analyses (Figure 3). A J-curve is visible on continuous analyses using restricted cubic splines (see Figure 8-4 for all the association of all vascular events and one-month clinic blood pressure), but this looks to be driven mainly by cardiac outcomes when using HBPM (Figure 8-5), and the use of spline curves has been criticised by some as they might tend to exaggerate trends at both ends of the curve even in the absence of fewer events.[392]

8.4 Figures

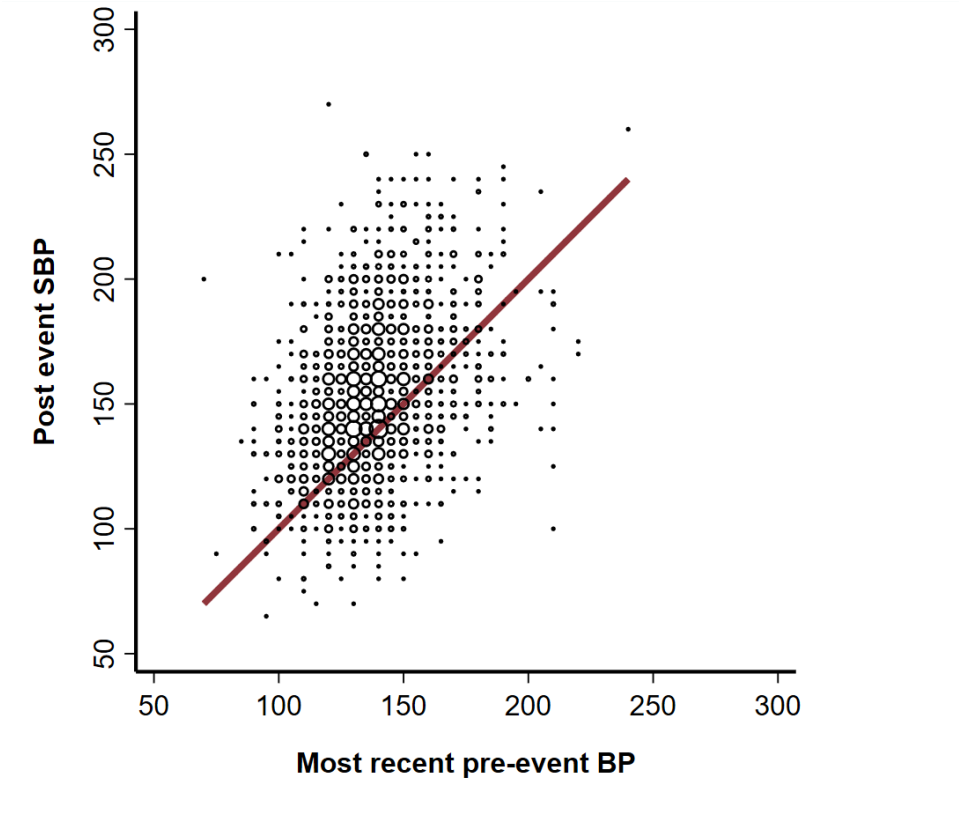


Figure 8-1 Scatterplot of first post-event systolic blood pressure (SBP) versus the most proximal premorbid SBP recording from primary care, in the OXVASC population

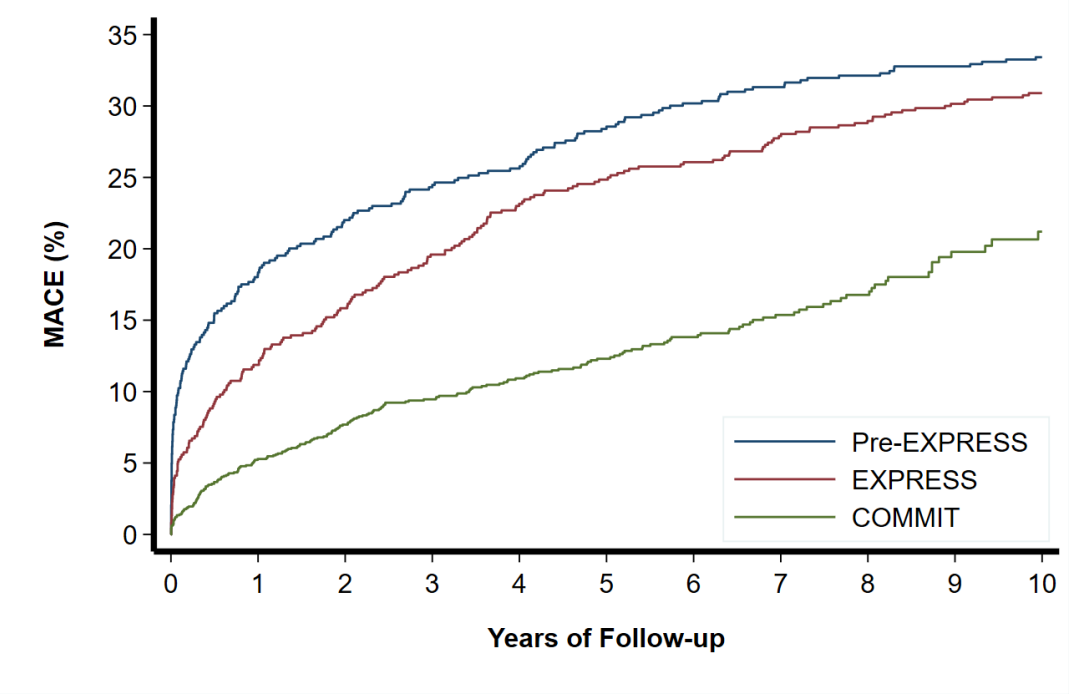


Figure 8-2 The cumulative incidence of recurrent major adverse cardiovascular events (MACE) in three phases of the OXVASC study

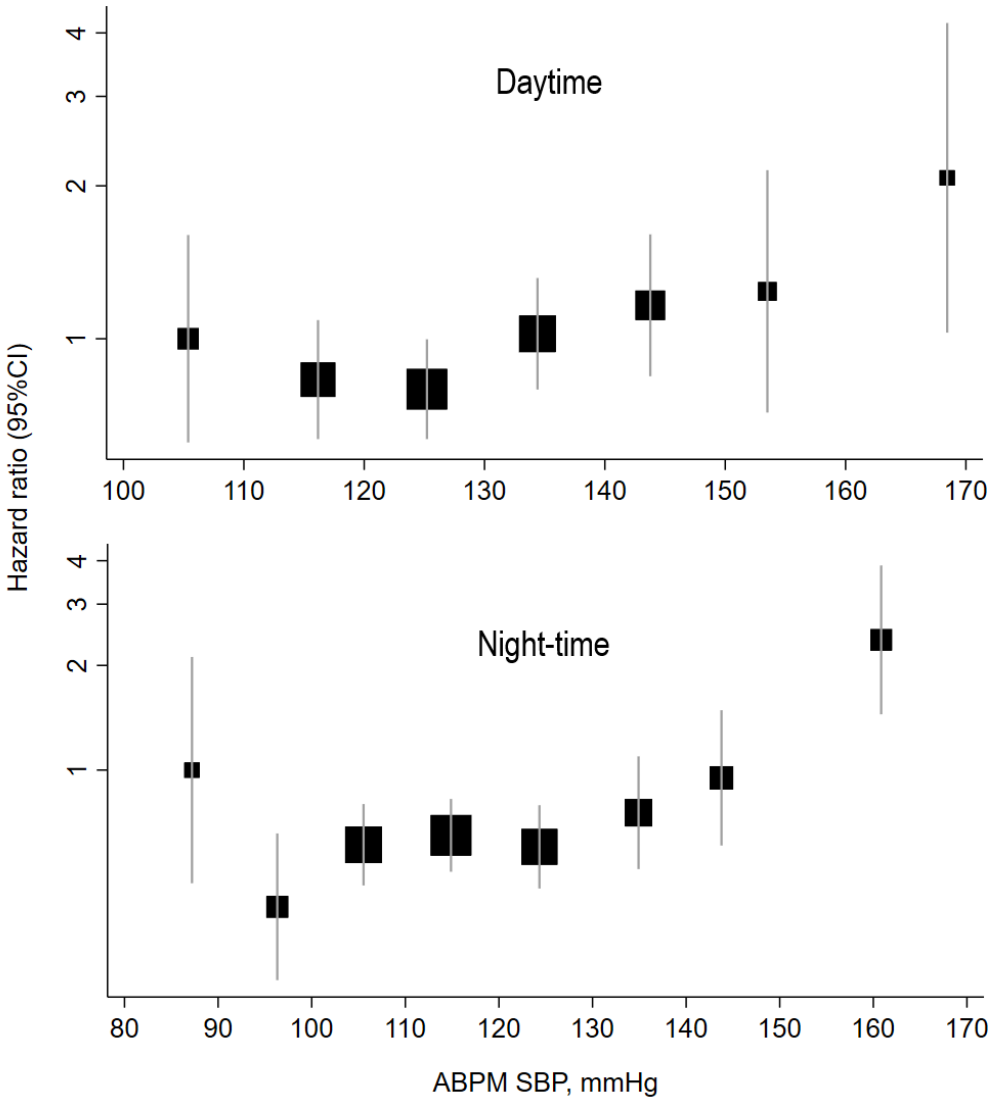


Figure 8-3 Risk of recurrent major vascular events (log scale) plotted against the mean of each 10 mmHg category of daytime and night-time mean systolic blood pressure (SBP) on 24-hour ambulatory blood pressure monitoring (ABPM), in the COMMIT study population.

The area of each square is inversely proportional to the variance of the log risk. 95% CIs for floated hazard ratios reflect uncertainty in the log risk for each estimate

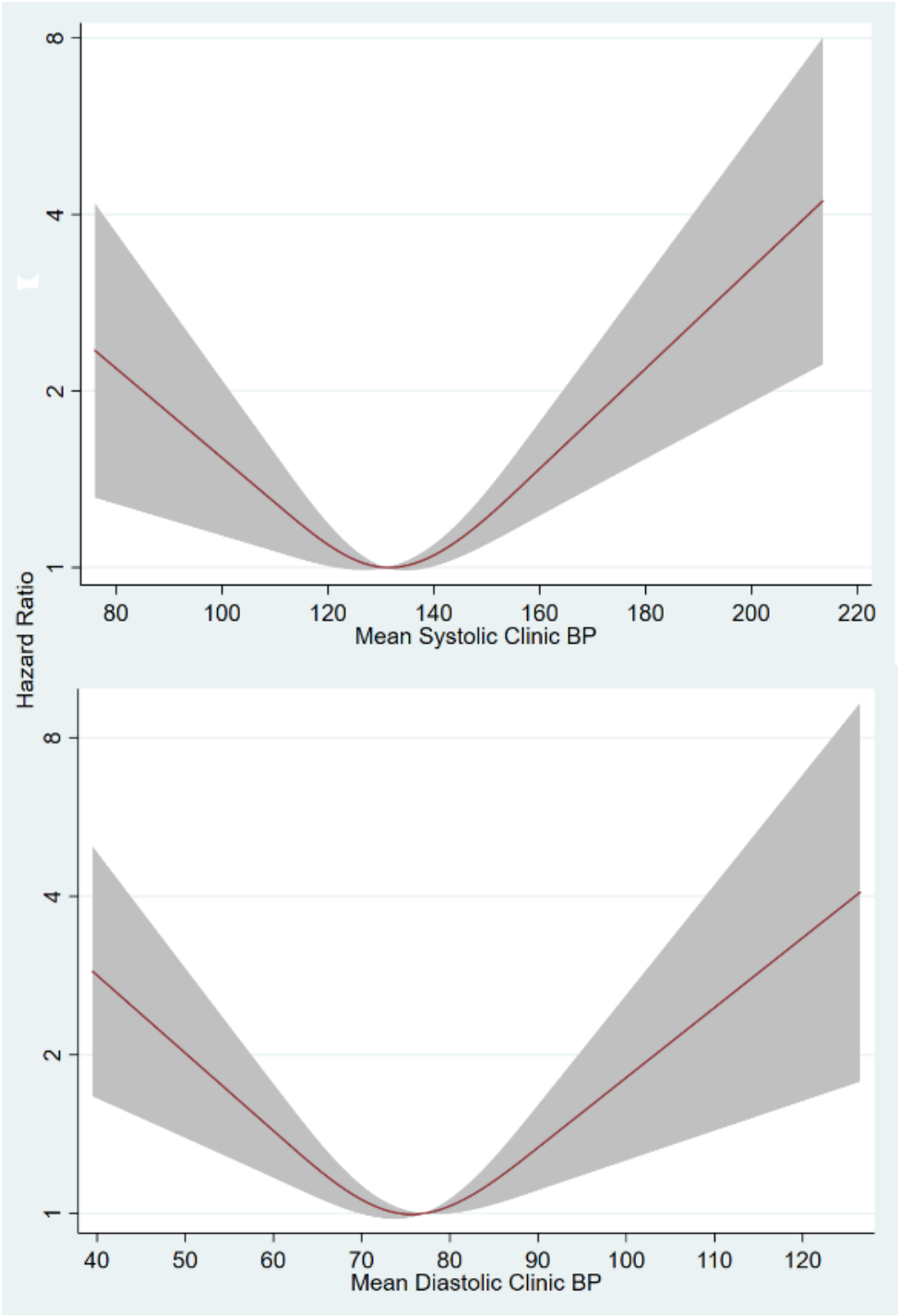


Figure 8-4 Hazard ratio of recurrent vascular events (95% CI shaded) plotted on a log scale against mean one-month follow-up clinic blood pressure fitted as a continuous variable in the COMMIT study, using a restricted cubic spline (3 knots)

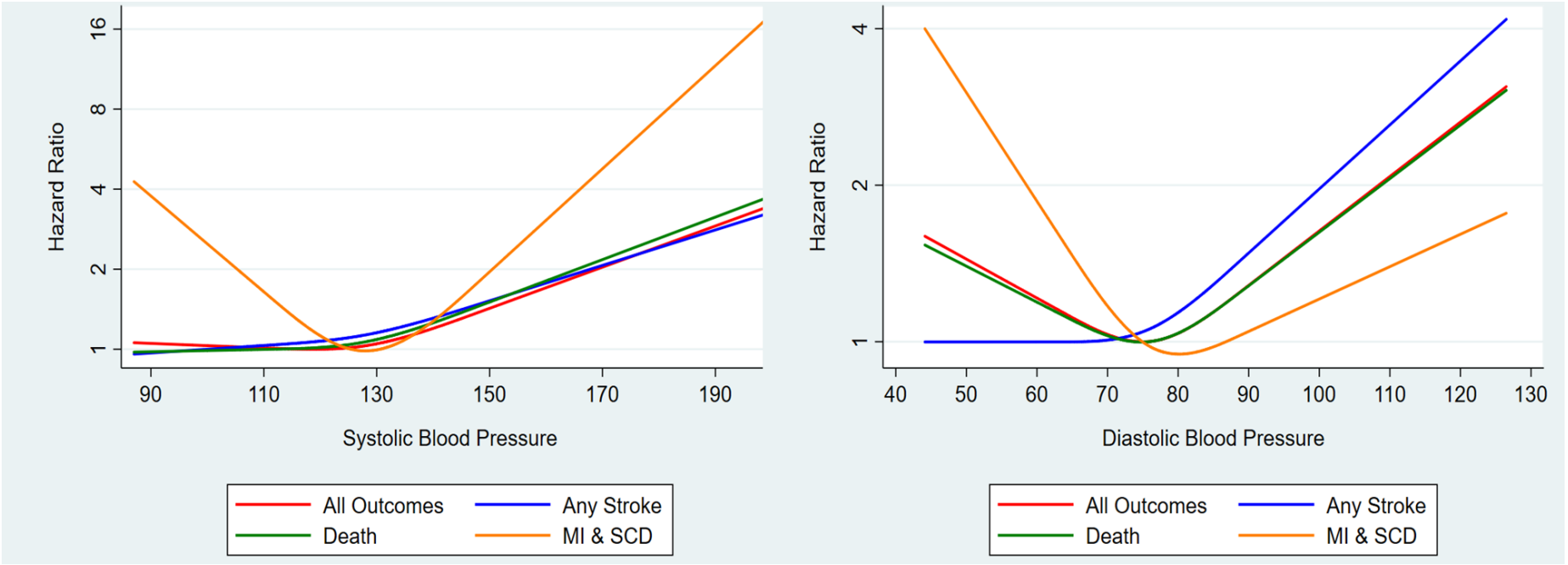


Figure 8-5 Hazard ratios of all recurrent vascular events (all outcomes), all-cause mortality, stroke, and myocardial infarction / sudden cardiac death (MI & SCD) plotted on a log scale against mean 7-day blood pressure on home blood pressure monitoring immediately preceding the one-month follow-up clinic, fitted as a continuous variable

References

1. Hay, J., *A British Medical Association Lecture on THE SIGNIFICANCE OF A RAISED BLOOD PRESSURE.* Br Med J, 1931. **2**(3679): p. 43-7.
2. Feigin, V.L., B. Norrving, and G.A. Mensah, *Global Burden of Stroke.* Circulation Research, 2017. **120**(3): p. 439-448.
3. Stanaway, J.D., et al., *Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Stu.* The Lancet, 2018. **392**(10159): p. 1923-1994.
4. Lawes, C.M., et al., *Blood pressure and cardiovascular disease in the Asia Pacific region.* J Hypertens, 2003. **21**(4): p. 707-16.
5. Lewington, S., et al., *Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.* Lancet, 2002. **360**(9349): p. 1903-13.
6. Ettehad, D., et al., *Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis.* The Lancet, 2016. **387**(10022): p. 957-967.
7. Law, M.R., J.K. Morris, and N.J. Wald, *Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies.* BMJ, 2009. **338**.
8. Amarenco, P., et al., *One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke.* New England Journal of Medicine, 2016. **374**(16): p. 1533-1542.
9. Rothwell, P.M., A. Algra, and P. Amarenco, *Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke.* The Lancet, 2011. **377**(9778): p. 1681-1692.
10. Akijian, L., et al., *Why do transient ischemic attack patients have higher early stroke recurrence risk than those with ischemic stroke? Influence of patient behavior and other risk factors in the North Dublin Population Stroke Study.* International Journal of Stroke, 2017. **12**(1): p. 96-104.
11. Katsanos, A.H., et al., *Blood Pressure Reduction and Secondary Stroke Prevention.* Hypertension, 2017. **69**(1): p. 171-179.
12. Klungel, O.H., et al., *Excess Stroke Among Hypertensive Men and Women Attributable to Undertreatment of Hypertension.* Stroke, 1999. **30**(7): p. 1312-1318.
13. Kernan, W.N., et al., *Blood Pressure Exceeding National Guidelines Among Women After Stroke.* Stroke, 2000. **31**(2): p. 415-419.
14. Glader, E.-L., et al., *Persistent Use of Secondary Preventive Drugs Declines Rapidly During the First 2 Years After Stroke.* Stroke, 2010. **41**(2): p. 397-401.
15. Lager, K.E., et al., *Quality of secondary prevention measures in TIA patients: a retrospective cohort study.* Postgraduate Medical Journal, 2012. **88**(1040): p. 305.
16. Doogue, R., et al., *Blood pressure control in patients with a previous stroke/transient ischaemic attack in primary care in Ireland: a cross sectional study.* BMC Family Practice, 2020. **21**(1).
17. Zakopoulos, N., et al., *Assessment of blood pressure control in hypertensive stroke survivors: an ambulatory blood pressure monitoring study.* Blood Pressure Monitoring, 2006. **11**(5): p. 235-241.

18. Dalli, L.L., et al., *Patterns of Use and Discontinuation of Secondary Prevention Medications After Stroke.* Neurology, 2021. **96**(1): p. e30-e41.
19. Ovbiagele, B., et al., *Level of systolic blood pressure within the normal range and risk of recurrent stroke.* Jama, 2011. **306**(19): p. 2137-44.
20. Hackam, D.G. and J.D. Spence, *Combining Multiple Approaches for the Secondary Prevention of Vascular Events After Stroke.* Stroke, 2007. **38**(6): p. 1881-1885.
21. Collins, R. and S. MacMahon, *Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease.* Br Med Bull, 1994. **50**(2): p. 272-98.
22. Rahimi, K., et al., *Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis.* The Lancet, 2021. **397**(10285): p. 1625-1636.
23. Lawes, C.M.M., et al., *Blood Pressure and Stroke: An Overview of Published Reviews.* Stroke, 2004. **35**(3): p. 776-785.
24. Lawes, C.M., et al., *Blood pressure and stroke: an overview of published reviews.* Stroke, 2004. **35**(4): p. 1024.
25. Howard, G., et al., *Racial Differences in the Impact of Elevated Systolic Blood Pressure on Stroke Risk.* JAMA Internal Medicine, 2013. **173**(1): p. 46.
26. Rodgers, A., et al., *Blood pressure and risk of stroke in patients with cerebrovascular disease.* BMJ, 1996. **313**(7050): p. 147-147.
27. Zonneveld, T.P., et al., *Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack.* Cochrane Database of Systematic Reviews, 2018.
28. Kitagawa, K., et al., *Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke.* JAMA Neurology, 2019. **76**(11): p. 1309.
29. The SPS3 Study Group, *Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial.* The Lancet, 2013. **382**(9891): p. 507-515.
30. Mant, J., et al., *Different systolic blood pressure targets for people with history of stroke or transient ischaemic attack: PAST-BP (Prevention After Stroke—Blood Pressure) randomised controlled trial.* BMJ, 2016: p. i708.
31. Bath, P.M., et al., *Intensive versus Guideline Blood Pressure and Lipid Lowering in Patients with Previous Stroke: Main Results from the Pilot 'Prevention of Decline in Cognition after Stroke Trial' (PODCAST) Randomised Controlled Trial.* PLOS ONE, 2017. **12**(1): p. e0164608.
32. Kleindorfer, D.O., et al., *2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association.* Stroke, 2021.
33. Zia, E., et al., *Blood Pressure in Relation to the Incidence of Cerebral Infarction and Intracerebral Hemorrhage.* Stroke, 2007. **38**(10): p. 2681-2685.
34. Fischer, U., et al., *Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study.* Lancet Neurol, 2014. **13**(4): p. 374-84.
35. Chapman, N., et al., *Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial.* Stroke, 2004. **35**(1): p. 116-21.
36. Khan, U., et al., *Risk factor profile of cerebral small vessel disease and its subtypes.* J Neurol Neurosurg Psychiatry, 2007. **78**(7): p. 702-6.
37. Li, L., et al., *Time course of blood pressure control prior to lacunar TIA and stroke: Population-based study.* Neurology, 2018. **90**(20): p. e1732-e1741.
38. Boiten, J., et al., *Risk factors for lacunes.* Neurology, 1996. **47**(4): p. 1109.

39. Jackson, C.A., et al., *Differing Risk Factor Profiles of Ischemic Stroke Subtypes.* Evidence for a Distinct Lacunar Arteriopathy?, 2010. **41**(4): p. 624-629.
40. Lau, K.K., et al., *Long-Term Premorbid Blood Pressure and Cerebral Small Vessel Disease Burden on Imaging in Transient Ischemic Attack and Ischemic Stroke.* Stroke, 2018. **49**(9): p. 2053-2060.
41. Rothwell, P.M., et al., *A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack.* Lancet, 2005. **366**(9479): p. 29-36.
42. Rothwell, P.M., et al., *Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison.* Lancet, 2007. **370**(9596): p. 1432-42.
43. Rothwell, P.M., et al., *Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials.* The Lancet, 2016. **388**(10042): p. 365-375.
44. Obaid, M., et al., *Can we prevent poststroke cognitive impairment? An umbrella review of risk factors and treatments.* BMJ Open, 2020. **10**(9): p. e037982.
45. Rost, N.S., et al., *Cognitive Impairment and Dementia After Stroke: Design and Rationale for the DISCOVERY Study.* Stroke, 2021. **52**(8): p. e499-e516.
46. Pendlebury, S.T. and P.M. Rothwell, *Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study.* The Lancet Neurology, 2019. **18**(3): p. 248-258.
47. Qiu, C., B. Winblad, and L. Fratiglioni, *The age-dependent relation of blood pressure to cognitive function and dementia.* Lancet Neurol, 2005. **4**(8): p. 487-99.
48. Emdin, C.A., et al., *Blood Pressure and Risk of Vascular Dementia.* Stroke, 2016. **47**(6): p. 1429-1435.
49. Williamson, J.D., et al., *Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia.* JAMA, 2019. **321**(6): p. 553.
50. Chiuve, S.E., et al., *Primary Prevention of Stroke by Healthy Lifestyle.* Circulation, 2008. **118**(9): p. 947-954.
51. Elmer, P.J., et al., *Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial.* Ann Intern Med, 2006. **144**(7): p. 485-95.
52. Tuck, M.L., et al., *The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients.* N Engl J Med, 1981. **304**(16): p. 930-3.
53. Warburton, D.E., et al., *A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults.* International Journal of Behavioral Nutrition and Physical Activity, 2010. **7**(1): p. 39.
54. He, F.J., J. Li, and G.A. Macgregor, *Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials.* BMJ, 2013. **346**(apr03 3): p. f1325-f1325.
55. Appel, L.J., et al., *Dietary Approaches to Prevent and Treat Hypertension.* Hypertension, 2006. **47**(2): p. 296-308.
56. Whelton, P.K., et al., *Sodium Reduction and Weight Loss in the Treatment of Hypertension in Older Persons.* JAMA, 1998. **279**(11): p. 839.
57. Ascherio, A., et al., *A prospective study of nutritional factors and hypertension among US men.* Circulation, 1992. **86**(5): p. 1475-1484.
58. Turan, T.N., et al., *Relationship between Risk Factor Control and Compliance with a Lifestyle Modification Program in the Stenting Aggressive Medical Management for Prevention of Recurrent Stroke in Intracranial Stenosis Trial.* Journal of Stroke and Cerebrovascular Diseases, 2018. **27**(3): p. 801-805.

59. Williams, B., et al., *2018 ESC/ESH Guidelines for the management of arterial hypertension.* European Heart Journal, 2018. **39**(33): p. 3021-3104.
60. Rudd, A.G., et al., *National clinical guideline for stroke: 5th edition 2016.* Clinical Medicine, 2017(1470-2118).
61. PROGRESS Collaborative Group, *Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack.* Lancet, 2001. **358**(9287): p. 1033-41.
62. Czernichow, S., et al., *The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials.* Journal of Hypertension, 2011. **29**(1): p. 4-16.
63. Arima, H., et al., *Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial.* J Hypertens, 2006. **24**(6): p. 1201-1208.
64. Yusuf, S., et al., *Telmisartan to prevent recurrent stroke and cardiovascular events.* N Engl J Med, 2008. **359**(12): p. 1225-37.
65. Rothwell, P.M., S.C. Howard, and J.D. Spence, *Relationship between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease.* Stroke, 2003. **34**(11): p. 2583-90.
66. Amin-Hanjani, S., et al., *Higher Stroke Risk with Lower Blood Pressure in Hemodynamic Vertebrobasilar Disease: Analysis from the VERiTAS Study.* Journal of Stroke and Cerebrovascular Diseases, 2017. **26**(2): p. 403-410.
67. Shimbo, D., et al., *Short-Term Risk of Serious Fall Injuries in Older Adults Initiating and Intensifying Treatment With Antihypertensive Medication.* Circulation: Cardiovascular Quality and Outcomes, 2016. **9**(3): p. 222-229.
68. Group, T.S.R., *A Randomized Trial of Intensive versus Standard Blood-Pressure Control.* New England Journal of Medicine, 2015. **373**(22): p. 2103-2116.
69. Oppenheimer, S. and V. Hachinski, *Complications of acute stroke.* The Lancet, 1992. **339**(8795): p. 721-724.
70. Britton, M., A. Carlsson, and U. de Faire, *Blood pressure course in patients with acute stroke and matched controls.* Stroke, 1986. **17**(5): p. 861-4.
71. Morfis, L., et al., *Blood pressure changes in acute cerebral infarction and hemorrhage.* Stroke, 1997. **28**(7): p. 1401-5.
72. Qureshi, A.I., *Acute Hypertensive Response in Patients With Stroke.* Circulation, 2008. **118**(2): p. 176-187.
73. Harper, G., C.M. Castleden, and J.F. Potter, *Factors affecting changes in blood pressure after acute stroke.* Stroke, 1994. **25**(9): p. 1726-9.
74. Wallace, J.D. and L.L. Levy, *Blood pressure after stroke.* Jama, 1981. **246**(19): p. 2177-80.
75. Olsen, T.S., et al., *Blood flow and vascular reactivity in collaterally perfused brain tissue. Evidence of an ischemic penumbra in patients with acute stroke.* Stroke, 1983. **14**(3): p. 332-41.
76. Rothwell, P.M., *Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension.* The Lancet, 2010. **375**(9718): p. 938-948.
77. Willmot, M., J. Leonardi-Bee, and P.M.W. Bath, *High Blood Pressure in Acute Stroke and Subsequent Outcome.* Hypertension, 2004. **43**(1): p. 18-24.
78. Leonardi-Bee, J., et al., *Blood Pressure and Clinical Outcomes in the International Stroke Trial.* Stroke, 2002. **33**(5): p. 1315-1320.
79. Ahmed, N., P. Nasman, and N.G. Wahlgren, *Effect of intravenous nimodipine on blood pressure and outcome after acute stroke.* Stroke, 2000. **31**(6): p. 1250-5.

80. He, J., et al., *Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: The catis randomized clinical trial.* JAMA, 2014. **311**(5): p. 479-489.
81. Potter, J.F., et al., *Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial.* Lancet Neurol, 2009. **8**(1): p. 48-56.
82. Robinson, T.G., et al., *Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial.* Lancet Neurol, 2010. **9**(8): p. 767-75.
83. Sandset, E.C., et al., *The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial.* The Lancet, 2011. **377**(9767): p. 741-750.
84. Wang, H., et al., *Effects of early blood pressure lowering on early and long-term outcomes after acute stroke: an updated meta-analysis.* PLoS One, 2014. **9**(5): p. e97917.
85. Investigators, T.E.T., *Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial.* The Lancet, 2015. **385**(9968): p. 617-628.
86. Bath, P.M., et al., *Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial.* The Lancet, 2019. **393**(10175): p. 1009-1020.
87. Anderson, C.S., et al., *Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial.* The Lancet, 2019. **393**(10174): p. 877-888.
88. Bath, P.M. and K. Krishnan, *Interventions for deliberately altering blood pressure in acute stroke.* Cochrane Database of Systematic Reviews, 2014.
89. Rordorf, G., et al., *Pharmacological Elevation of Blood Pressure in Acute Stroke.* Stroke, 1997. **28**(11): p. 2133-2138.
90. Kim, H.-J. and D.-W. Kang, *Induced Hypertensive Therapy in an Acute Ischemic Stroke Patient with Early Neurological Deterioration.* Journal of Clinical Neurology, 2007. **3**(4): p. 187.
91. Lee, M.H., et al., *Pharmacologically Induced Hypertension Therapy for Acute Stroke Patients.* Journal of Stroke, 2019. **21**(2): p. 228-230.
92. Bang, O.Y., et al., *Therapeutic-induced hypertension in patients with noncardioembolic acute stroke.* Neurology, 2019. **93**(21): p. e1955-e1963.
93. Hillis, A.E., et al., *A Pilot Randomized Trial of Induced Blood Pressure Elevation: Effects on Function and Focal Perfusion in Acute and Subacute Stroke.* Cerebrovascular Diseases, 2003. **16**(3): p. 236-246.
94. Zhang, W.W., et al., *Hypertension and TIA.* International Journal of Stroke, 2009. **4**(3): p. 206-214.
95. Whelton, P.K., et al., *2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Pr.* Hypertension, 2018. **71**(6): p. e13-e115.
96. Pedelty, L. and P.B. Gorelick, *Chronic Management of Blood Pressure After Stroke.* Hypertension, 2004. **44**(1): p. 1-5.
97. Law, M.R., J.K. Morris, and N.J. Wald, *Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised*

trials in the context of expectations from prospective epidemiological studies. BMJ, 2009. **338**(may19 1): p. b1665-b1665.
98. Castilla-Guerra, L. and M.D.C. Fernández-Moreno, *Update on the Management of Hypertension for Secondary Stroke Prevention.* European Neurology, 2012. **68**(1): p. 1-7.
99. Kjeldsen, S.E., et al., *Unattended Blood Pressure Measurements in the Systolic Blood Pressure Intervention Trial.* Hypertension, 2016. **67**(5): p. 808-812.
100. The ACCORD Study Group, *Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus.* New England Journal of Medicine, 2010. **362**(17): p. 1575-1585.
101. Qureshi, A.I., A.D. Mendelow, and D.F. Hanley, *Intracerebral haemorrhage.* The Lancet, 2009. **373**(9675): p. 1632-1644.
102. van Asch, C.J., et al., *Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis.* Lancet Neurol, 2010. **9**(2): p. 167-76.
103. Feigin, V.L., et al., *Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review.* Lancet Neurol, 2009. **8**(4): p. 355-69.
104. O'Donnell, M.J., et al., *Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study.* Lancet, 2010. **376**(9735): p. 112-23.
105. Poon, M.T., A.F. Fonville, and R. Al-Shahi Salman, *Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis.* J Neurol Neurosurg Psychiatry, 2014. **85**(6): p. 660-7.
106. Krishnamurthi, R.V., et al., *Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010.* Lancet Glob Health, 2013. **1**(5): p. e259-81.
107. Jorgensen, H.S., et al., *Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study.* Neurology, 1997. **48**(4): p. 891-5.
108. Moulin, S., et al., *Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study.* Lancet Neurol, 2016. **15**(8): p. 820-829.
109. Feldmann, E., et al., *Major risk factors for intracerebral hemorrhage in the young are modifiable.* Stroke, 2005. **36**(9): p. 1881-5.
110. Biffi, A., et al., *Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage.* Jama, 2015. **314**(9): p. 904-12.
111. Rodriguez-Luna, D., et al., *Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage.* Eur J Neurol, 2013. **20**(9): p. 1277-83.
112. Sakamoto, Y., et al., *Systolic Blood Pressure After Intravenous Antihypertensive Treatment and Clinical Outcomes in Hyperacute Intracerebral Hemorrhage.* Stroke, 2013. **44**(7): p. 1846-1851.
113. Butcher, K.S., et al., *The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial.* Stroke, 2013. **44**(3): p. 620-6.
114. Gould, B., et al., *Autoregulation of cerebral blood flow is preserved in primary intracerebral hemorrhage.* Stroke, 2013. **44**(6): p. 1726-8.
115. Anderson, C.S., et al., *Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage.* N Engl J Med, 2013. **368**(25): p. 2355-65.
116. Qureshi, A.I., et al., *Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage.* New England Journal of Medicine, 2016. **375**(11): p. 1033-1043.
117. Boulouis, G., et al., *Intensive blood pressure lowering in patients with acute intracerebral haemorrhage: clinical outcomes and haemorrhage expansion. Systematic review and meta-analysis of randomised trials.* Journal of Neurology, Neurosurgery & Psychiatry, 2017. **88**(4): p. 339-345.

118. Tsivgoulis, G., et al., *Intensive blood pressure reduction in acute intracerebral hemorrhage.* A meta-analysis, 2014. **83**(17): p. 1523-1529.
119. Gong, S., et al., *Effects of intensive blood pressure reduction on acute intracerebral hemorrhage: a systematic review and meta-analysis.* Scientific reports, 2017. **7**(1): p. 1-9.
120. Lattanzi, S., et al., *How Should We Lower Blood Pressure after Cerebral Hemorrhage? A Systematic Review and Meta-Analysis.* Cerebrovascular Diseases, 2017. **43**(5-6): p. 207-213.
121. Shi, L., et al., *Blood pressure management for acute intracerebral hemorrhage: a meta-analysis.* Scientific reports, 2017. **7**(1): p. 1-8.
122. Moullaali, T.J., et al., *Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data.* The Lancet Neurology, 2019. **18**(9): p. 857-864.
123. A. Divani, A., et al., *The Magnitude of Blood Pressure Reduction Predicts Poor In-Hospital Outcome in Acute Intracerebral Hemorrhage.* Neurocritical Care, 2020.
124. Qureshi, A.I., et al., *Outcomes of Intensive Systolic Blood Pressure Reduction in Patients With Intracerebral Hemorrhage and Excessively High Initial Systolic Blood Pressure.* JAMA Neurology, 2020.
125. Birns, J., H. Markus, and L. Kalra, *Blood pressure reduction for vascular risk: is there a price to be paid?* Stroke, 2005. **36**(6): p. 1308-13.
126. Eriksson, S., B. Olofsson, and P. Wester, *Atenolol in Secondary Prevention after Stroke.* Cerebrovascular Diseases, 1995. **5**(1): p. 21-25.
127. PATS Collaborating Group, *Post-stroke antihypertensive treatment study. A preliminary result.* Chin Med J (Engl), 1995. **108**(9): p. 710-7.
128. The Dutch TIA Trial Study Group, *Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. The Dutch TIA Trial Study Group.* Stroke, 1993. **24**(4): p. 543-548.
129. Cates, C., *The lowering of blood pressure after stroke.* The Lancet, 2001. **358**(9297): p. 1993.
130. Psaty, B.M., N.S. Weiss, and C.D. Furberg, *The PROGRESS trial: questions about the effectiveness of angiotensin converting enzyme inhibitors.* American Journal of Hypertension, 2002. **15**(5): p. 472-474.
131. Schrader, J., et al., *Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention.* Stroke, 2005. **36**(6): p. 1218-1224.
132. Wang, W.-T., et al., *Comparative Effectiveness of Blood Pressure-lowering Drugs in Patients who have Already Suffered From Stroke: Traditional and Bayesian Network Meta-analysis of Randomized Trials.* Medicine, 2016. **95**(15).
133. Suchard, M.A., et al., *Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis.* The Lancet, 2019. **394**(10211): p. 1816-1826.
134. Chen, G.J. and M.S. Yang, *The Effects of Calcium Channel Blockers in the Prevention of Stroke in Adults with Hypertension: A Meta-Analysis of Data from 273,543 Participants in 31 Randomized Controlled Trials.* PLoS ONE, 2013. **8**(3): p. e57854.
135. Rothwell, P.M., *Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension.* Lancet, 2010. **375**(9718): p. 938-948.
136. Rothwell, P.M., et al., *Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke.* Lancet Neurol, 2010. **9**(5): p. 469-80.
137. Webb, A.J., et al., *Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis.* Lancet, 2010. **375**(9718): p. 906-15.

138. Millar-Craig, M.W., C.N. Bishop, and E.B. Raftery, *Circadian variation of blood-pressure.* Lancet, 1978. **1**(8068): p. 795-7.
139. Fagard, R.H., et al., *Night–day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension.* Journal of Human Hypertension, 2009. **23**(10): p. 645-653.
140. Boggia, J., et al., *Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study.* Lancet, 2007. **370**(9594): p. 1219-29.
141. Hermida, R.C., et al., *INFLUENCE OF CIRCADIAN TIME OF HYPERTENSION TREATMENT ON CARDIOVASCULAR RISK: RESULTS OF THE MAPEC STUDY.* Chronobiology International, 2010. **27**(8): p. 1629-1651.
142. Hermida, R.C., et al., *Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial.* European Heart Journal, 2020. **41**(48): p. 4565-4576.
143. Crespo, J.J., et al., *The Hygia Project and Hygia Chronotherapy Trial: insights of we clinical investigators on the impact of the embedded continuing medical education on primary-care practice and improved patient cardiovascular health.* Chronobiology International, 2020. **37**(5): p. 759-766.
144. Guthrie, G., et al., *Chronotherapy in hypertension: the devil is in the details.* European Heart Journal, 2020. **41**(16): p. 1606-1607.
145. Kreutz, R., et al., *Blood pressure medication should not be routinely dosed at bedtime. We must disregard the data from the HYGIA project.* Blood Pressure, 2020. **29**(3): p. 135-136.
146. Lemmer, B. and M. Middeke, *A commentary on the Spanish hypertension studies MAPEC and HYGIA.* Chronobiology International, 2020. **37**(5): p. 728-730.
147. Kario, K., et al., *Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers.* Hypertension, 1996. **27**(1): p. 130-5.
148. Pierdomenico, S.D., et al., *Circadian blood pressure changes and myocardial ischemia in hypertensive patients with coronary artery disease.* J Am Coll Cardiol, 1998. **31**(7): p. 1627-34.
149. Suzuki, Y., et al., *Prognostic value of nighttime blood pressure in the elderly: a prospective study of 24-hour blood pressure.* Hypertens Res, 2000. **23**(4): p. 323-30.
150. Rorie, D.A., et al., *Methods of a large prospective, randomised, open-label, blinded end-point study comparing morning versus evening dosing in hypertensive patients: the Treatment In Morning versus Evening (TIME) study.* BMJ Open, 2016. **6**(2): p. e010313.
151. Chow, C.K., *Prevalence, Awareness, Treatment, and Control of Hypertension in Rural and Urban Communities in High-, Middle-, and Low-Income Countries.* JAMA, 2013. **310**(9): p. 959.
152. Nguyen, T.N. and C.K. Chow, *Global and national high blood pressure burden and control.* The Lancet, 2021. **398**(10304): p. 932-933.
153. Bahiru, E., et al., *Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases.* Cochrane Database of Systematic Reviews, 2017.
154. Joseph, P., et al., *Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis.* The Lancet, 2021.
155. Chow, C.K., et al., *Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial.* The Lancet, 2021.

156. Saiz, L.C., et al., *Blood pressure targets for the treatment of people with hypertension and cardiovascular disease.* The Cochrane database of systematic reviews, 2020. **9**(9): p. CD010315-CD010315.
157. Webb, A.J.S. and P.M. Rothwell, *Effect of Dose and Combination of Antihypertensives on Interindividual Blood Pressure Variability.* A Systematic Review, 2011. **42**(10): p. 2860-2865.
158. Brugts, J.J., et al., *The incidence and clinical predictors of ACE-inhibitor induced dry cough by perindopril in 27,492 patients with vascular disease.* International Journal of Cardiology, 2014. **176**(3): p. 718-723.
159. To, T., et al., *Global asthma prevalence in adults: findings from the cross-sectional world health survey.* BMC Public Health, 2012. **12**(1): p. 204.
160. Marentette, M.A., et al., *Antihypertensive persistence and drug class.* Can J Cardiol, 2002. **18**(6): p. 649-56.
161. Cuffe, R.L., et al., *Medium-Term Variability of Blood Pressure and Potential Underdiagnosis of Hypertension in Patients With Previous Transient Ischemic Attack or Minor Stroke.* Stroke, 2006. **37**(11): p. 2776-2783.
162. Howard, S.C. and P.M. Rothwell, *Reproducibility of measures of visit-to-visit variability in blood pressure after transient ischaemic attack or minor stroke.* Cerebrovasc Dis, 2009. **28**(4): p. 331-40.
163. Muntner, P., et al., *Reproducibility of visit-to-visit variability of blood pressure measured as part of routine clinical care.* Journal of Hypertension, 2011. **29**(12): p. 2332-2338.
164. Rothwell, P.M., et al., *Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension.* Lancet, 2010. **375**(9718): p. 895-905.
165. Gosmanova, E.O., et al., *Association of Systolic Blood Pressure Variability With Mortality, Coronary Heart Disease, Stroke, and Renal Disease.* Journal of the American College of Cardiology, 2016. **68**(13): p. 1375-1386.
166. Tai, C., et al., *Prognostic significance of visit-to-visit systolic blood pressure variability: a meta-analysis of 77,299 patients.* J Clin Hypertens (Greenwich), 2015. **17**(2): p. 107-15.
167. Wang, J., et al., *Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: a systematic review and meta-analysis.* J Hypertens, 2017. **35**(1): p. 10-17.
168. Diaz, K.M., et al., *Visit-to-Visit Variability of Blood Pressure and Cardiovascular Disease and All-Cause Mortality.* Hypertension, 2014. **64**(5): p. 965-982.
169. Stevens, S.L., et al., *Blood pressure variability and cardiovascular disease: systematic review and meta-analysis.* BMJ, 2016: p. i4098.
170. Mehlum, M.H., et al., *Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks.* European Heart Journal, 2018. **39**(24): p. 2243-2251.
171. Smith, T.R., et al., *Medication class effects on visit-to-visit variability of blood pressure measurements: analysis of electronic health record data in the "real world".* J Clin Hypertens (Greenwich), 2013. **15**(9): p. 655-62.
172. Muntner, P., et al., *Effect of chlorthalidone, amlodipine, and lisinopril on visit-to-visit variability of blood pressure: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.* Journal of clinical hypertension (Greenwich, Conn.), 2014. **16**(5): p. 323-330.
173. Webb, A.J.S., et al., *Prognostic Significance of Blood Pressure Variability on Beat-to-Beat Monitoring After Transient Ischemic Attack and Stroke.* Stroke, 2018. **49**(1): p. 62-67.
174. Webb, A.J., et al., *Response of day-to-day home blood pressure variability by antihypertensive drug class after transient ischemic attack or nondisabling stroke.* Stroke, 2014. **45**(10): p. 2967-73.

175. Fisher, J.W., *The Diagnostic Value of the Sphygmomanometer in Examinations for Life Insurance.* Journal of the American Medical Association, 1914. **LXIII**(20): p. 1752.
176. Lewington, S., et al., *Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.* Lancet, 2002. **360**(9349): p. 1903-13.
177. Parati, G., J.E. Ochoa, and G. Bilo, *Moving Beyond Office Blood Pressure to Achieve a Personalized and More Precise Hypertension Management.* Hypertension, 2017. **70**(3): p. e20-e31.
178. Kallioinen, N., et al., *Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: a systematic review.* Journal of Hypertension, 2017. **35**(3): p. 421-441.
179. Parati, G., et al., *European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring.* Journal of Hypertension, 2008. **26**(8): p. 1505-1526.
180. Mancia, G., *EFFECTS OF BLOOD-PRESSURE MEASUREMENT BY THE DOCTOR ON PATIENT'S BLOOD PRESSURE AND HEART RATE.* The Lancet, 1983. **322**(8352): p. 695-698.
181. Pickering, T.G., et al., *How common is white coat hypertension?* Jama, 1988. **259**(2): p. 225-8.
182. Myers, M.G., M. Valdivieso, and A. Kiss, *Use of automated office blood pressure measurement to reduce the white coat response.* Journal of Hypertension, 2009. **27**(2): p. 280-286.
183. The SPRINT Research Group, *A Randomized Trial of Intensive versus Standard Blood-Pressure Control.* New England Journal of Medicine, 2015. **373**(22): p. 2103-2116.
184. Andreadis, E.A., et al., *Automated Office Blood Pressure and 24-h Ambulatory Measurements are Equally Associated With Left Ventricular Mass Index.* American Journal of Hypertension, 2011. **24**(6): p. 661-666.
185. Campbell, N.R.C., et al., *Automated oscillometric blood pressure versus auscultatory blood pressure as a predictor of carotid intima–medial thickness in male firefighters.* Journal of Human Hypertension, 2007. **21**(7): p. 588-590.
186. Nerenberg, K.A., et al., *Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children.* Canadian Journal of Cardiology, 2018. **34**(5): p. 506-525.
187. Muntner, P., et al., *Measurement of Blood Pressure in Humans: A Scientific Statement From the American Heart Association.* Hypertension, 2019. **73**(5).
188. de la Sierra, A., et al., *Ambulatory blood pressure in hypertensive patients with inclusion criteria for the SPRINT trial.* J Am Soc Hypertens, 2016. **10**(12): p. 947-953.e5.
189. Asayama, K., et al., *Comparison of blood pressure values-self-measured at home, measured at an unattended office, and measured at a conventional attended office.* Hypertens Res, 2019. **42**(11): p. 1726-1737.
190. Gaborieau, V., N. Delarche, and P. Gosse, *Ambulatory blood pressure monitoring versus self-measurement of blood pressure at home: correlation with target organ damage.* Journal of Hypertension, 2008. **26**(10): p. 1919-1927.
191. Clement, D.L., et al., *Prognostic Value of Ambulatory Blood-Pressure Recordings in Patients with Treated Hypertension.* New England Journal of Medicine, 2003. **348**(24): p. 2407-2415.
192. Fagard, R.H., et al., *Daytime and Nighttime Blood Pressure as Predictors of Death and Cause-Specific Cardiovascular Events in Hypertension.* Hypertension, 2008. **51**(1): p. 55-61.

193. Sega, R., et al., *Prognostic Value of Ambulatory and Home Blood Pressures Compared With Office Blood Pressure in the General Population.* Circulation, 2005. **111**(14): p. 1777-1783.
194. Dolan, E., et al., *Superiority of Ambulatory Over Clinic Blood Pressure Measurement in Predicting Mortality.* Hypertension, 2005. **46**(1): p. 156-161.
195. Staessen, J.A., et al., *Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension.* JAMA, 1999. **282**(6): p. 539-546.
196. Björklund, K., et al., *Prognostic significance of 24-h ambulatory blood pressure characteristics for cardiovascular morbidity in a population of elderly men.* Journal of Hypertension, 2004. **22**(9): p. 1691-1697.
197. Hansen, T.W., et al., *Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7030 individuals.* Journal of Hypertension, 2007. **25**(8): p. 1554-1564.
198. Piper, M.A., et al., *Diagnostic and Predictive Accuracy of Blood Pressure Screening Methods With Consideration of Rescreening Intervals: A Systematic Review for the U.S. Preventive Services Task Force.* Annals of Internal Medicine, 2015. **162**(3): p. 192.
199. National Institute for Health and Care Excellence (NICE), *NICE guideline [NG136] Hypertension in adults: diagnosis and management.* NICE, 2019.
200. Unger, T., et al., *2020 International Society of Hypertension Global Hypertension Practice Guidelines.* Hypertension, 2020. **75**(6): p. 1334-1357.
201. Krist, A.H., et al., *Screening for Hypertension in Adults.* JAMA, 2021. **325**(16): p. 1650.
202. Umemura, S., et al., *The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019).* Hypertension Research, 2019. **42**(9): p. 1235-1481.
203. Joint Committee for Guideline, R., *2018 Chinese Guidelines for Prevention and Treatment of Hypertension-A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension.* Journal of geriatric cardiology : JGC, 2019. **16**(3): p. 182-241.
204. Kario, K., et al., *Guidance on ambulatory blood pressure monitoring: A statement from the HOPE Asia Network.* The Journal of Clinical Hypertension, 2021. **23**(3): p. 411-421.
205. Lee, H.-Y., et al., *2018 Korean Society of Hypertension Guidelines for the management of hypertension: part II-diagnosis and treatment of hypertension.* Clinical Hypertension, 2019. **25**(1).
206. Bo, Y., et al., *Short-term reproducibility of ambulatory blood pressure measurements: a systematic review and meta-analysis of 35 observational studies.* Journal of Hypertension, 2020. **38**(11): p. 2095-2109.
207. Keren, S., et al., *Limited reproducibility of 24-h ambulatory blood pressure monitoring.* Clin Exp Hypertens, 2015. **37**(7): p. 599-603.
208. Van Der Steen, M., et al., *Reproducibility of ambulatory blood pressure monitoring in daily practice.* Journal of Human Hypertension, 1999. **13**(5): p. 303-308.
209. Ringrose, J.S., et al., *Patient perceptions of ambulatory blood pressure monitoring testing, tolerability, accessibility, and expense.* The Journal of Clinical Hypertension, 2020. **22**(1): p. 16-20.
210. O'Brien, E., et al., *European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring.* Journal of Hypertension, 2013. **31**(9): p. 1731-1768.
211. Lindroos, A.S., et al., *Comparison of Acceptability of Traditional and Novel Blood Pressure Measurement Methods.* American Journal of Hypertension, 2016. **29**(6): p. 679-683.

212. Bliziotis, I.A., A. Destounis, and G.S. Stergiou, *Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: a systematic review and meta-analysis.* J Hypertens, 2012. **30**(7): p. 1289-99.
213. Stergiou, G.S. and I.A. Bliziotis, *Home Blood Pressure Monitoring in the Diagnosis and Treatment of Hypertension: A Systematic Review.* American Journal of Hypertension, 2011. **24**(2): p. 123-134.
214. Stergiou, G.S., K.C.M. Siontis, and J.P.A. Ioannidis, *Home Blood Pressure as a Cardiovascular Outcome Predictor.* Hypertension, 2010. **55**(6): p. 1301-1303.
215. Ward, A.M., et al., *Home measurement of blood pressure and cardiovascular disease: systematic review and meta-analysis of prospective studies.* Journal of Hypertension, 2012. **30**(3): p. 449-456.
216. Cappuccio, F.P., *The Role of Nocturnal Blood Pressure and Sleep Quality in Hypertension Management.* European cardiology, 2020. **15**: p. e60-e60.
217. Kario, K., *Nocturnal Hypertension.* Hypertension, 2018. **71**(6): p. 997-1009.
218. Kario, K., et al., *Nighttime Blood Pressure Measured by Home Blood Pressure Monitoring as an Independent Predictor of Cardiovascular Events in General Practice.* Hypertension, 2019. **73**(6): p. 1240-1248.
219. Mokwatsi, G.G., et al., *Direct Comparison of Home Versus Ambulatory Defined Nocturnal Hypertension for Predicting Cardiovascular Events.* Hypertension, 2020. **76**(2): p. 554-561.
220. Mengden, T., et al., *Reliability of reporting self-measured blood pressure values by hypertensive patients.* American Journal of Hypertension, 1998. **11**(12): p. 1413-1417.
221. Parati, G. and S. Omboni, *Role of home blood pressure telemonitoring in hypertension management.* Blood Pressure Monitoring, 2010. **15**(6): p. 285-295.
222. Johnson, K.A., et al., *Reliability of Self-reported Blood Pressure Measurements.* Archives of Internal Medicine, 1999. **159**(22): p. 2689.
223. Nordmann, A., et al., *Reliability of patients measuring blood pressure at home: prospective observational study.* BMJ, 1999. **319**(7218): p. 1172-1172.
224. Omboni, S., et al., *Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies.* J Hypertens, 2013. **31**(3): p. 455-67; discussion 467-8.
225. Parati, G., et al., *Home blood pressure telemonitoring in the 21st century.* The Journal of Clinical Hypertension, 2018. **20**(7): p. 1128-1132.
226. Parati, G., et al., *Home blood pressure telemonitoring improves hypertension control in general practice. The TeleBPCare study.* Journal of Hypertension, 2009. **27**(1): p. 198-203.
227. McManus, R.J., et al., *Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial.* The Lancet, 2018. **391**(10124): p. 949-959.
228. Shimbo, D., et al., *Studies comparing ambulatory blood pressure and home blood pressure on cardiovascular disease and mortality outcomes: a systematic review.* Journal of the American Society of Hypertension, 2016. **10**(3): p. 224-234.e17.
229. Hodgkinson, J., et al., *Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review.* BMJ, 2011. **342**(jun24 1): p. d3621-d3621.
230. Lovibond, K., et al., *Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study.* The Lancet, 2011. **378**(9798): p. 1219-1230.
231. Beyhaghi, H. and A.J. Viera, *Comparative Cost-Effectiveness of Clinic, Home, or Ambulatory Blood Pressure Measurement for Hypertension Diagnosis in US Adults.* Hypertension, 2019. **73**(1): p. 121-131.

232. Webb, A.J.S. and P.M. Rothwell, *Physiological Correlates of Beat-to-Beat, Ambulatory, and Day-to-Day Home Blood Pressure Variability After Transient Ischemic Attack or Minor Stroke.* Stroke, 2014. **45**(2): p. 533-538.
233. Gladstone, D.J., et al., *Canadian Stroke Best Practice Recommendations: Secondary Prevention of Stroke Update 2020.* Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques, 2021: p. 1-69.
234. Kleindorfer, D.O., et al., *2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association.* Stroke, 2021. **52**(7).
235. National Institute for Health and Care Excellence (NICE), *NICE Clinical Knowledge Summaries, Stroke and TIA: Scenario: Secondary prevention following stroke and TIA.* NICE, 2020.
236. Stergiou, G.S., et al., *Prognosis of White-Coat and Masked Hypertension.* Hypertension, 2014. **63**(4): p. 675-682.
237. Uhlig, K., et al., *Self-measured blood pressure monitoring in the management of hypertension: a systematic review and meta-analysis.* Ann Intern Med, 2013. **159**(3): p. 185-94.
238. L. Tucker, K., et al., *Self-monitoring of blood pressure in hypertension: A systematic review and individual patient data meta-analysis.* PLOS Medicine, 2017. **14**(9): p. e1002389.
239. Kerry, S.M., et al., *Home blood pressure monitoring with nurse-led telephone support among patients with hypertension and a history of stroke: a community-based randomized controlled trial.* Cmaj, 2013. **185**(1): p. 23-31.
240. Mcmanus, R.J., et al., *Effect of Self-monitoring and Medication Self-titration on Systolic Blood Pressure in Hypertensive Patients at High Risk of Cardiovascular Disease.* JAMA, 2014. **312**(8): p. 799.
241. J. Davison, W., et al., *Does self-monitoring and self-management of blood pressure after stroke or transient ischemic attack improve control? TEST-BP, a randomized controlled trial.* 2018. **203**: p. 105-108.
242. Glader, E.L., et al., *Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke.* Stroke, 2010. **41**(2): p. 397-401.
243. Bushnell, C.D., et al., *Secondary preventive medication persistence and adherence 1 year after stroke.* Neurology, 2011. **77**(12): p. 1182-1190.
244. Perreault, S., et al., *Adherence to antihypertensive agents after ischemic stroke and risk of cardiovascular outcomes.* Neurology, 2012. **79**(20): p. 2037-2043.
245. Al Alshaikh, S., et al., *Predictive factors of non-adherence to secondary preventative medication after stroke or transient ischaemic attack: A systematic review and meta-analyses.* European Stroke Journal, 2016. **1**(2): p. 65-75.
246. Kronish, I.M., et al., *Key Barriers to Medication Adherence in Survivors of Strokes and Transient Ischemic Attacks.* Journal of General Internal Medicine, 2013. **28**(5): p. 675-682.
247. Dalli, L.L., et al., *Disparities in Antihypertensive Prescribing After Stroke.* Stroke, 2019. **50**(12): p. 3592-3599.
248. Fodor, G.J., et al., *Is interview a reliable method to verify the compliance with antihypertensive therapy? An international central-European study.* J Hypertens, 2005. **23**(6): p. 1261-6.
249. McHorney, C.A., *The Adherence Estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease.* Curr Med Res Opin, 2009. **25**(1): p. 215-38.
250. Lam, W.Y. and P. Fresco, *Medication Adherence Measures: An Overview.* Biomed Res Int, 2015. **2015**: p. 217047.
251. Inui, T.S., E.L. Yourtee, and J.W. Williamson, *Improved outcomes in hypertension after physician tutorials. A controlled trial.* Ann Intern Med, 1976. **84**(6): p. 646-51.

252. Gallagher, B.D., et al., *Are two commonly used self-report questionnaires useful for identifying antihypertensive medication nonadherence?* Journal of Hypertension, 2015. **33**(5): p. 1108-1113.
253. Sutherland, J.J., et al., *Assessment of Patient Medication Adherence, Medical Record Accuracy, and Medication Blood Concentrations for Prescription and Over-the-Counter Medications.* JAMA Network Open, 2018. **1**(7): p. e184196.
254. Hafezi, H., et al., *An Ingestible Sensor for Measuring Medication Adherence.* IEEE Transactions on Biomedical Engineering, 2015. **62**(1): p. 99-109.
255. Moorhead, P., et al., *Efficacy and safety of a medication dose reminder feature in a digital health offering with the use of sensor-enabled medicines.* Journal of the American Pharmacists Association, 2017. **57**(2): p. 155-161.e1.
256. Noble, K., et al., *Medication adherence and activity patterns underlying uncontrolled hypertension: Assessment and recommendations by practicing pharmacists using digital health care.* Journal of the American Pharmacists Association, 2016. **56**(3): p. 310-315.
257. Osterberg, L. and T. Blaschke, *Adherence to Medication.* New England Journal of Medicine, 2005. **353**(5): p. 487-497.
258. Martani, A., et al., *Digital pills: a scoping review of the empirical literature and analysis of the ethical aspects.* BMC Medical Ethics, 2020. **21**(1).
259. Feldman, R., et al., *Adherence to pharmacologic management of hypertension.* Canadian journal of public health, 1998. **89**(5): p. I16-I18.
260. Butterworth, S.W., *Influencing Patient Adherence to Treatment Guidelines.* Journal of Managed Care Pharmacy, 2008. **14**(6 Supp B): p. 21-25.
261. Ruppar, T.M., et al., *Medication adherence interventions among hypertensive black adults: a systematic review and meta-analysis.* J Hypertens, 2017. **35**(6): p. 1145-1154.
262. Thakkar, J., et al., *Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease.* JAMA Internal Medicine, 2016. **176**(3): p. 340.
263. Bamford, J., et al., *A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haem.* Journal of Neurology, Neurosurgery & Psychiatry, 1990. **53**(1): p. 16-22.
264. Rothwell, P., et al., *Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study).* The Lancet, 2005. **366**(9499): p. 1773-1783.
265. Coull, A.J., et al., *Direct assessment of completeness of ascertainment in a stroke incidence study.* Stroke, 2004. **35**(9): p. 2041-5.
266. Sacco, R.L., et al., *An Updated Definition of Stroke for the 21st Century.* Stroke, 2013. **44**(7): p. 2064-2089.
267. Adams, H.P., et al., *Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment.* Stroke, 1993. **24**(1): p. 35-41.
268. TOAST Investigators, *Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators.* Jama, 1998. **279**(16): p. 1265-72.
269. Hemphill, J.C., 3rd, et al., *Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association.* Stroke, 2015. **46**(7): p. 2032-60.
270. National Institute for Health and Care Excellence (NICE), *NICE guideline [NG128] Stroke and transient ischaemic attack in over 16s: diagnosis and initial management.* NICE, 2019.

271. Hypertension-Stroke Cooperative Study Group, *Effect of antihypertensive treatment on stroke recurrence. Hypertension-Stroke Cooperative Study Group.* Jama, 1974. **229**(4): p. 409-18.
272. Bosch, J., *Use of ramipril in preventing stroke: double blind randomised trial.* BMJ, 2002. **324**(7339): p. 699-699.
273. Liu, L.S., L.S. Gong, and W. Wang, *[Effects of blood pressure lowering treatment on stroke recurrence in patients with cerebrovascular diseases-a large-scale, randomized, placebo controlled trial].* Zhonghua Xin Xue Guan Bing Za Zhi, 2005. **33**(7): p. 613-7.
274. James, P.A., et al., *2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults.* JAMA, 2014. **311**(5): p. 507.
275. Castilla-Guerra, L., et al., *Ambulatory blood pressure monitoring in stroke survivors: Do we really control our patients?* European Journal of Internal Medicine, 2009. **20**(8): p. 760-763.
276. Castilla-Guerra, L., et al., *Nocturnal hypotension in patients after ischemic stroke: Does it really matter?* European Journal of Internal Medicine, 2011. **22**(5): p. 501-504.
277. Cugini, P., et al., *[The role and chronobiometric study of ambulatory arterial pressure monitoring in hypertensive patients with a recent cerebral ischemia episode].* Recenti Prog Med, 1997. **88**(9): p. 383-7.
278. Davison, W.J., et al., *Blood pressure differences between home monitoring and daytime ambulatory values and their reproducibility in treated hypertensive stroke and TIA patients.* American Heart Journal, 2019. **207**: p. 58-65.
279. Harbison, J.A., S. Walsh, and R.A. Kenny, *Hypertension and daytime hypotension found on ambulatory blood pressure is associated with fatigue following stroke and TIA.* QJM, 2008. **102**(2): p. 109-115.
280. Nakamura, K., J. Oita, and T. Yamaguchi, *Nocturnal blood pressure dip in stroke survivors. A pilot study.* Stroke, 1995. **26**(8): p. 1373-8.
281. Phillips, R.A., et al., *The association of blunted nocturnal blood pressure dip and stroke in a multiethnic population.* American Journal of Hypertension, 2000. **13**(12): p. 1250-1255.
282. Sasaki, M., H. Ando, and A. Fujimura, *Lack of Nocturnal Blood Pressure Fall in Elderly Bedridden Hypertensive Patients With Cerebrovascular Disease.* Chronobiology International, 2012. **29**(1): p. 62-65.
283. Staals, J., et al., *Brain Microbleeds Relate to Higher Ambulatory Blood Pressure Levels in First-Ever Lacunar Stroke Patients.* Stroke, 2009. **40**(10): p. 3264-3268.
284. Tao, Y., et al., *Short-term blood pressure variability and long-term blood pressure variability: which one is a reliable predictor for recurrent stroke.* Journal of Human Hypertension, 2017. **31**(9): p. 568-573.
285. Xu, J., et al., *Ambulatory blood pressure profile and stroke recurrence.* Stroke and Vascular Neurology, 2021: p. svn-2020-000526.
286. Yamamoto, Y., et al., *Adverse Effect of Nighttime Blood Pressure on the Outcome of Lacunar Infarct Patients.* Stroke, 1998. **29**(3): p. 570-576.
287. Yamamoto, Y., et al., *Twenty-four–Hour Blood Pressure and MRI as Predictive Factors for Different Outcomes in Patients With Lacunar Infarct.* Stroke, 2002. **33**(1): p. 297-305.
288. Yamamoto, Y., et al., *Chronic kidney disease, 24-h blood pressure and small vessel diseases are independently associated with cognitive impairment in lacunar infarct patients.* Hypertension Research, 2011. **34**(12): p. 1276-1282.
289. Dai, L., et al., *Different contribution of SBP and DBP variability to vascular events in patients with stroke.* Stroke and Vascular Neurology, 2020. **5**(2): p. 110-115.

290. Hanley, J., et al., *Mixed methods feasibility study for a trial of blood pressure telemonitoring for people who have had stroke/transient ischaemic attack (TIA).* Trials, 2015. **16**(1).
291. N. Kernan, W., et al., *Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack.* Stroke, 2014. **45**(7): p. 2160-2236.
292. Mancia, G. and A. Zanchetti, *White-coat hypertension: misnomers, misconceptions and misunderstandings. What should we do next?* J Hypertens, 1996. **14**(9): p. 1049-52.
293. Myers, M.G., et al., *Prevalence of white coat effect in treated hypertensive patients in the community.* Am J Hypertens, 1995. **8**(6): p. 591-7.
294. Peacock, J., et al., *Unmasking masked hypertension: prevalence, clinical implications, diagnosis, correlates and future directions.* Journal of Human Hypertension, 2014. **28**(9): p. 521-528.
295. Pickering, T.G., et al., *Masked hypertension.* Hypertension, 2002. **40**(6): p. 795-6.
296. Carlberg, B., K. Asplund, and E. Hägg, *Factors influencing admission blood pressure levels in patients with acute stroke.* Stroke, 1991. **22**(4): p. 527-530.
297. Britton, M., A. Carlsson, and U. De Faire, *Blood pressure course in patients with acute stroke and matched controls.* Stroke, 1986. **17**(5): p. 861-864.
298. Rothwell, P., et al., *Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study).* The Lancet, 2004. **363**(9425): p. 1925-1933.
299. Béjot, Y., et al., *Impact of completeness of ascertainment of minor stroke on stroke incidence: implications for ideal study methods.* Stroke, 2013. **44**(7): p. 1796-802.
300. J. Powers, W., et al., *Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke.* 2019. **50**.
301. Jansen, P.A., et al., *Course of blood pressure after cerebral infarction and transient ischemic attack.* Clin Neurol Neurosurg, 1987. **89**(4): p. 243-6.
302. Sackley, C.M., et al., *Functional and emotional outcomes after transient ischemic attack: A 12-month prospective controlled cohort study.* International Journal of Stroke, 2019. **14**(5): p. 522-529.
303. Parati, G., et al., *European Society of Hypertension practice guidelines for home blood pressure monitoring.* J Hum Hypertens, 2010. **24**(12): p. 779-85.
304. Banegas, J.R., et al., *Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality.* New England Journal of Medicine, 2018. **378**(16): p. 1509-1520.
305. Hansen, T.W., et al., *Ambulatory Blood Pressure and Mortality.* Hypertension, 2005. **45**(4): p. 499-504.
306. Dolan, E., et al., *Superiority of Ambulatory Over Clinic Blood Pressure Measurement in Predicting Mortality.* The Dublin Outcome Study, 2005. **46**(1): p. 156-161.
307. Hansen, T.W., et al., *Predictive Role of the Nighttime Blood Pressure.* Hypertension, 2011. **57**(1): p. 3-10.
308. Imai, Y., et al., *Predictive power of screening blood pressure, ambulatory blood pressure and blood pressure measured at home for overall and cardiovascular mortality: a prospective observation in a cohort from Ohasama, northern Japan.* Blood pressure monitoring, 1996. **1**(3): p. 251-254.
309. Fagard, R.H., C. Van Den Broeke, and P. De Cort, *Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice.* Journal of Human Hypertension, 2005. **19**(10): p. 801-807.

310. Niiranen, T.J., et al., *Office, Home, and Ambulatory Blood Pressures as Predictors of Cardiovascular Risk.* Hypertension, 2014. **64**(2): p. 281-286.
311. Mancia, G., et al., *Adding Home and/or Ambulatory Blood Pressure to Office Blood Pressure for Cardiovascular Risk Prediction.* Hypertension, 2021. **77**(2): p. 640-649.
312. Casadei, R., et al., *24-Hour blood pressure monitoring: evaluation of Spacelabs 5300 monitor by comparison with intra-arterial blood pressure recording in ambulant subjects.* Journal of Hypertension, 1988. **6**(10): p. 797-804.
313. Mena, L., et al., *A reliable index for the prognostic significance of blood pressure variability.* J Hypertens, 2005. **23**(3): p. 505-11.
314. Stergiou, G.S., A. Ntineri, and A. Kollias, *Changing Relationship Among Office, Ambulatory, and Home Blood Pressure With Increasing Age.* Hypertension, 2014. **64**(5): p. 931-932.
315. Masoli, J.A.H., et al., *Blood pressure in frail older adults: associations with cardiovascular outcomes and all-cause mortality.* Age and Ageing, 2020. **49**(5): p. 807-813.
316. Beckett, N.S., et al., *Treatment of Hypertension in Patients 80 Years of Age or Older.* New England Journal of Medicine, 2008. **358**(18): p. 1887-1898.
317. Conen, D., et al., *Age-Specific Differences Between Conventional and Ambulatory Daytime Blood Pressure Values.* Hypertension, 2014. **64**(5): p. 1073-1079.
318. Ishikawa, J., et al., *Age and the difference between awake ambulatory blood pressure and office blood pressure.* Blood Pressure Monitoring, 2011. **16**(4): p. 159-167.
319. Mcgowan, N. and P.L. Padfield, *Self blood pressure monitoring: a worthy substitute for ambulatory blood pressure?* Journal of Human Hypertension, 2010. **24**(12): p. 801-806.
320. Future NHS Collaboration Platform, *Standard operating procedure: blood pressure monitoring @home for people with diagnosed hypertension*. 2021.
321. Department of Health, *National Stroke Strategy*. 2007: London.
322. Etienne Santos, et al., *Post-stroke follow-up: Time to organize.* Revue Neurologique, 2019. **175**(1-2): p. 59-64.
323. Bobrie, G., et al., *Masked hypertension: a systematic review.* Journal of Hypertension, 2008. **26**(9): p. 1715-1725.
324. Niiranen, T.J., et al., *Home-Measured Blood Pressure Is a Stronger Predictor of Cardiovascular Risk Than Office Blood Pressure.* Hypertension, 2010. **55**(6): p. 1346-1351.
325. Shimada, K., et al., *The Importance of Home Blood Pressure Measurement for Preventing Stroke and Cardiovascular Disease in Hypertensive Patients: A Sub-Analysis of the Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) Study, a Prospectiv.* Hypertension Research, 2008. **31**(10): p. 1903-1911.
326. Stergiou, G.S., N.M. Baibas, and P.G. Kalogeropoulos, *Cardiovascular risk prediction based on home blood pressure measurement: The Didima Study.* Journal of Hypertension, 2007. **25**(8): p. 1590-1596.
327. Okumiya, K., et al., *A U-Shaped Association Between Home Systolic Blood Pressure and Four-Year Mortality in Community-Dwelling Older Men.* Journal of the American Geriatrics Society, 1999. **47**(12): p. 1415-1421.
328. Ohkubo, T., et al., *Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement.* Journal of Hypertension, 1998. **16**(7): p. 971-975.
329. Castilla-Guerra, L. and M.D.C. Fernandez-Moreno, *Chronic Management of Hypertension after Stroke: The Role of Ambulatory Blood Pressure Monitoring.* Journal of Stroke, 2016. **18**(1): p. 31-37.

330. Law, M.R., et al., *Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study.* BMJ, 1994. **308**(6925): p. 363-366.
331. Davison, W.J., et al., *Does self-monitoring and self-management of blood pressure after stroke or transient ischemic attack improve control? TEST-BP, a randomized controlled trial.* American Heart Journal, 2018. **203**: p. 105-108.
332. Gale, C.R., C. Cooper, and A. Aihie Sayer, *Prevalence and risk factors for falls in older men and women: The English Longitudinal Study of Ageing.* Age and Ageing, 2016. **45**(6): p. 789-794.
333. Little, P., et al., *Comparison of acceptability of and preferences for different methods of measuring blood pressure in primary care.* BMJ (Clinical research ed.), 2002. **325**(7358): p. 258-259.
334. Cacciolati, C., et al., *Feasibility of Home Blood Pressure Measurement in Elderly Individuals: Cross-Sectional Analysis of a Population-Based Sample.* American Journal of Hypertension, 2012.
335. Mancia, G., et al., *Long-Term Risk of Mortality Associated With Selective and Combined Elevation in Office, Home, and Ambulatory Blood Pressure.* Hypertension, 2006. **47**(5): p. 846-853.
336. Jansen, P.A.F., et al., *Course of blood pressure after cerebral infarction and transient ischemic attack.* Clinical Neurology and Neurosurgery, 1987. **89**(4): p. 243-246.
337. Krishnamurthi, R.V., T. Ikeda, and V.L. Feigin, *Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017.* Neuroepidemiology, 2020. **54**(2): p. 171-179.
338. Béjot, Y., et al., *Temporal trends in early case-fatality rates in patients with intracerebral hemorrhage.* Neurology, 2017. **88**(10): p. 985-990.
339. Jolink, W.M.T., et al., *Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage.* Neurology, 2015. **85**(15): p. 1318-1324.
340. Li, L., et al., *Ten-year risks of recurrent stroke, disability, dementia and cost in relation to site of primary intracerebral haemorrhage: population-based study.* Journal of Neurology, Neurosurgery & Psychiatry, 2020: p. jnnp-2019-32266.
341. McKinstry, B., et al., *Telemonitoring based service redesign for the management of uncontrolled hypertension: multicentre randomised controlled trial.* BMJ : British Medical Journal, 2013. **346**.
342. M. Hansen, B., et al., *Applicability of Clinical Trials in an Unselected Cohort of Patients With Intracerebral Hemorrhage.* Stroke, 2016. **47**(10): p. 2634-2637.
343. Mcgurgan, I.J., et al., *Acute intracerebral haemorrhage: diagnosis and management.* Practical Neurology, 2021. **21**(2): p. 128-136.
344. Klungel, O.H., et al., *Undertreatment of hypertension in a population-based study in The Netherlands.* Journal of Hypertension, 1998. **16**(9): p. 1371-1378.
345. Burnier, M. and B.M. Egan, *Adherence in Hypertension.* Circulation Research, 2019. **124**(7): p. 1124-1140.
346. Lafleur, J., et al., *Overestimation of the effects of adherence on outcomes: a case study in healthy user bias and hypertension.* Heart, 2011. **97**(22): p. 1862-1869.
347. Brookhart, M.A., et al., *Adherence to Lipid-lowering Therapy and the Use of Preventive Health Services: An Investigation of the Healthy User Effect.* American Journal of Epidemiology, 2007. **166**(3): p. 348-354.
348. Rockhill, B., B. Newman, and C. Weinberg, *Use and misuse of population attributable fractions.* Am J Public Health, 1998. **88**(1): p. 15-9.
349. Natarajan, S., S.R. Lipsitz, and E. Rimm, *A simple method of determining confidence intervals for population attributable risk from complex surveys.* Statistics in Medicine, 2007. **26**(17): p. 3229-3239.

350. Lewis, G., et al., *Maintenance or Discontinuation of Antidepressants in Primary Care.* New England Journal of Medicine, 2021. **385**(14): p. 1257-1267.
351. Walma, E., et al., *Withdrawal of long term diuretic medication in elderly patients: a double blind randomised trial.* BMJ, 1997. **315**(7106): p. 464-468.
352. Iyer, S., et al., *Medication Withdrawal Trials in People Aged 65 Years and Older.* Drugs & Aging, 2008. **25**(12): p. 1021-1031.
353. Reeve, E., et al., *Withdrawal of antihypertensive drugs in older people.* Cochrane Database of Systematic Reviews, 2020(6).
354. Van Der Wardt, V., et al., *Withdrawal of antihypertensive medication.* Journal of Hypertension, 2017. **35**(9): p. 1742-1749.
355. Sheppard, J.P., et al., *Effect of Antihypertensive Medication Reduction vs Usual Care on Short-term Blood Pressure Control in Patients With Hypertension Aged 80 Years and Older.* JAMA, 2020. **323**(20): p. 2039.
356. Perreault, S., et al., *Adherence to antihypertensive agents after ischemic stroke and risk of cardiovascular outcomes.* Neurology, 2012. **79**(20): p. 2037-2043.
357. Elijovich, F. and C.L. Laffer, *Discontinuation of Therapy in Hypertension Research.* Hypertension, 2017. **69**(5): p. 795-797.
358. Krishnaswami, A., et al., *Deprescribing in Older Adults With Cardiovascular Disease.* Journal of the American College of Cardiology, 2019. **73**(20): p. 2584-2595.
359. Boan, A.D., D.T. Lackland, and B. Ovbiagele, *Lowering of blood pressure for recurrent stroke prevention.* Stroke, 2014. **45**(8): p. 2506-13.
360. Rashid, P., J. Leonardi-Bee, and P. Bath, *Blood Pressure Reduction and Secondary Prevention of Stroke and Other Vascular Events.* Stroke, 2003. **34**(11): p. 2741-2748.
361. Lammie, G.A., et al., *Stress-Related Primary Intracerebral Hemorrhage.* Stroke, 2000. **31**(6): p. 1426-1428.
362. Papadopoulos, D.P., et al., *Hypertension crisis.* Blood Press, 2010. **19**(6): p. 328-36.
363. Cruickshank, J.M., J.M. Thorp, and F.J. Zacharias, *Benefits and potential harm of lowering high blood pressure.* Lancet, 1987. **1**(8533): p. 581-4.
364. Anderson, T.W., *Re-examination of some of the Framingham blood-pressure data.* Lancet, 1978. **2**(8100): p. 1139-41.
365. Stewart, I.M., *Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension.* Lancet, 1979. **1**(8121): p. 861-5.
366. Management Committee of the Australian Therapeutic Trial in Mild Hypertension, *UNTREATED MILD HYPERTENSION: A Report by the Management Committee of the Australian Therapeutic Trial in Mild Hypertension.* The Lancet, 1982. **319**(8265): p. 185-191.
367. D'Agostino, R.B., et al., *Relation of low diastolic blood pressure to coronary heart disease death in presence of myocardial infarction: the Framingham Study.* BMJ, 1991. **303**(6799): p. 385-389.
368. Lindholm, L., et al., *Both high and low blood pressures risk indicators of death in middle-aged males. Isotonic regression of blood pressure on age applied to data from a 13-year prospective study.* Acta Med Scand, 1985. **218**(5): p. 473-80.
369. Vokó, Z.N., et al., *J-Shaped Relation Between Blood Pressure and Stroke in Treated Hypertensives.* Hypertension, 1999. **34**(6): p. 1181-1185.
370. Bangalore, S., et al., *J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial†.* European Heart Journal, 2010. **31**(23): p. 2897-2908.
371. Messerli, F.H., et al., *Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous?* Ann Intern Med, 2006. **144**(12): p. 884-93.

372. Fagard, R.H., et al., *On-treatment diastolic blood pressure and prognosis in systolic hypertension.* Archives of internal medicine, 2007. **167**(17): p. 1884-1891.
373. Farnett, L., et al., *The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous?* Jama, 1991. **265**(4): p. 489-95.
374. Böhm, M., et al., *Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials.* The Lancet, 2017. **389**(10085): p. 2226-2237.
375. Malyszko, J., et al., *Blood Pressure Levels and Stroke: J-curve Phenomenon?* Current Hypertension Reports, 2013. **15**(6): p. 575-581.
376. Ovbiagele, B., *Low-Normal Systolic Blood Pressure and Secondary Stroke Risk.* Journal of Stroke and Cerebrovascular Diseases, 2013. **22**(5): p. 633-638.
377. Irie, K., et al., *The J-curve phenomenon in stroke recurrence.* Stroke, 1993. **24**(12): p. 1844-1849.
378. Park, J.-H. and B. Ovbiagele, *Post-stroke diastolic blood pressure and risk of recurrent vascular events.* European Journal of Neurology, 2017. **24**(11): p. 1416-1423.
379. Odden, M.C., et al., *Achieved Blood Pressure and Outcomes in the Secondary Prevention of Small Subcortical Strokes Trial.* Hypertension, 2016. **67**(1): p. 63-69.
380. PROGRESS Management Commitee, *Blood pressure lowering for the secondary prevention of stroke: rationale and design for PROGRESS.* J Hypertens Suppl, 1996. **14**(2): p. S41-5; discussion S45-6.
381. Glodzik, L., et al., *Different Relationship Between Systolic Blood Pressure and Cerebral Perfusion in Subjects With and Without Hypertension.* Hypertension, 2019. **73**(1): p. 197-205.
382. Spence, J., *Spectral analysis of carotid vs femoral Doppler velocity patterns: a clue to genesis of flow disturbances in cerebral arteries.* Frontiers of Engineering in Health Care, 1981: p. 355-81.
383. Domanski, M.J., et al., *Isolated Systolic Hypertension.* Hypertension, 1999. **34**(3): p. 375-380.
384. Grabska, K., et al., *Pulse Pressure – Independent Predictor of Poor Early Outcome and Mortality following Ischemic Stroke.* Cerebrovascular Diseases, 2009. **27**(2): p. 187-192.
385. Lovett, J.K., S.C. Howard, and P.M. Rothwell, *Pulse pressure is independently associated with carotid plaque ulceration.* Journal of Hypertension, 2003. **21**(9).
386. Tsivgoulis, G., *Twenty four hour pulse pressure predicts long term recurrence in acute stroke patients.* Journal of Neurology, Neurosurgery & Psychiatry, 2005. **76**(10): p. 1360-1365.
387. Spence, J.D., W.J. Sibbald, and R.D. Cape, *Direct, indirect and mean blood pressures in hypertensive patients: the problem of cuff artefact due to arterial wall stiffness, and a partial solution.* Clin Invest Med, 1979. **2**(4): p. 165-73.
388. Blanco, P.J., L.O. Müller, and J.D. Spence, *Blood pressure gradients in cerebral arteries: a clue to pathogenesis of cerebral small vessel disease.* Stroke and Vascular Neurology, 2017. **2**(3): p. 108-117.
389. Marschner, I.C., R.J. Simes, and A. Keech, *Biases in the Identification of Risk Factor Thresholds and J-Curves.* American Journal of Epidemiology, 2007. **166**(7): p. 824-831.
390. Zanchetti, A., et al., *Continuation of the ESH-CHL-SHOT trial after publication of the SPRINT: rationale for further study on blood pressure targets of antihypertensive treatment after stroke.* Journal of Hypertension, 2016. **34**(3): p. 393-396.

391. Liu, L. and G. Mancia, *Termination of the ESH-CHL-SHOT trial.* Journal of Hypertension, 2020. **38**(12): p. 2542-2543.
392. Nilsson, P.M., *The J-Shaped Curve in Secondary Prevention.* Hypertension, 2012. **59**(1): p. 8-9.

Appendix

Appendix 1.1

COMMIT Study Protocol

Aims of the study

To remotely monitor blood pressure (BP) at home in patients with TIA or stroke in order to:

1. Assess the feasibility of BP self-monitoring at home in this predominantly elderly patient group;
2. Evaluate patients' perception of BP monitoring;
3. Frequency of masked hypertension;
4. Extent of diurnal variation in BP and of day-to-day variability;
5. Feasibility of tailoring BP-lowering drugs in individual patients in "real time" according to BP level and response;
6. Determine the impact of tailored management of BP on rates of BP control at regular clinic follow-up;
7. Determine the impact of tailored management of BP on the number and dose of BP-lowering drugs prescribed and on longer-term patient compliance;
8. Identify any risks associated with tailored management of BP (e.g. falls, fractures, electrolyte imbalances etc).

Inclusion criteria

1. Patient consent or assent from relatives;
2. All outpatients with a first TIA and/or stroke referred to OXVASC during the study period.

- Patients seen through clinic will be asked to start monitoring then
- Patients seen in clinic who are admitted will be asked to start monitoring on discharge
- Patients in nursing care will be asked to try monitoring
- Patients excluded from monitoring in previous phases can be included in Phase 4 if inclusion criteria met.
- Patients who have completed 5 years of follow up who present with a new event can be included and BP follow up started (even if TIA after stroke).
- Strokes from previous phases who have a recurrent stroke in Phase 3 will have their BP assessed and start/restart Bluetooth monitoring if BP uncontrolled.

Patients who do not consent to Bluetooth monitoring should be offered conventional, 24 hour monitoring or both. If there is no consent/assent to BP monitoring, assess BP at follow up as normal and use this to maintain good BP control.

Exclusion criteria

1. Age <18 (no upper age limit);
2. Patients seen in the OXVASC outpatient clinic found not to have a stroke or TIA (OCAs).
3. Patients from previous phases who have recurrent TIAs, or TIA after stroke within their 5 years of follow up.

Please note: Late exclusions - if a patient is entered in to the BP study and later found to meet the exclusion criteria, the patient should stop monitoring as soon as possible, and arrangements should be made for their equipment to be returned or collected.

Patient ascertainment

Eligible clinic patients will have their BP taken and treatment started. Patients will receive a Bluetooth BP monitor, with appropriate cuff, and information sheet, and receive training how to use it.

BP will be taken after rest, once in each arm, patients taking one of these readings themselves. In the absence of significant weakness or other co-morbidity, the non-dominant arm will be used unless ≥20mmHg difference is found between arms. If required, patients or carers can practice further until able to achieve reliable readings independently.

Patient study ID and DoB will be registered on the tplus website https://euro1.tplusbloodpressure.com/ . Patient details will be added on the Excel sheet (I-Drive: Blood pressure > BP Patients). The date of ascertainment will be used to calculate dates of future follow up for clinic patients, and event date used to calculate follow up for in-patients.

Measuring the blood pressure with Bluetooth BP monitors

Patients will be asked to measure their BP three times over 10 minutes, three times a day:
Set 1: as soon as possible after wakening (which will usually be prior to taking any antihypertensive medication)
Set 2: mid morning – around 10 am if possible
Set 3: Just before they go to bed

On each occasion, patients will be asked to measure their BP after a few minutes of rest in a sitting position, at a table if possible, remaining quiet and still, using the same arm each time, three times within 10 minutes.

Please note: If patients are going away from home they will be asked to take the BP monitor (with or without hub) and take their readings as normal (they may miss out mid-morning reading if necessary). If the length of holiday will exceed the memory capacity of the monitor (99 readings), they will be asked to take the BP monitor (without hub) and take write the results down.

Monitoring protocol for Bluetooth BP monitors

1. Each working day, Bluetooth BP readings will be checked (Nicola Lovett, Michelle Wilson, Fiona Cuthbertson), and the BP spreadsheet updated to indicate BP control.
2. If readings are absent the patient will be phoned to check if:
- The BP was measured.
- The Bluetooth kit is working.
3. Technical problems will be resolved with the patient by phone where possible, or reported to t-plus medical
4. If required, a replacement kit will be provided and the data merged after Bluetooth monitoring is completed.
5. In the case of unexpected readings (e.g. high peaks), the patient will be phoned to check if there is anything which may account for them.

Blood pressures are checked via https://euro1.tplusbloodpressure.com/. The BP spreadsheet is found in (I-Drive: Blood pressure > BP Patients). Problems with Bluetooth kits will be documented in (I-Drive: Blood pressure > Problems with monitors) and where necessary reported to t-plus medical by phone or by e-mailing support@tplusmedical.com.

Management protocol

1. All patients will be treated for BPs above 130/80mmHg unless there are contraindications e.g. posterior circulation stenosis
2. The BP fellow will make changes to the antihypertensives by:
- Phoning the patient to increase a current medication
- Sending a prescription for a new medication
- Making recommendations to the GP, including the percentage above guidelines (BP Audit letter).
3. BP values will be discussed with Peter Rothwell on a regular basis, and a hypertension specialist when required.

Any medications changes made will be recorded on the Excel sheet 'Interventions'

Follow up

This will be done face-to-face in clinic or at home.
Those ascertained though clinic will be reviewed at 1, 3, 6, 12 and 60 months.
All patients will be contacted by phone / post at 18 and 24 months.
Please consult with Nicola Lovett, Michelle Wilson or Fiona Cuthbertson prior to the follow up to identify any medication or equipment changes required.

Common themes at follow up

1. If Bluetooth BPs are within guidelines, Bluetooth monitors will be collected and conventional monitors issued. Patients will be asked to take 3 readings after breakfast once a week and write down their results. Patients are instructed to phone if:
- The 3rd systolic reading is >160mmHg, or >140mmHg for 2 consecutive weeks.
- Any changes to antihypertensive medications are made by other parties.

After the 12 month follow up, patients may monitor their BP once monthly, if weekly readings are not tolerated.

2. If the Bluetooth BPs are above guidelines, Bluetooth monitoring will continue and antihypertensive medications may be changed by:
- Issuing a new prescription.
- Making recommendations to the GP.
3. The BP will be taken twice and mean results above 130/80mmHg discussed with the research fellow / Peter Rothwell.
4. If any unexpected changes to antihypertensive medications are identified, patients will be asked about the time and reason for the change.
5. The type of BP monitoring and any recommendations will be included in a letter to the GP.

Returned Bluetooth monitors are downloaded, cleaned, their information filed and data archived. Data collected during the follow up is entered on the Database.

Additional themes

1. Once using conventional monitors, patient's home readings will be collected at each subsequent follow up, and a new blank sheet given to the patient. Unexpected high readings will be discussed with the research fellow / Peter Rothwell

Collected sheets are photocopied for the patient notes, and the originals filed.

Between follow-up visits

1. If the Bluetooth BPs are *within* guidelines Bluetooth monitors may be collected from home / work and conventional monitors issued, with instructions as above.
2. If the home BPs are *above* guidelines, (observed through daily checks of Bluetooth readings or self-reported by patients / carers using conventional monitors), antihypertensive medications may be changed by issuing a new prescription, or making recommendations to the GP. BP monitoring continues.

24-hour BP monitoring

1. Those ascertained through clinic will be asked to have a 24 hour BP monitor at 1 and 12 months. Patients will receive instruction on how to use the monitor, using the same arm as for home monitoring.
2. Results will be reviewed by the BP fellow, and considered alongside home readings. If the mean systolic is >130mmHg, results will be discussed with Peter Rothwell.

Patient admissions

1. Patients who are admitted to hospital during any stage of their blood pressure monitoring will be asked to resume their monitoring as soon as possible after their discharge.
2. Any changes made to their anti-hypertensive medication will be identified, either from the patient, their family/carers or their discharge summary / medical notes

Changes are recorded on the Database.

3. If a patient is no longer independently able to monitor their blood pressure, they will be asked if carers or family are available to provide assistance.

Patients' perceptions

1. At the 1 month follow up, all clinic patients using Bluetooth kits will receive a questionnaire (with a stamped addressed envelope) asking them to evaluate their experience with the BP monitor.

Returned questionnaires will be marked with the date of receipt, and results entered (I-Drive: Blood Pressure > Questionnaire > Results to date) and filed.

Patients who move out of area

1. Patients will be asked if they are happy to continue conventional BP monitoring, and followed up by telephone.

P M Rothwell MB ChB MD PhD FRCP FMedSci
Action Research Professor of Neurology
Honorary Consultant Neurologist

Appendix 1.2

Nuffield Department of Clinical Neurosciences
WCPSD
The Wolfson Building
John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU
Tel: (01865) 234893

Loan of medical equipment

As part of your investigations you will be asked to use some medical equipment at home. This equipment is property of the Stroke Prevention Unit. Failure to return equipment promptly and in good order may result in cancellation of appointments for other patients.
Items of equipment loaned:

			Please circle				Date	Signature
Bluetooth BP monitor	**Kit number** **STR**		Phone Hub	IEM A&D	**Cuff** Med / Lg Sm	Left / Right Arm		
24 hour BP ascertainment	**Kit number**				Sm / Med / Lg	Left / Right Arm		
24 hour BP monitor 1mth	**Kit number**				Sm / Med / Lg	Left / Right Arm		
24 hour BP monitor 1 yr	**Kit number**				Sm / Med / Lg	Left / Right Arm		
Conventional BP monitor Issued Asc/1m/3m/other	**Kit number**				Sm / Med / Lg	Left / Right Arm		
R Test Ascertainment	**Kit number**							
R Test 1 mth	**Kit number**							
R Test 1 yr	**Kit number**							
R Test 5 yr	**Kit number**							

BP Target: 130/80 other ……. Reason: ……..

Sticker

Please circle the relevant information:

Tel/contact					***OXVASC ID***		***DOB***		
Stroke	***TIA***	***OCA***	***First event***	***Recurrent event***	***GP referral***	***In patient***	***A&E***	***Other***	
Beaumont St	***EOHC***	***Berinsfield***	***Malthouse***	***Marcham Rd***	***Stert St***	***Wantage***	***KEY***	***Other***	

Appendix 1.3

P M Rothwell MB ChB MD PhD FRCP FMedSci
Action Research Professor of Neurology
Honorary Consultant Neurologist

Oxford University Hospitals NHS
NHS Trust
Nuffield Department of Clinical Neurosciences
WCPSD
Wolfson Building
John Radcliffe Hospital
Headley Way, Oxford
OX3 9DU
Tel: (01865) 234893 or (01865) 231601

PLEASE NOTE

For your safety, the blood pressure machine should not be switched on whilst driving.

During the 24 hours: you should not do any vigorous sport or use machinery
you are asked not to shower or bath

The recorder is programmed to take your blood pressure automatically half hourly during the day and hourly at night (2300-0700). Once switched on you do not need to do anything else to it.

You should be seated and remain QUIET and STILL while the recorder is taking your blood pressure and avoid any sudden movement.

When the recorder starts to take a measurement SIT DOWN if possible. Rest the arm with the cuff on it on the chair arm or table, with the hand relaxed and the palm facing upwards. If you cannot sit down, rest your arm on your midriff until you feel the cuff deflate.
The measurement process may take 20-30 seconds. Do not worry if the cuff inflates again – this is perfectly normal.

To turn the monitor on:
When the monitor is switched off it will display a blank black screen. Press either the **EVENT** or the **START/STOP** button once and the current time and battery symbol will appear.
Press and hold the **EVENT** button for approximately 3 seconds.
The symbol ◴ will appear on the left hand side above the battery symbol.
The machine will now automatically take your blood pressure as per set up.

To switch the machine off:
The machine is set to switch off automatically 24hours after it was switched on.
If the machine does not switch off please follow the instructions below.

If the display is showing a black blank screen press either the **START/STOP** or **EVENT** button once. The display screen with the time, battery and ◴ symbol will appear.
To switch the machine off press and hold the **EVENT** button for 3 seconds.
The symbol ◴ will disappear and the time and battery symbol will remain on the screen. The display will then revert back to a black screen.

Please switch the machine off after you have completed 24 hours and remove the cuff. If there are any problems with the machine then please contact us on the numbers above. In an emergency the machine can be switched off and the cuff removed.

P M Rothwell MB ChB MD PhD FRCP FMedSci
Action Research Professor of Neurology
Honorary Consultant Neurologist

Oxford University Hospitals NHS
NHS Trust
Nuffield Department of Clinical Neurosciences
WCPSD
The Wolfson Building
John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU

Tel: (01865) 234893

REMOVE:

COLLECT:

Patient Details and Diary

Monitor Number: **TEST:**

Date recording commenced:

Full name:

OXVASC No:

The following questions will be useful in the analysis of your recording:

Today were you at work? ☐ at home? ☐

What sort of day did you have?

Average ☐ Unusually quiet ☐ Unusually busy ☐ Unusually stressful ☐

How well did you sleep?

What time did you go to bed? What time did you get up?

Were you awake during the night?

Appendix 1.4

OXFORD VASCULAR STUDY

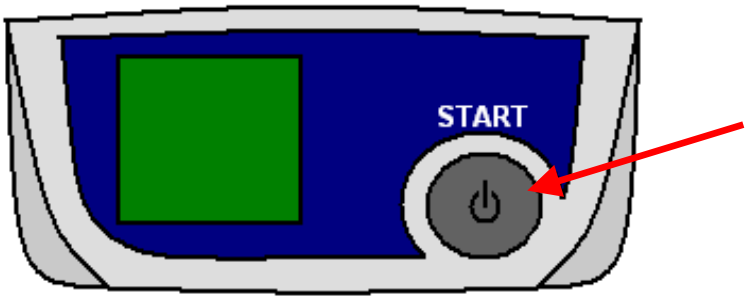
Principal Investigator: Professor Peter M Rothwell

Wolfson Centre for Prevention of Stroke and Dementia
The Wolfson Building
John Radcliffe Hospital site, Oxford, OX3 9DU
www.stroke.ox.ac.uk

01865 231601
orh-tr.oxvasc@nhs.net

How to check your blood pressure

- Sit down and take a few moments rest.
- Wrap the cuff around your bare arm approximately 2-3 cm above your elbow crease (as shown in the diagram printed on the cuff).
- The rubber lead should be going away from you towards your wrist on the inside of your arm. You
- If the cuff is tightened correctly you should be able to fit up to 2 fingers between your skin and the cuff. Make sure that the rubber lead is firmly inserted into the BP monitor and that it is free from obstruction.
- **Please ensure that your legs are not crossed and that your feet are flat on the ground.**
- **Press the START button firmly once -** the cuff will automatically inflate.



- Try not to talk or move while the cuff is inflating. Do not be concerned if the BP monitor has to inflate more than once to take your blood pressure.
- Once the BP monitor displays a result make a note on the reading on the record sheet provided. Wait for the screen to turn off.
- **You can now repeat this action to take your next reading.** After your third reading you can remove the cuff.

Appendix 1.5

Oxford University Hospitals NHS
NHS Trust
Nuffield Department of Clinical Neurosciences
Level 6, West Wing
John Radcliffe Hospital
Headley Way
Oxford
0X3 9DU

Tel: (01865) 234893
Fax: (01865) 234629

P M Rothwell MB ChB MD PhD FRCP FMedSci
Action Research Professor of Neurology
Honorary Consultant Neurologist

INFORMATION

Digital Blood Pressure Monitor

You have been issued with a **home digital blood pressure monitor** as part of your investigations. The purpose of this is to try and make sure that your blood pressure (BP) is well controlled – a couple of measurements by us and your GP may not be a true reflection of your blood pressure. Our experience has shown that the best way to do this is to measure your blood pressure regularly so that when we review you in a month's time we will be able to make a more informed decision about your ongoing treatment.

Mobile telephone

You are also being issued with a **mobile telephone** that will send your blood pressure readings directly to us so that we can monitor your progress - you do not have to write anything down. For the blood pressure monitor to transmit readings to the telephone they need to be within a 10 metre range of each other, so where possible please try to use your blood pressure monitor in the same room as the phone.

The telephone will be attached to a charger and timer. **Please plug these into a socket as soon as you get home.** Please ensure the socket is left turned on. The timer has been set to charge the battery for approximately 20 hours a day. The phone will be set up for you, so once the phone has been plugged in at home you do not need to touch it. If you find that the light on the phone disturbs you then you can simply turn it upside down or put a towel over it.

NB. It is NOT possible to make phone calls with the telephone.

Blood Pressure Cuffs

We will advise you on which arm we would like you to measure and provide you with the appropriate size of cuff for your arm.

Measuring your blood pressure

We will instruct you on how to use the home BP monitor either in the clinic or at home if appropriate. Please refer to the attached instructions for further information.

When to take your readings

Set 1 – as soon after wakening as possible
Set 2 – mid morning – around 10 am if possible
Set 3 – just before you go to bed

At each sitting we would like you to measure your blood pressure **3 times**. You should allow a couple of minutes in between each of the 3 blood pressure measurements – remember to **let the BP monitor turn itself off each time**.

If you wish you can take your blood pressure more than this but please make sure that this is in addition to the above schedule, not instead of it.

How to take your readings

For the best results:

- Please **rest for a few minutes** prior to taking your readings.
- All measurements should be done **sitting,** at a table if possible.
- Please always take your blood pressure in the **same arm.**
- Try **not to talk or move** around whilst the cuff is inflating.

It is important that **only you** use the BP monitor. Please do not allow anyone else to use the machine or interfere with the equipment.

If you are going to be away from home please take the BP monitor with you, leaving the mobile telephone at home, and take your readings as normal. It can store up to 40 readings and will automatically download these the next time you take your blood pressure in range of the telephone.

Please contact us on 01865 234893 or 01865 231601 if you have any problems, or if any changes are made to your blood pressure medications. Someone is available from 8.30am until 5pm Monday to Friday (excluding Bank Holidays).

INSTRUCTIONS

To take a reading:

Sit down and take a few moments rest.

Place the cuff around your bare arm L E F T R I G H T

approximately 2-3 cm above your elbow crease (see the diagram on the cuff). The rubber lead should be going away from you towards your wrist on the inside of your arm. If the cuff is tightened correctly you should be able to fit up to 2 fingers between your skin and the cuff. Make sure that the rubber lead is firmly inserted into the BP monitor and that it is free from obstruction.

Press the START/STOP button firmly once. The cuff will automatically inflate. Try not to talk or move while the cuff is inflating. Do not be concerned if the BP monitor has to inflate more than once to take your blood pressure. Once the blood pressure monitor has finished it will display your reading. It will show 'CO2' as it transmits the information to the phone and onto our computer. When it has finished it will return to the date and time.

You can now repeat this action to take your next reading. After your third reading you can remove the cuff.

TROUBLESHOOTING

Problems with the mobile telephone

Before and after you take your blood pressure, the mobile telephone should show **"Please take a reading using your Blood Pressure meter"**. There should also be **2 green bars** at the bottom (last server contact and last meter contact). Please note it is normal to see some other information immediately after you have taken a reading.

There may be a problem with your mobile telephone if the screen

- is black
- shows the time
- says "Charging" or "Fully Charged"
- shows a red bar (last server contact or last meter contact)
- or if there is music playing

If you notice any of these please telephone us as soon as possible. We may be able to talk you, a friend or relative through the process of fixing it. Please continue to take your blood pressure as normal until the problem is resolved.

Problems with the Blood Pressure monitor

If the screen on the BP monitor shows ERR, the BP monitor has not able to take a reading on that occasion. Please check that

- you are quiet and still during the reading, with your arm supported (level with your heart) (ERR 01)
- the cuff is on properly (ERR 02)
    - that it is high enough up your arm to be level with your heart
    - that it is facing the correct way, with the tube going down the inside of your arm
    - that it is directly over your skin (not over clothing) and that you do not have tight clothing constricting your arm
    - that it is tight enough (you should be able to fit up to 2 fingers between your skin and the cuff)
- the tubing between the cuff and the monitor is well connected, and not obstructed.

and try again after 30 seconds. If you are known to have an irregular heart beat, ERR may also show. If you continue to have problems, please telephone us.

Batteries

If the batteries run out (ERR 04), please contact us to arrange replacements. Once the batteries are changed you may need to **reset the date and time** on the BP monitor.

To do this

- Press and hold the right button until Mon, Day, Hour and Min flash.
- Press the left button repeatedly until the correct minute is set.
- Press the right button to move on to the next item (Hour, Year, Month, Day), and the left button to set the correct number.
- The process ends by pressing the right button until the year no longer appears (or if no button has been pressed for 30 seconds).

Someone is available on 01865 234893 or 01865 231601 from 8.30am until 5pm Monday to Friday (excluding Bank Holidays).

Appendix 1.6

THINK POSITIVE®

blood pressure



OXVASC Patient Information

Doc Ref: 001-2027-LMAN2 Version: R2, Issue Date: 25 Oct 2017

Trademarks: t+ Medical® is a registered trade mark of OBS Medical Ltd.

Contents

Introduction 4
- Indications 4
- Welcome to t+ blood pressure 4
- How does t+ blood pressure work? 5
- Why should I use t+ blood pressure? 6
- When should I not use t+ blood pressure? 6
- Caution 6

Getting Started 7
- Set up instructions 7
- Bluetooth Hub 8
- Blood Pressure Meter 9
- Blood Pressure Cuffs 9
- Taking a blood pressure reading 9

Troubleshooting and Support 11
- Description of maintenance 11
- Storage instructions 11
- Troubleshooting – Blood Pressure Meter 12
- Troubleshooting – Bluetooth Hub 13
- t+ blood pressure support 14
- OXVASC contact information 14
- T+ contact information 14

Introduction

Indications

The t+ blood pressure is intended for periodically recording blood pressure readings for the purpose of improving blood pressure management.

The t+ blood pressure provides real-time readings, graphs, and trends directly to healthcare professionals. It is intended to be used in the home to aid you to monitor your blood pressure in between surgery visits.

The t+ blood pressure is available only through healthcare professionals.

Welcome to t+ blood pressure

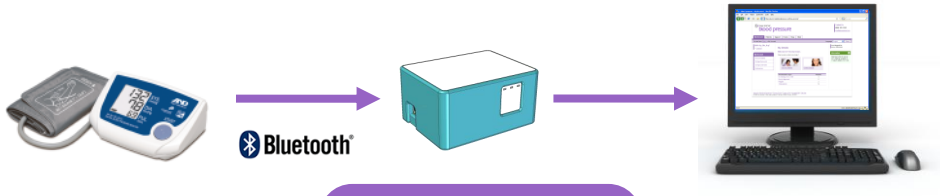
t+ blood pressure is a simple tool to help you and your health care professional keep track of your blood pressure in between surgery visits. This means they can spot any changes and track any trends as they happen.

How does t+ blood pressure work?

t+ blood pressure uses a Bluetooth Hub and a blood pressure meter (with Bluetooth) to safely and securely send information about your blood pressure directly to your health care professionals.

The information about your blood pressure is automatically sent to your health care professional who can look at it on their surgery computer.

It is really simple for you to use, all you have to do is put the blood pressure cuff on your arm and press the Start button.



You take your blood pressure at home using the Blood Pressure monitor (with Bluetooth)

The readings are automatically transmitted via Bluetooth to the Bluetooth Hub and onto the t+ System Servers

Your healthcare professionals are then able to see your readings via a secure web site

Why should I use t+ blood pressure?

You will have been specifically chosen by your healthcare professional to use this equipment, and advised by them how to use it.

Through the use t+ blood pressure, both you and your healthcare professional will have a much greater insight into your health. It will help you both monitor your condition more closely.

When should I not use t+ blood pressure?

You should not use t+ blood pressure if you feel unwell before, during or after taking your blood pressure. Please inform your healthcare professional.

Caution

Please read all the instructions provided in this user guide, and ensure you are confident using the equipment. If you need any additional help using the equipment please speak to your healthcare professional.

This equipment is intended only to be used by the person it was supplied to, and must only be used as instructed.

Getting Started

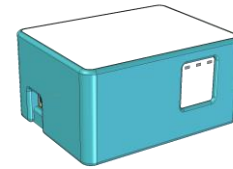
You will have been specifically chosen by your healthcare professional to use this equipment, and advised by them how to use it.

Set up instructions

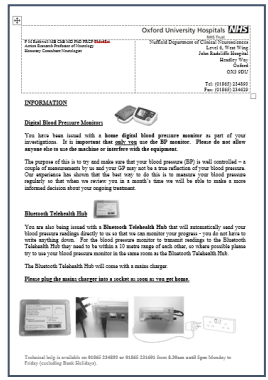
You will have received:



Blood pressure meter and medium sized cuff *



Bluetooth Hub



Healthcare Organisation Patient Leaflet

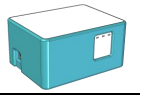
Or



A t+ blood pressure Patient user guide

*Other cuff sizes are available please discuss with you healthcare professional

Bluetooth Hub



You have been issued a Bluetooth Hub that will automatically send your blood pressure readings directly to your healthcare professional to monitor your progress.

For the blood pressure monitor to transmit readings to the Bluetooth Hub, they need to be within a 10 meter range of each other, so where possible please try to use your blood pressure monitor in the same room as the Bluetooth Hub.

The Bluetooth Hub will come with a mains charger. Please plug the mains charger into a socket as soon as you get home.

Once plugged in, the three indication lights will illuminate for 10 seconds then go off.



Then one or more indication lights will illuminate as follows:

- Green Light (Status)
  - Intermitted flashing – the hub is trying to connect to the secure t+ servers
  - When permanently illuminated – the hub is now connected to secure t+ servers
- Blue Light *(Bluetooth)*
  - When illuminated – the BP Meter is transmitting readings to Bluetooth Hub
- Red Light *(Memory)*
  - When illuminated – the BP Readings have been stored awaiting transmission when connected

We would recommend leaving the Bluetooth Hub plugged in and switched on at all times.

Blood Pressure Meter



You have been issued with a home digital blood pressure monitor as part of your investigations.

It is important that only you use the BP monitor.

Please do not allow anyone else to use the machine or interfere with the equipment.

The purpose of this is to try and make sure that your blood pressure (BP) is well controlled. A couple of measurements by your GP may not be a true reflection of your blood pressure.

Our experience has shown that the best way to do this is to measure your blood pressure regularly so that when your healthcare professional reviews you in a month's time they will be able to make a more informed decision about your ongoing treatment.

Blood Pressure Cuffs

Your healthcare professional will advise you on which arm we would like you to measure and provide you with the appropriate size of cuff for your arm.

Taking a blood pressure reading

Your healthcare professional will instruct you on how to use the home BP monitor either in the clinic or at home if appropriate.

Please refer to the below instructions for further information.

When to take your readings

Set 1 – as soon after wakening as possible

Set 2 – mid morning – around 10 am

Set 3 – just before you go to bed

Blood pressure varies in everyone throughout the day. Having a mid-morning reading better informs your healthcare professionals' management of your blood pressure.

At each sitting we would like you to measure your blood pressure **3 times**.

You should allow a couple of minutes in between each of the 3 blood pressure measurements.

If you wish to take your blood pressure more frequently, please ensure that this is in addition to the above schedule, not instead of it.

How to take your readings

For the best results:

- Please rest for a few minutes prior to taking your readings.
- All measurements should be done sitting, at a table if possible.
- Please always take your blood pressure on the same arm.
- Try not to talk or move whilst the cuff is inflating.

Troubleshooting and Support

Description of maintenance

Product damage may occur if proper care is not taken whilst unpacking, installation and use.

Do not submerge any of the components in water or any other fluids. If the equipment does get wet, dry immediately.



If the batteries in the blood pressure meter run low, the battery power indicator will begin to blink.

The meter takes 2x AA batteries. More information on replacing the batteries this can be found in the BP meter user guide.

Important: When the battery symbol on the BP Meter begins to blink; you should replace the batteries immediately.

The Bluetooth Hub is mains powered and should be left on at all times to ensure the timely receipt and transmission of your daily BP readings for clinical review.

Storage instructions

Store the t+ blood pressure equipment in a dry area, and remove batteries from the BP meter if it is to be stored for extended periods of time.

Troubleshooting – Blood Pressure Meter



Problem	Possible Reason	Recommended Action
Nothing appears in the display even when the power is turned on	Batteries are drained	Replace all batteries with new ones
	Battery terminals are not in the correct position	Reinstall the batteries with negative and positive terminals matching those indicated on the battery compartment.
The Cuff does not inflate	Battery power is low Low Battery Mark – blinks If the batteries are drained completely, the mark does not appear	Replace all batteries with new ones
The unit does not measure. Readings are too high or too low	The cuff is not applied properly	Apply the cuff correctly
	You moved your arm or body during the measurement	Make sure you remain very still and quite during the measurement
	The cuff position is not correct	Sit comfortably and still. Raise your hand so that the cuff is at the same level as your heart
		If you have a very weak or irregular heartbeat, the device may have difficulty in determining your blood pressure
Other		Remove the batteries. Place them back properly and try the measurement again.

Troubleshooting – Bluetooth Hub



Problem	Possible Reason	Recommended Action
BT Hub Status (Green) indication light is not ON or flashing	Mains power not connected	Check the mains power is connected to the BT Hub and that mains power is switched on at the plug socket.
BT Hub Status (Green) indication light is flashing intermittently	Poor network signal at the current BT Hub location	Relocate the BT Hub to another part of the building and retry. The Status (Green) indication light needs to be permanently ON
BT Hub Bluetooth (Blue) indication light does not come on when taking a BP reading	The BT Hub and BP Meter are not within 10 meters of each other	Check both the BT Hub and BP Meter are within 10 meters of each other and retry reading
	The BP meter needs to be reconnected with the BT Hub	BP Meter - Press and hold the start button until the word **uPr** appears. Lift and re-press the start button and the words **END** appears. Now retake a BP reading. The Bluetooth (Blue) indication light should now come on.
BT Hub Memory (Red) indication light is on.	BT Hub is not connected to secure t+ system so it is storing readings	Check the Status (Green) indication light is permanently ON

t+ blood pressure support

For study specific questions, please contact the relevant research team as detailed via your Patient Information Letter issued along with the t+ blood pressure system.

OXVASC contact information

If you have any concerns or questions regards your blood pressure investigations, please contact the OXVASC team during office hours Monday – Friday 8:30am until 5pm

Call: 01865 234 893

T+ contact information

If you have any technical problems, please contact the customer service team who can be reached during office hours Monday - Friday 9am to 5pm excluding bank holidays.

Call: 01235 432050
Email: support@tplusmedical.com

This page has intentionally been left blank



UK Head Office
5G Park Square
Milton Park
Abingdon
OX14 4RR
UK

Appendix 1.7

Oxford University Hospitals NHS
NHS Foundation Trust

P M Rothwell MB ChB MD PhD FRCP FMedSci
Action Research Professor of Neurology
Honorary Consultant Neurologist

Nuffield Department of Clinical Neurosciences
Level 6, West Wing
John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU

Tel: (01865) 234893
Fax: (01865) 234629

INFORMATION

Digital Blood Pressure Monitors



You have been issued with a **home digital blood pressure monitor** as part of your investigations. **It is important that only you use the BP monitor. Please do not allow anyone else to use the machine or interfere with the equipment.**

The purpose of this is to try and make sure that your blood pressure (BP) is well controlled – a couple of measurements by us and your GP may not be a true reflection of your blood pressure. Our experience has shown that the best way to do this is to measure your blood pressure regularly so that when we review you in a month's time we will be able to make a more informed decision about your ongoing treatment. **Please do not attempt to change the date and time on the BP monitor even if it is incorrect.**

Bluetooth Telehealth Hub



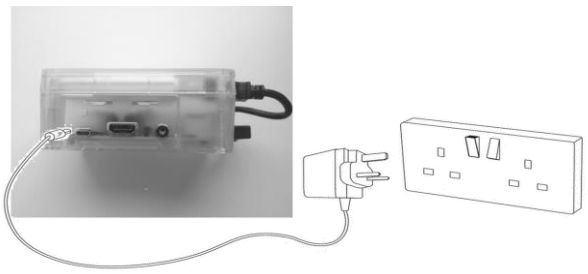
You are also being issued with a **Bluetooth Telehealth Hub** that will automatically send your blood pressure readings directly to us so that we can monitor your progress - you do not have to write anything down. For the blood pressure monitor to transmit readings to the Bluetooth Telehealth Hub they need to be within a 10 metre range of each other, so where possible please try to use your blood pressure monitor in the same room as the Bluetooth Telehealth Hub.

The Bluetooth Telehealth Hub will come with a mains charger.

Please plug the mains charger into a socket as soon as you get home.









Green / Yellow / Red

- Once plugged in, the three indication lights will illuminate for 10 seconds then go off. Then one or more indication lights will illuminate as follows:
    - Green Light *(Connection)*
        - Steady Green – Connected ok
        - Flashing Green – Trying to connect
    - Yellow Light *(BP Meter)*
        - When illuminated – BP Meter readings being received ok
    - Red Light *(Stored Readings)*
        - When illuminated – BP Readings stored awaiting transmission when Green light stops flashing
- We would recommend leaving the hub plugged in and switched on at all times.

Blood Pressure Cuffs

We will advise you on which arm we would like you to measure and provide you with the appropriate size of cuff for your arm.

Measuring your blood pressure

We will instruct you on how to use the home BP monitor either in the clinic or at home if appropriate. Please refer to the attached instructions for further information.

When to take your readings

Set 1 – as soon after wakening as possible
Set 2 – mid morning – around 10 am. Blood pressure varies in everyone throughout the day – having a mid-morning reading better informs our management of your blood pressure. If you are unable to do a reading at this time then please do a daytime reading at your convenience whenever possible.
Set 3 – just before you go to bed

At each sitting we would like you to measure your blood pressure **3 times**. You should allow a couple of minutes in between each of the 3 blood pressure measurements – remember to **let the BP monitor return to the time and date each time** or after you hear a loud beep, confirming reading has completed.

If you wish to take your blood pressure more frequently, please ensure that this is in addition to the above schedule, not instead of it.

If you are going to be away from home please take the BP monitor with you, leaving the Bluetooth Telehealth Hub at home, and take your readings as normal. It can store up to 99 readings and will automatically download these the next time you take your blood pressure in range of the Bluetooth Telehealth Hub.

Please contact us on 01865 234893 or 01865 231601 if you have any problems, or if any changes are made to your blood pressure medications.

Someone is available from 8.30am until 5pm Monday to Friday (excluding Bank Holidays).

INSTRUCTIONS

How to take your readings

For the best results:

- Please **rest for a few minutes** prior to taking your readings.
- All measurements should be done **sitting,** at a table if possible.
- Please always take your blood pressure in the **same arm.**
- Try **not to talk or move** whilst the cuff is inflating.

Place the cuff around your bare arm L E F T R I G H T

approximately 2-3 cm above your elbow crease (see the diagram on the cuff). The rubber lead should be going away from you towards your wrist on the inside of your arm. If the cuff is tightened correctly you should be able to fit up to 2 fingers between your skin and the cuff. Make sure that the rubber lead is firmly inserted into the BP monitor and that it is free from obstruction.



Press the START/STOP button firmly once. The cuff will automatically inflate. Try not to talk or move while the cuff is inflating. Do not be concerned if the BP monitor has to inflate more than once to take your blood pressure. Once the blood pressure monitor has finished it will display your reading. It will show **'CO2'** as it transmits the information to the Bluetooth Telehealth Hub and onto our computer. If you can see the Bluetooth Telehealth Hub, the BP Meter **(Yellow Light)** will illuminate, confirming readings being received ok. When it has finished, the BP Meter will return to the date and time screen.

You can now repeat this action to take your next reading. After your third reading you can remove the cuff.



TROUBLESHOOTING

Problems with the Bluetooth Telehealth Hub

The Bluetooth Telehealth Hub should automatically transmit your BP data to our computer, however if your IEM BP Meter shows a "COD" message on the display, this might indicate a problem with the hub. If the **Green Light is flashing** try:

- re-locating the hub to another part of your home. The hub relies on a mobile phone network to securely transmit your readings and the signal may be too weak in its current location.
- Remember to keep the BP meter within 10 meters of your Bluetooth Telehealth Hub.

If you continue to see "COD", and have run through the above checks please telephone us.

Note: The hub will continue to store your BP readings and the Red Light (Stored Readings) will illuminate to confirm readings are being stored. Once Connected (Green light is steady), all stored readings will be sent to us and the Red light will no longer illuminate.

Alternatively if we do not receive any BP readings after a period of time – usually 3 days, we will be in touch with you to check the Bluetooth Telehealth Hub and ensure all is working correctly.



Problems with the Blood Pressure monitor

If the screen on the BP monitor shows ERR, the BP monitor has not able to take a reading on that occasion. Please check that

- You are quiet and still during the reading, with your arm supported (level with your heart) (ERR 01)
- The cuff is on properly (ERR 02)
  - that it is high enough up your arm to be level with your heart
  - that it is facing the correct way, with the tube going down the inside of your arm
  - that it is directly over your skin (not over clothing) and that you do not have tight clothing constricting your arm
  - that it is tight enough (you should be able to fit up to 2 fingers between your skin and the cuff)
- The tubing between the cuff and the monitor is well connected, and not obstructed. and try again after 30 seconds.

If you are known to have an irregular heartbeat, ERR01 and ERR02 may also show. If you continue to have problems, please telephone us.

Batteries

Spare batteries have been provided in the kit carry case. Please swap batteries out as required or telephone us if you require more:

	 Low Battery	If the batteries in the blood pressure meter run low, the battery image displayed on the meter will turn black or it will display an error message (ERR 04).

Someone is available on **01865 234893 or 01865 231601** from **8.30am until 5pm** Monday to Friday (excluding Bank Holidays).

Appendix 2.1











Short Title: PROHIBIT-ICH Sponsor code: PROHIBIT-ICH01

Clinical Investigational Plan (CIP) for Medical Device Studies

Full title of Investigation:	**PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment**
Short title:	**PROHIBIT-ICH**
Version and date of Clinical Investigation Plan (CIP):	Version 9.0, 14th December 2020
Sponsor:	University College London
Sponsor CIP number:	PROHIBIT-ICH01
Funder (s):	Stroke Association Priority Programme Grant

Revision History:

Version numbers	Date	Summary of revisions in the case of amendments	Protocol Updated by [insert name & Signature]
1.0	**12/12/2017**	Template and list of amendments requested by Sponsor	Professor David Werring Professor Peter Rothwell Shahena Butt Ian McGurgan Louise Silver
2.0	**21/02/2018**	Section: a.7.4 who will hand the information sheets out, who will go through this with the patients. when does the research team get involved, do they do the second approach Section: A8 when will consent be taken, how long between receiving the PIS will the patients be expected to consent	Shahena Butt
3.0	**15/03/2018**	This needs to state how capacity will be assessed by who and how	Shahena Butt
4.0	**18/04/2018**	Section 13.5 of the protocol states that only initials and unique trial number will be stored on the CRF. Please consider updating this section so it is consistent with the information in section A11 of the Protocol	Shahena Butt
5.0	**13/06/2019**	Amendments 1. Removing inclusion criteria 4 (no need for a plan for home discharge) 2. Reducing the age limit to 30 and above 3. Displaying posters for patients and doctors in clinics and wards	Shahena Butt

		4. Patients can be identified from site databases (clinical and research) and then invited to consider participation in the study 5. NHS Patient Identification Centre (PIC) sites will be identified for the study. 6. 3 month and 12-24 month GP letters	
6.0	**25/09/2019**	1. potential participants will be contacted by email and post 2. participants are sent the invitation letter/PIS by post	Shahena Butt
7.0	**04/11/2019**	Amendments 1. Minor changes to the primary and secondary BP outcomes. (p. 12-13, 31-32, 34-35) 2. Minor changes to data collection and procedures due to COVID-19. (p.29)	Maja Dabagh
8.0	**14/12/2020**	Amendments: 1. Standard clinical MRI scans are permitted at baseline (in lieu of baseline research MRI scans) when performed within 6 months after the ICH 2. For participants in whom MRI is contraindicated or not possible, recruitment without MRI is permitted (as long as the qualifying ICH is confirmed by a CT scan) 3. The 12-month follow-up can be delayed for up to approximately 24 months from the baseline visit, to allow MRI scan completion (where applicable) and blood pressure measures to be performed on the	Shahena Butt

		same visit date.	

Signatures

The Chief Investigator (CI) and the JRO have discussed this Clinical Investigation Plan (CIP). The investigator agrees to perform the investigations and to abide by this CIP.

The investigator agrees to conduct the Investigation in compliance with the approved CIP, EU Good Clinical Practice (GCP) and UK Regulations for Devices (SI 2002/618; as amended) for regulated studies, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Professor David Werring



Signature — **14/12/2020** Date

Co-Chief investigator

Professor Peter Rothwell
University of Oxford



Signature — **14/12/2020** Date

Sponsor Representative



Pushpsen Joshi

Research Management and Governance Manager
UCL

Signature — **25/03/2021** Date

Contents

Clinical Investigational Plan (CIP) for Medical Device Studies 0
Signatures **3**
Sponsor **8**
Principal Investigator, Coordinating Investigator and Investigation site(s) **8**
A.1 Overall Synopsis of Clinical Investigation **10**
A.2 Background and Rationale **14**
A.3 Identification and description of the Investigational Device **14**
A.4 Justification for the design of the clinical investigation **16**
A.5 Risks and benefits of the Investigational device and clinical Investigation **18**
A.6 Objectives and hypotheses of the clinical investigation **19**
A.7 Design of the clinical investigation **22**
A.7.1 General *22*
A.7.2 Investigational device and comparators *22*
A.7.3 Subjects *24*
Inclusion criteria 24
Exclusion criteria 23
Subject Eligibility 25
Subject Identfication. 24
A.7.4 Recruitment *26*
A.7.5 Randomisation Procedures *26*
A.7.6 Procedures *26*
A.8 Informed Consent Process **27**
A.9 Schedule of assessments and interventions by visit **28**
A.9.1 *Laboratory Assessments and Procedures* 28
A.10 Device accountability **28**
A.11 Monitoring Plan **28**
Confidentiality 29
Record keeping and archiving 29
A.12 Statistical Considerations **29**
A.13 Data Management **36**
A.13.1 Procedures for data review, database cleaning, and issuing and resolving data queries. 37
A.13.2 Procedures for verification, validation and securing of electronic clinical data systems 37
A.13.3 Data retention. 38
A.13.4 Clinical quality assurance 38
A.13.5 Completion of Case Report Forms 38
A.13.6 Retention of Documentation 36
A.13.7 Training *38*

A.14 Amendments to the CIP 39

A.15 Deviations from clinical investigation plan 39
A.15.1 Procedures for recording, reporting and analysing CIP deviations. 40
A.15.2 Procedure for reporting any protocol deviations 38

A.16 Insurance 38

A.17 Adverse events, adverse device effects and device deficiencies 39
a-c) Definitions 39
Seriousness 44
Causality 44
Expectedness 45
f) Procedures for recording and reporting Adverse Events and Device Deficiencies 45
Investigator responsibilities: 45
Reporting of all Adverse Events and Device Deficiencies: Investigator and Sponsor responsibilities 46
Progress reports 46

A.18 Oversight Committees 46

A.19 Vulnerable population 47

A.20 Suspension or premature termination of the clinical investigation 47

A.21 Definition of End of Trial 47

A.22 Publication policy 48

A.23 Bibliography 48

Appendix 1: Schedule of Assessments 49

Appendix 2: Cognitive functional change (modified mentreal cognitive assessment) 50

Appendix 3: EQ-5D Questionnaire 52

Appendix 4: Home BP participant acceptability questionnaire 54

LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ABPM	Ambulatory Blood Pressure Monitoring
BP	Blood Pressure
CMB	Cerebral microbleed
CA	Competent Authority
CI	Chief Investigator
CIA	Clinical Investigation Agreement
CIP	Clinical Investigation Plan
eCRF	electronic Case Report Form
CRO	Contract Research Organisation
DCF	Data Clarification Form
DD	Device Deficiency
EC	European Commission
EU	European Union
EUDAMED	European Medical Devices Regulatory Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IMD	Investigational Medical Device
ISF	Investigator Site File
JRO	Joint Research Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Competent Authority
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute of Clinical Excellence

NIST	National Institute of Standards and Technology
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SVD	Small Vessel Disease
TMG	Trial Management Group
TSC	Trial Steering Committee
UADE	Unanticipated Adverse Device Effect
UK	United Kingdom
USADE	Unanticipated Serious Adverse Device Effect
WMH	White Matter Hyperintensities

Sponsor

Sponsor's representative Pushpsen Joshi	Joint Research Office, UCL, 1st Floor Maple House, 149 Tottenham Court Road, London W1T 7NF Postal address: Joint Research Office, UCL Gower Street, London WC1E 6BT

Principal Investigator, Coordinating Investigator and Investigation site(s)

Chief Investigator (CI) [CI of Imaging study]	Professor David Werring Professor of Clinical Neurology Stroke Research Centre UCL institute of Neurology Russell Square House 10-12 Russell Square London WC1B 5EH d.werring@ucl.ac.uk +44 (0)20 3108 7493
Co-Chief Investigator [CI of BP study]	Professor Peter Rothwell Action Research Professor of Neurology and Director of the stroke prevention research unit Centre for Prevention of Stroke and Dementia University of Oxford Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU peter.rothwell@ndcn.ox.ac.uk Tel: 01865 231603
Trial Coordinator	Shahena Butt Stroke Research Centre UCL Institute of Neurology Russell Square House 10-12 Russell Square, First Floor London WC1B 5EH shahena.butt@ucl.ac.uk Tel: 0203 108 6181
Imaging study co-lead (UCL)	Professor Rolf Jager Neuroimaging Centre UCL Institute of Neurology Queen Square London WC1N 3BG r.jager@ucl.ac.uk Tel: 020 34484726
Imaging study co-lead (UCL)	Professor Frederik Barkhof

	Chair of Neuroradiology Brain Repair and Rehabilitation UCL Institute of Neurology Faculty of Brain Sciences f.barkhof@ucl.ac.uk
MR Physicist (UCL)	Dr David Thomas Neuroimaging Analysis Centre Department of Brain Repair and Rehabilitation, UCL Institute of Neurology d.thomas@ucl.ac.uk Tel: 020 3448 3115
BP Clinical Research Fellow: (BP Monitoring Centre)	Iain McGurgan Centre for Prevention of Stroke and Dementia University of Oxford Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU ian.mcgurgan@ndcn.ox.ac.uk Tel: 01865 231601
BP Research Coordinator: (BP Monitoring Centre)	Louise Silver Centre for Prevention of Stroke and Dementia University of Oxford Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU louise.silver@ndcn.ox.ac.uk Tel: 01865 234622
BP Clinical Research Therapist: (BP Monitoring Centre)	Michelle Wilson Centre for Prevention of Stroke and Dementia University of Oxford Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU michelle.wilson@ndcn.ox.ac.uk Tel: 01865 231601
Statistician	Ziyah Mehta Centre for Prevention of Stroke and Dementia University of Oxford Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU Tel: 01865 234622 ziyah.mehta@ndcn.ox.ac.uk

A.1 Overall Synopsis of Clinical Investigation

Title:	**PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment**
Short title:	**PROHIBIT-ICH**
Device:	A&D BP Digital Blood Pressure Monitor (UA-767PBT-Ci) CE Declaration UA-767PBT-Ci
Objectives:	The trial will investigate whether intensive lowering of blood pressure (BP) using telemetric home monitoring in survivors of intracerebral haemorrhage (ICH) is feasible, safe and effective in reducing brain injury. If successful this study will be a precursor for a larger definitive trial. Our intervention should allow survivors of ICH to know, understand, and manage their own BP to prevent strokes and cognitive impairment, and improve outcomes. Our **primary objectives** are: (i) BP study. Does the use of centralised telemetric home BP monitoring in patients with spontaneous (non-traumatic) ICH achieve a reduction in 3-month BP compared with standard care? (ii) Imaging study. Does intensive BP treatment using centralised telemetric home monitoring result in a reduction in progression of small vessel disease (SVD)-related brain injury assessed on MRI (including, but not limited to, white matter hyperintensities (WMH), white matter structural integrity, incident cerebral microbleeds (CMBs), and brain atrophy) compared with standard care? Our **secondary objectives** are: (i) BP study 1. Is it feasible in a multi-site setting to intensively lower BP using centralised telemetric home BP monitoring for an extended period of time following spontaneous ICH? 2. Is it safe to intensively lower BP for an extended period of time following spontaneous ICH, or are there adverse responses (including increased progression of cognitive decline)? 3. Is the intervention acceptable to participants, including measures of quality of life? (ii) Imaging study 1. Does any reduction in recurrent vascular events (including ICH) or progression of cognitive decline on

	intensive BP treatment correlate with baseline measures of changes in quantitative and structural brain scan markers of small blood vessel health? 2. Are there any adverse effects on neuroimaging measures (e.g. increased white matter ischaemic injury) associated with intensive BP treatment?
Type of Investigation:	A pilot multi-site randomised controlled trial in approximately 112 adult survivors of spontaneous (SVD-related) ICH.
Investigation design and methods:	PROHIBIT-ICH will randomise participants to compare a strategy of intensive BP treatment (target <120/80 mm Hg) guided by telemetric home monitoring, versus standard primary care (current RCP guideline is 130/80 mm Hg), in 112 adult survivors of hypertension-related ICH. We will establish the feasibility and safety of the intervention, the efficacy of BP reduction, and explore whether it reduces the progression of SVD-related injury on brain MRI.
Investigation duration per participant:	Up to 24 Months
Estimated total Investigation duration:	48 Months
Planned Investigation sites:	Multi-Site
Total number of participants planned:	112
Main inclusion/exclusion criteria:	**Inclusion criteria:** 1. Adults (≥30 years) with spontaneous primary ICH (i.e. without known underlying structural, macrovascular or other cause (e.g. arteriovenous malformation, tumour) after adequate investigation at the discretion of the local investigator). This will include participants presumed to have cerebral SVD (both hypertensive arteriopathy and cerebral amyloid angiopathy) 2. Clinical team opinion that BP control since the ICH is not adequate AND the measured SBP prior to randomisation is ≥130 mm Hg 3.There is no time limit for recruitment; however, recruitment as soon as is practical after the ICH is encouraged. Recruitment at a later stage is acceptable as long as there is evidence of inadequate BP control AND SBP at randomisation is ≥130 mm Hg 4. Ability and willingness to undertake BP measurements,

either unassisted or with the help of a relative, friend or carer; this can be undertaken in any destination after hospital discharge (e.g. home, rehabilitation unit, nursing or care home)
5. Ability and willingness to attend and complete the study assessments including cognitive screen
6. Ability and willingness to provide informed consent, or with a suitable consultee available and able to participate in the intervention (e.g. with a motivated carer)

Exclusion criteria:
1. Inability to provide informed consent or lack of suitable consultee (if unable to provide personal consent, lack of suitable consultee)
2. Evidence of a macrovascular or structural cause for ICH (e.g. AVM or tumour)
3. Diagnosis of dementia (DSM IV criteria, or self-reported or documented in medical records)
4. Low Functional status (MRS ≥4) before or after ICH or frailty likely to make participation in 1-year follow-up difficult for the participant
5. Life expectancy <2 years
6. Taking more than 2 BP-lowering medications (i.e. 3 or more) at the time of consent
7. Consistently good BP control (below 130/80 mm Hg on measures taken as part of routine clinical care) prior to planned recruitment, judged not to require more intensive treatment
8. Known flow-restricting intracranial/extracranial large arterial stenosis
9. Known absence of mobile phone coverage from all network operators and home internet at the participant's home
10. Known sensitivity or contra-indication to BP treatments (e.g. symptomatic postural hypotension) is not an absolute exclusion criterion, but more information must be provided
11. Note that participation in other CTIMP or device trial is NOT an automatic exclusion criterion

Statistical methodology and analysis:

Primary outcomes:
(a) BP study
(i) Efficacy: the magnitude of difference in assessment BP at 3 months in the intervention arm versus the control arm compared with baseline measures
(ii) Feasibility: consent rate; dropout rate from the intervention prior to 1 month; patient approval of the monitoring process
(iii) Safety: serious adverse event related to reducing BP in intervention arm

(b) Imaging study
(i) Efficacy: the progression in MRI white matter hyperintensity (WMH) volume since baseline

Secondary outcomes:
(a) BP study: clinical outcomes including recurrent vascular events and cognition; number of BP lowering drugs at 3 months and at follow-up visits; the magnitude of difference in mean daytime BP measured on 3-month and 12-month ABPM in the intervention arm versus the control arm compared with baseline ABPM
(b) Imaging study: neuroimaging outcomes including (but not limited to) the proportion of patients who develop new cerebral microbleeds (CMBs) since baseline; number of new CMBs since baseline; new infarcts or intracerebral haemorrhages since baseline; change in mean diffusivity (MD), fractional anisotropy (FA) and other 3T DTI metrics; change in cerebral blood flow (CBF) on 3T PCASL; change in total brain volume, white matter volume and grey matter volume on 3T T1 volumetric images; composite neuroimaging measures (e.g summary SVD scores)

A.2 Background and Rationale

Intracerebral haemorrhage (ICH)

Spontaneous intracerebral haemorrhage (ICH) is a type of stroke due to bleeding within the brain parenchyma (which may also extend to ventricular and subarachnoid space) that is not caused by trauma.(1) ICH accounts for 10-15% of all strokes in Western populations, while in Asia it accounts for 15-30%.(1, 2) In the UK, out of the total 150,000 strokes per year, about 15,000 to 23,000 are due to ICH. The 30-day case-fatality for ICH is about 40%(2) (higher than the other stroke types, ischaemic stroke (IS) or subarachnoid haemorrhage (SAH)). Less than a half of patients with ICH survive 1 year and less than a third survive 5 years, while survivors have substantial cognitive and physical impairments.(3) ICH additionally places a substantial economic burden on society, a challenge which will increase with our ageing population;(4) a meta-analysis demonstrated that ICH incidence remained constant between 1980 and 2008,(2) making ICH a persistent challenge for stroke research.

The challenge of secondary prevention after ICH

About 40% of ICH strokes are recurrent, resulting in higher mortality and disability than the first occurrence.(5) A recent systematic review of mainly hospital-based ICH cohorts found that the rate of recurrent ICH is between about 1.4% and 7.4% per year.(3) There is also a high risk of dementia after ICH (incidence 14.1% at one year in a recent prospective observational cohort study),(6) making reduction of cognitive and physical disability a key research challenge. Recurrent ICH risk seems to reduce over time: one study found that in the first year, the rate of recurrence was 2.1 out of 100 patients per year, which decreased to 1.2 out of 100 patients per year, but remained comparable with ischaemic stroke recurrence rates (1.3 out of 100 patients per year)).(7) 'Lobar-lobar'(8) is reported to be the most common pattern of ICH recurrence, likely due to cerebral amyloid angiopathy (CAA); moreover, CAA-related ICH has been reported to have a much higher recurrence risk than other types.(9) With the high incidence, prevalence, mortality, disability, socioeconomic impact and recurrence rates of ICH, the benefits of high-quality research to improve outcome are likely to be significant. However, there remains a lack of randomised controlled trials of interventions in ICH survivors to reduce recurrence, brain injury, and cognitive impairment. Well-established risk factors for ICH recurrence include increasing age,(10) hypertension,(11) smoking,(12) excessive alcohol use,(13) and the presence of cerebral microbleeds on magnetic resonance imaging (MRI).(8) The most important and prevalent risk factor for recurrent stroke, including ICH, is hypertension, making this an obvious therapeutic target. Recent observational research suggests that improving long-term lowering of BP after stroke due to ICH might reduce recurrence.(11)

Hypertension and ICH

Long-term hypertension is the most significant risk factor for stroke in general, but particularly for ICH. People with hypertension have five times the risk of ICH compared to those without.(14) This association might be explained by the effect of poorly controlled hypertension on small blood vessel walls, leading to hypertensive arteriopathy, a form of cerebral small vessel disease (SVD) which causes

them to weaken and rupture. Small vessel disease (including hypertensive arteriopathy and CAA) is the major cause of spontaneous (non-traumatic) ICH.

Research on lowering blood pressure after ICH

Following ICH, patients often have early hematoma expansion, a marker of poor prognosis.(15) Admission systolic BP (SBP) of ≥200 mm Hg is associated with haematoma expansion and higher mortality.(16) A recent trial showed that acute lowering of BP (within the first 6 hours) improves outcomes after ICH (INTERACT-2).(17) Recent observational data suggests that even short-term increases in BP might trigger ICH(18) and emphasises the important role of BP management as means of secondary prevention for ICH. BP variability (e.g. day-to-day or between hospital visits) has also recently been shown to be an independent risk factor for stroke, and to influence outcome after ICH.(19)

Less research has focused on sustained post-acute BP management, which holds the most potential to improve long-term prognosis and recurrence following an ICH. There have been no dedicated trials targeting long term BP reduction after ICH. The main prospective randomised data on the effects of long term BP lowering after ICH come from the PROGRESS trial, in which treatment of patients with ICH with the BP lowering agents perindopril (an angiotensin-converting enzyme inhibitor) and indapamide (a thiazide-like diuretic) led to a mean difference of 11 mm Hg systolic and 4 mm Hg diastolic BP between treated and placebo arm participants, with a reduction in the absolute rate of ICH from 2% to 1% over 3.9 years of follow-up. This 50% relative risk reduction for ICH was higher than the 24% reduction in ischaemic stroke.(20, 21) Consistent with this substantial risk reduction in ICH, a recent trial in 3020 patients with recent subcortical infarction (presumed due to SVD, the main cause of ICH) showed that the risk of future ICH was significantly reduced (by 60%) by intensive BP lowering (target systolic BP <130 mm Hg compared with 130-139 mm Hg).(22) There are, nevertheless, also concerns that intensive BP lowering may have an adverse impact in older populations by reducing cerebral perfusion, causing cerebral ischaemia, progression of cognitive impairment and falls.(23) Thus, although intensive BP lowering is a very promising secondary prevention intervention in ICH, the optimum long term target BP remains uncertain.

The challenge of long-term sustained blood pressure control after stroke

Current UK guidelines suggest a systolic BP target after stroke of 130 mm Hg (Royal College of Physicians National Guideline for Stroke, 2016). Nevertheless, in practice control of BP remains poor. In the UK, only 35% of stroke patients achieved the guideline standard,(24) while 41% of stroke patients in the PROFESS study had systolic BP >140 mm Hg at follow-up, with an increased risk of recurrent stroke.(25) The proportion of stroke patients taking antihypertensive drugs declines rapidly (by about 25%) in the first 2 years after stroke,(26) suggesting that patient adherence is an important barrier to effective BP treatment. Poor adherence to BP medications is also clearly associated with an increased risk of stroke.(27) Adherence for secondary prevention after stroke is challenging because: (1) many new medications (e.g. antithrombotic drugs, statins, antihypertensives) are all started at once; (2) there are often physical or cognitive impairments; (3) there is no immediate relief of symptoms; and

(4) reductions in future vascular events may take months or years to accrue. A systematic review of interventions to improve adherence found few high-quality studies, with a need to improve objective monitoring of adherence and BP.(28) A recent comprehensive review of research gaps in BP treatment after stroke concluded that clinical trials evaluating implementation of evidence-based strategies for BP control to prevent recurrent stroke are needed.(29)

A.3 Identification and description of the investigational device

Home telemetric home monitoring device for PROHIBIT-ICH

Telemetric home monitoring is a promising strategy to facilitate home BP monitoring after stroke, which should improve adherence and optimize medication to better control BP. Telemetry allows patients with hypertension to monitor their own BP and automatically send the information to a secure website, available to their clinicians to monitor and adjust their treatment. Home telemetric Bluetooth BP monitoring has been evaluated in patients with TIA and predominantly non-disabling stroke in the setting of the Oxford Vascular (OXVASC) Study by the Centrally Observed home telemetric Monitoring of BP to Manage Intensive Treatment (COMMIT) Study. In this population, the intervention was safe and effective, with few adverse events and high patient satisfaction. However, more research is required on the feasibility of use of this strategy in more disabling stroke and in patients with ICH, as well as on transferability to multiple centres beyond the previous research setting in Oxfordshire. A key aim of the present application is to obtain essential feasibility data in a pilot randomised controlled trial in a cohort of ICH survivors (in whom the expected benefit of the intervention is the largest of all stroke types) in a multi-site setting. In the COMMIT Study, we studied consecutive eligible consenting patients in the Oxford Vascular Study. After prescription of initial BP-lowering therapy, if required, patients measured their BP 3 times over 10 minutes on 3 occasions per day at home with a Bluetooth-equipped monitor for 1-3 months, depending on control. Measurements transmitted automatically in real time were checked daily on a secure web page. If BP was consistently above 130/80 mm Hg or below 100/60 mm Hg antihypertensive therapy was adjusted. The results outlined below are from the first 1000 recruits (mean/SD age=69/13; range=21-98yr; 23% ≥ 80 years): (1) Rates and risk factors for masked hypertension. The prevalence of hypertension after TIA and stroke is often underestimated, with rates of “masked” hypertension (normal clinic BP but elevated home readings) ranging from 10-30%. In COMMIT, masked hypertension (BP ≤ 140/90 mm Hg at initial assessment and mean BP > 135/85 mm Hg across the first 3 days of monitoring; AHA definition) was found in 344 (34.4%). The much more detailed record of BP obtained on home telemetric BP-monitoring thus provided clinically important data that were not available from occasional clinic measurements. Masked hypertension has not been investigated in ICH; (2) Feasibility, medication changes and control of BP. BP-lowering medication was initiated or increased at the pre-monitoring baseline visit in 555 (55.5%) patients. Medication was further initiated or adjusted at least once within the first month of home-monitoring in 558 (55.8%) patients and from 1-3 months in 393 (39%) patients. Mean BP measured on clinic follow-up fell from 141/83 mm Hg at entry to 130/74 mm Hg at 1-month ($p<0.001$) and to 127/72 mm Hg at 3-months ($p<0.001$) (see Figure 1 for an example BP trace). Telemetric home BP monitoring was feasible irrespective of age, and informed titration of medication in the majority of patients and was associated

with good BP control; (3) Acceptability of telemetric home-monitoring to patients. Of 1000 patients recruited, 576 (57.6%) returned an anonymised questionnaire after 1 month of monitoring. 533 (90.8%) approved of the intensive monitoring, 522 (89%) felt reassured by the central surveillance and 500 (85.2%) thought it helpful to be able to discuss their BP readings over the phone. However, 72 (12.3%) patients reported that monitoring their BP made them anxious and 83 (14.1%) felt it was time consuming. Mean (SD) overall satisfaction (0%-extremely dissatisfied to 100%–extremely satisfied) was 89 (14) %; (4) Comparison with 24-hour ambulatory monitoring (ABPM). We validated telemetric HBPM and ABPM by association with hypertensive arteriopathy and risk of recurrent vascular events. Mean SBP at 1-month on nocturnal ABPM, awake ABPM and HBPM (3 measurements, 3 times daily for 7 days) was related to five markers of hypertensive arteriopathy (creatinine > 120 mmol/L; aortic pulse wave velocity > 12m/s; advanced leukoaraiosis on brain imaging; Montreal Cognitive Assessment < 25; stroke vs. TIA) and to risk of recurrent stroke, coronary events and death. Among 1000 patients, hypertensive arteriopathy was more strongly associated (p-diff=0.007) with HBPM-SBP (odds ratio per 10 mm Hg: 1.42, 1.28-1.56, p<0.0001) than with awake or nocturnal ABPM (awake 1.11, 1.00-1.24; nocturnal 1.28, 1.17-1.40). During 2775 patient-years of follow-up, residual hypertension at 1-month on HBPM (n=218/23%) predicted the risk of recurrent events (HR=2.00, 1.28-3.12, p=0.002) better than on awake ABPM (n=207/20%, HR=1.24, 0.78-1.98, p=0.37) or nocturnal ABPM (n=307/39%, HR=1.47, 0.95-2.26, p=0.08). In models combining all 3 measures, only HBPM independently predicted recurrent events (HR=1.34, 1.11–1.63, p=0.003). Thus, residual hypertension is more strongly associated with hypertensive arteriopathy and risk of recurrent vascular events on HBPM than on ABPM. HBPM is therefore likely to be the better measure of BP-control after TIA/stroke, but has not yet been tested in major stroke or ICH.

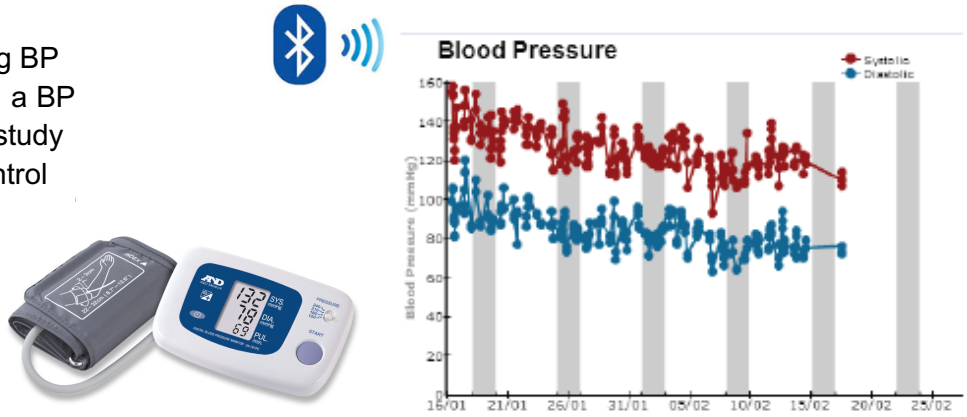


Figure 1: Home monitoring BP cuff and monitor (left), and a BP trace from the COMMIT study showing improved BP control over time (right)

Potential role of MRI in understanding the effects of BP treatment after ICH

MRI has rapidly improved our ability to see SVD disease processes related to ICH in vivo. Markers of small vessel disease on standard MRI include white matter hyperintensities (WMH), dilated perivascular spaces, lacunes and cerebral microbleeds (CMBs) whereas quantitative measures (e.g. diffusion tensor imaging (DTI)) provides information on microscopic tissue changes. White matter hyperintensities are the commonest marker of SVD, and can assessed semi-quantitatively using rating scales or quantitatively. The inter-rater and intra-rater reliability for both qualitative and quantitative

analysis of white matter hyperintensity is high if done by trained raters, with intraclass correlation coefficients generally above 0.90.(30) CMBs are small areas of bleeding detected on blood-sensitive MRI sequences (including T2*-weighted gradient-echo and susceptibility–weighted imaging), found in about 50-80% of patients with ICH, with value in diagnosing the type of SVD.(31) CMBs are also related to the risk of future ICH.(8) We showed that in patients with ischaemic stroke and TIA that the development of new CMBs was strongly related to baseline BP (Figure 2).(32) CMB accumulation might thus be plausibly reduced by intensive BP lowering

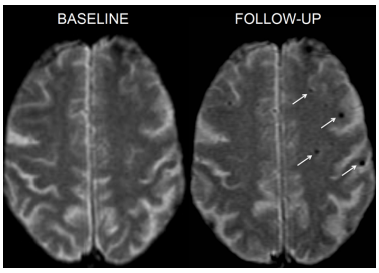


Figure 2. *Axial GRE T2* MRI scans at baseline and follow-up (after 5 years) showing the development of new CMBs (small black dots; white arrows). The development of new CMBs was strongly related to baseline systolic BP (OR 1.28 per unit increase, 95%CI 1.23-1.33, p<0.001). (from ref 32)*

In spontaneous ICH there is also a high prevalence of clinically "silent" acute ischaemic lesions (about 20% of patients),(33, 34) which has been associated with rapid acute BP lowering.(35) Longer term BP lowering in SVD has been hypothesised to cause white matter ischaemia or infarction, potentially worsening cognitive outcomes.(23) Thus, any treatment aiming to reduce recurrent ICH must also consider the risk of ischaemic brain injury. The key MRI manifestations of SVD have recently been reviewed (including WMH, lacunes, and CMBs).(30) These abnormalities evolve over time, and reflect brain injury relevant to the adverse consequences of SVD, including cognitive impairment. Measuring these as a surrogate outcome marker is attractive for a clinical trial, because it may be possible to assess beneficial or hazardous effects of an intervention in a much small number of participants in comparison to clinical event outcomes (e.g. recurrent stroke). Observational longitudinal studies in SVD indicate that WMH volume and diffusion tensor imaging (DTI) parameters are most sensitive to change and therefore have the smallest sample size estimates for trials of interventions, and progress over shorter time periods than cognition.(36) A recent review of imaging outcome markers for clinical trials in CAA suggested that CMBs and WMH were promising surrogate measures of SVD-injury, but further prospective data are needed to validate them.(37) In the PROHIBIT-ICH trial, we will test the hypothesise that intensive and sustained long-term BP control after ICH might reduce the progression of MRI markers of SVD, the underlying process that is likely to cause the long term adverse outcomes following ICH.

A.4 Justification for the design of the clinical investigation

Summary of rationale for the trial

ICH remains a devastating disease for which prevention of recurrent stroke is a research priority. BP lowering is the most promising preventive strategy, but adherence and BP control in clinical practice remain poor. There is thus an urgent need to improve ICH secondary prevention through improved long term BP control, including outcomes related to cognition and progression of the underlying SVD process. The concerns and views of stroke survivors, the recent development of home telemetric monitoring technology and improved understanding of MRI markers of SVD make this a unique and timely opportunity to commence a pilot a trial addressing these important research questions.

A.5 Risks and benefits of the investigational device and clinical investigation

The table below summaries the risks and mitigations of **the investigational procedures** that are being performed:

Table 1

Name of IMD	**Potential risk**	**Risk Frequency**	**Risk Management**
To be invited in the study by giving them an invitation letter and patient information sheet (PIS)	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.
Baseline consent	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.
Completion of eCRFs (baseline (visit one), 3 month follow up (visit two) and 12-24 month follow up (last visit)).	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.
Cognitive functional assessment (Montreal Cognitive Assessment)	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.
EQ-5D questionnaire	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.

The table below summaries the risks and mitigations of all tests above standard care that are being performed:

Table 2

Intervention	Potential risk	Risk Management
Blood Test	May cause discomfort or result in brusing	Performed by trained phlebotomist. Follow trust standard operational procedures.
MRI Scan	Patients may experience claustrophobia	Performed by a competent professional. Follow trust standard operational procedures.
Blood Pressure	The squeezing sensation may be uncomfortable but only lasts a few seconds.	Performed by the informed participant (if at home) and a competent professional.

The classification of medical devices in the European Union is outlined in Annex IX of the Council Directive 93/42/EEC (as amended). There are four classes, ranging from low risk to high risk.

Class I
Class IIa
Class IIb
Class III

The Medical Device used in this investigation is classified as **Class I**

A.6 Objectives and hypotheses of the clinical investigation

A.6.1 Hypotheses

Primary and secondary, to be accepted or rejected by statistical data from the clinical investigation.

A.6.2 Primary Objective

(i) BP study

Does the use of centralised telemetric home BP monitoring to guide intensive BP treatment in patients with spontaneous (non-traumatic) ICH achieve a reduction in 3-month BP compared with standard primary care?

(ii) Imaging study

Does intensive BP treatment using centralised telemetric home monitoring result in a reduction in progression of small vessel disease (SVD)-related brain injury assessed on MRI (including, but not

limited to, white matter hyperintensities (WMH), white matter structural integrity, incident cerebral microbleeds (CMBs), and brain atrophy) compared with standard care?

A.6.3 Secondary Objective(s)

(i) BP study

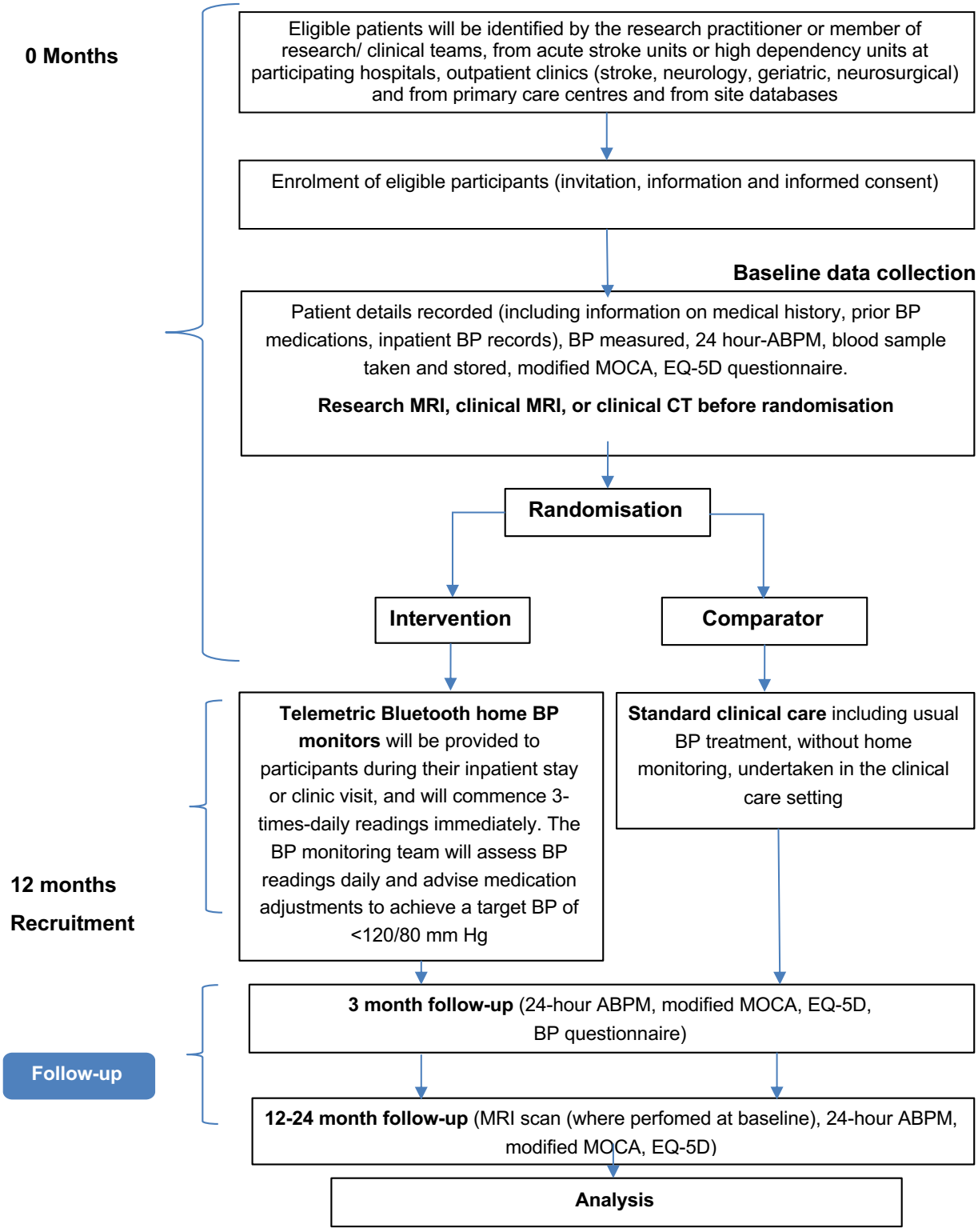
1. Is it feasible in a multi-site setting to intensively lower BP using telemetric home BP monitoring for an extended period of time following spontaneous ICH?
2. Is it safe to intensively lower BP for an extended period of time following a spontaneous ICH, or are there adverse responses (including increased progression of cognitive decline)?
3. Is the intervention acceptable to participants, including measures of quality of life?

(ii) Imaging study

1. Does any reduction in recurrent vascular events (including ICH) or progression of cognitive decline on intensive BP treatment correlate with baseline measures of changes in quantitative and structural brain scan markers of small blood vessel health?
2. Are there any adverse effects on neuroimaging measures (e.g. increased white matter ischaemic injury) associated with intensive BP treatment?

A.7 Design of the clinical investigation

A.7.1 General



A.7.2 Investigational device and comparators

Patients will be assessed for their eligibility during hospital inpatient stays, in outpatient clinics or primary care centres. Patients will also be identified from site records/databases and will be sent via post a patient invitation letter and patient information sheet (PIS). At the time of hospital discharge or at a dedicated clinic session with a research practitioner, eligible patients will be randomised in a 1:1 group assignment ratio to either telemetric home BP monitor-guided intensive BP lowering (intervention group) or standard care (control group) constituting usual primary-care led BP treatment, without home telemetric monitoring. For inpatients, the randomisation process will be undertaken as close as possible to discharge. All participants will be fitted with a 24-hour ABPM on the day of discharge (or in a dedicated clinic session for outpatients) by the research practitioner. The intervention group will also receive a telemetric Bluetooth home BP-monitoring device in addition to the ABPM and will be trained how to set this up in their home and use it. For the control group, the results of the baseline 24-hour ABPM (as for subsequent follow-up 24-hour ABPM) will not be communicated to the patient or GP unless mean daytime BP is sufficiently different to the patient's known recent daytime BP (based on recorded inpatient and baseline BP measurements) to justify informing on the basis of clinical need.

Intervention:

Participants randomised to the intervention group will receive a telemetric Bluetooth home BP-monitoring device. It will facilitate the Oxford BP-monitoring team to closely monitor the participant's BP to keep to the target of <120/80 mm Hg. If this is not achieved then BP medication will be adjusted accordingly in order to achieve the target by the 3 month follow-up visit. BP readings (3 readings over 10-minutes in the seated position in the non-dominant arm, unless there is severe hemiparesis) will be taken 3 times daily (early morning, early afternoon and evening). All BP data will be automatically transmitted centrally in real time to the device coordination site in Oxford. A dedicated BP-monitoring research team will be responsible for checking all BP data daily, and will directly advise patients by telephone on starting or adjusting BP medication according to a standard protocol based on the latest British Hypertension Society guideline, to ensure that BP is lowered to the intervention arm target. For the treatment-naïve participant, first line treatment (in the absence of contraindications) will usually be either combination therapy with perindopril arginine 5mg and indapamide MR 1.5mg per day, or amlodipine 5mg, increased to 10mg if needed. Subsequent treatment will be decided on a patient-specific basis, taking into account previous treatment trials and treatment responses, but will be likely to include the addition of spironolactone 25mg per day, doxasozin 4mg per day and nebivolol 2.5-5mg per day, alone or in combination. All such medication changes will be notified to the local research team and GP, with the GP providing prescriptions to participants based on correspondence from the central BP-monitoring team. If the target BP is consistently achieved after a minimum of one month of monitoring, Bluetooth monitors will be collected and conventional monitors issued to the intervention group only. At the 3 month follow-up visit, it is expected that the majority of patients will be able to replace their Bluetooth monitor for a conventional monitor, unless extenuating circumstances result in a need for prolonged monitoring and further treatment to achieve the BP target. The conventional monitors will be used at the patient's discretion to allow them to assess their own BP and contact their GP with any concerns about high/low readings. The responsibility for BP treatment will return to the GP

after 3 months of follow-up. Participants will also be asked to record a weekly BP reading on a sheet which will be returned with the monitor at the end of the 12-24 month follow-up period. GP letters will be sent at 3 month and 12-24 month follow up to provide the GPs with the patient's blood pressure readings.

A.7.3 Subjects

Inclusion criteria

1. Adults (≥30 years) with spontaneous primary ICH (i.e. without known underlying structural, macrovascular or other cause (e.g. arteriovenous malformation, tumour) after adequate investigation at the discretion of the local investigator). This will include participants presumed to have cerebral SVD (both hypertensive arteriopathy and cerebral amyloid angiopathy)
2. Clinical team opinion that BP control since the ICH is not adequate AND the measured SBP prior to randomisation is ≥130 mm Hg
3. There is no time limit for recruitment; however, recruitment as soon as is practical after the ICH is encouraged. Recruitment at a later stage is acceptable as long as there is evidence of inadequate BP control AND SBP at randomisation is ≥130 mm Hg
4. Ability and willingness to home BP measurements, either unassisted or with the help of a relative, friend or carer; this can be undertaken in any destination after hospital discharge (e.g. home, rehabilitation unit, nursing or care home).
5. Ability and willingness to attend and complete the study assessments including cognitive screen
6. Ability and willingness to provide informed consent, or with a suitable consultee available and able to participate in the intervention (e.g. with a motivated carer)

Exclusion criteria:

7. Inability to provide informed consent or lack of suitable consultee (if unable to provide personal consent, lack of suitable consultee)
8. Evidence of a macrovascular or structural cause for ICH (e.g. AVM or tumour)
9. Diagnosis of dementia (DSM IV criteria, or self-reported or documented in medical records)
10. Low Functional status (MRS ≥4) before or after ICH or frailty likely to make participation in 1-year follow-up difficult for the participant
11. Life expectancy <2 years
12. Taking more than 2 BP-lowering medications (i.e. 3 or more) at the time of consent
13. Consistently good BP control (below 130/80 mm Hg on measures taken as part of routine clinical care) prior to planned recruitment, judged not to require more intensive treatment
14. Known flow-restricting intracranial/extracranial large arterial stenosis
15. Known absence of mobile phone coverage from all network operators and home internet at the participant's home
16. Known sensitivity or contra-indication to BP treatments (e.g. symptomatic postural hypotension) is not an absolute exclusion criterion, but more information must be provided

17. Note that participation in other CTIMP or device trial is NOT an automatic exclusion criterion

Subject Eligibility

Once written informed consent has been obtained, the electronic case report form (eCRF) will be completed to document adherence to the inclusion and exclusion criteria.

Where a subject fails to fulfil any element of the inclusion and exclusion criteria, this will be documented and the signed consent form and completed inclusion/exclusion criteria retained by the principal investigator. The subject will not be advanced any further into this clinical investigation.

Subject Identification

Patients will be identified by members of the care team from the expected NHS hospital sites (acute stroke units or high dependency units), from outpatient clinics (stroke clinics, neurology clinics, geriatric clinics, neurosurgical clinics) and at primary care sites.

Patients can also be identified from site clinical and research databases of patients who have had a previous ICH at any time, including databases of participants included in previous clinical trials (subject to agreement with the Chief Investigator of the other trial). Potential eligible patients will be contacted email or post, for screening and informed consent. Patient Invitation letter and patient information sheet (PIS) will be sent to patients via post.

We will also provide posters which give information on the study, to be displayed at participating sites (including NHS PIC sites, see below); suitable locations include doctors or nurses offices, noticeboards, or in outpatient clinics.

NHS Patient Identification Centre (PIC) sites will be included in the study. These sites can will be NHS sites; the staff at these sites will identify potential patients and inform the study team at local PROHIBIT-ICH recruiting sites.

When a subject is identified and considered eligible for entry into this clinical investigation, the subject will be allocated the next available investigation number (subject ID number).

For subjects enrolled, this number will consist of 01 for the first subject, 02 for the second subject and so on. This number will be the unique identifier of the subject and noted on the electronic CRF and all other documentation relating to that subject.

Each subject that is enrolled into the study will have their study participation recorded and details of the device recorded in their hospital notes, a copy of their signed consent form and patient information sheet should also be placed on his/her hospitals notes to identify the subject as participating in a clinical investigation.

A.7.4 Recruitment

Participant recruitment at a site will only commence when the trial has been initiated by the Sponsor (or its delegated representative), and issued with the 'open to recruitment' letter.

Potentially eligible participants will be identified in person by the clinical staff at site during their inpatient stay or when they attend a clinic or primary care appointment or by site databases. The participants will be handed an information leaflet and a letter of invitation by the clinical staff at the site. Patients will have at least 24 hours to consider the information before being telephoned or approached by a member of the research practitioner or member of research/clinical teams at the NHS site to see if they are interested in taking part in the trial. If they are, a convenient time will be arranged for them to meet a research staff member delegated by the CI to discuss the study, go through the information sheet, assess eligibility and answer any questions they may have. Patients who are eligible and give consent will be enrolled and randomised to an intervention group or control group.
Patients will be provided with a participant information leaflet. An opportunity to meet a member of the research team will be arranged in person by a member of the clinical care team or subsequently by phone by a member of the research team. All interested participants will have an opportunity to ask questions about the study and these will be answered by a member of the research team prior to enrolment.

A.7.5 Randomisation Procedures

Following participant consent and confirmation of eligibility, the registration/randomisation procedure described below will be carried out.
Participants will be considered to be enrolled into the trial following: consent, pre-treatment assessments (see section A.7.6), confirmation of eligibility, completion of the registration/randomisation process, allocation of the participant trial number and treatment by the central coordinating team.
When a person agrees to participate, demographic, contact and medical history information necessary to conduct the study, including a record/chart of their inpatient BP measurements, will be recorded. Each participant will be allocated a unique trial number. Relevant sections of medical notes and data collected during the study may be looked at by the researchers from regulatory authorities or from the NHS Trust, where it is relevant to the subject's participation in the trial.
Patients will be randomised in a 1:1 group assignment ratio to intensive BP lowering (intervention group) or standard care (control group) using an online randomisation service (Sealed Envelope), available 24 hours a day.
Clinical data will be collected by an established electronic randomisation and eCRF system with a database managed from UCL by the study coordinator.

A.7.6 Procedures

The following examinations and investigations (if not already performed as part of routine standard of care) shall be performed for determining eligibility for enrolment into this investigation:

Pre-intervention assessments

Baseline

We will request that recruiting sites collect data on the number of patients who are potentially eligible for the study. At baseline, the following trial-specific procedures will be carried out after consent as a requirement for the study to commence:

- Medical history recorded, including details of the ICH, previous medical history, and inpatient BP records for every participant. The most recent three consecutive inpatient/outpatient BP readings, not including any taken specifically to assess for entry eligibility, will be used to assess for the BP inclusion and exclusion criteria
- Blood pressure medication and dose recorded, including reactions to prior poorly-tolerated BP medications, if applicable
- 3 BP measurements (2 seated and one standing after a minimum of 3 minutes). The initial measurement should be taken in both arms; if there is a significant difference (>20 mm Hg systolic) between them then the arm with the higher value should be used for subsequent monitoring
- Baseline 24-hour ABPM will be fitted and recorded in all participants
- Blood test (venepuncture)
- Research MRI brain scan or clinical MRI scan (performed within 6 months of ICH) or CT scan to show ICH prior to randomisation
- Cognitive functional assessment (modified Montreal Cognitive Assessment; see appendix 2)
- Completion of the EQ-5D questionnaire (appendix 3)

All pre-treatment procedures will be carried out as specified in the schedule of assessments (appendix 1).
For those patients having the research MRI scan:

The MRI protocol will be harmonised at all study sites based on EPAD (European Prevention of Alzheimer's Dementia) protocols for each major MRI scanner manufacturer (Siemens, GE, Philips), and will include the following sequences (with approximate timings):

1. 3D T1 (5min)
2. 3D FLAIR (5min)
3. DTI (simplified) (5min)
4. 3D SWI (5min)
5. Axial T2 (2min)

Other advanced MRI sequences (including, but not limited to, Arterial Spin Labelling (PCASL)) will be acquired as optional extra sequences at sites with capacity to undertake them. We aim to keep the total MRI scan time below 1 hour.

For those not having the research MRI scan:

1. **Allow standard clinical MRI scans at baseline**, which can be used in lieu of a baseline research scan when performed within 6 months after the ICH
2. **For participants in whom MRI is contraindicated or not possible**, recruitment can be undertaken with a CT scan confirming the qualifying ICH.

A.8 Informed Consent Process

It is the responsibility of the investigator, or a person delegated by the investigator to obtain written informed consent from each subject prior to participation in the Investigation, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.
The capacity of the patient will be assessed by a trained clinician on site that will be managing their clinical care.

The person taking consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI/PI on the delegation log.

“Adequate time” will be given for consideration by the patient before taking part. The PI must record when the patient information leaflet has been given to the patient. It must be recorded in the medical notes when the participant information leaflet has been given to the participant. Patients will have at least 24 hours to consider the information before being telephoned or approached by a member of the research practitioner or member of research/clinical teams at the NHS site to see if they are interested in taking part in the trial. If they are, a convenient time will be arranged for them to meet a research staff member delegated by the CI to discuss the study, go through the information sheet, assess eligibility and answer any questions they may have and Informed consent will be obtained.

The investigator or designee will explain the patients are under no obligation to enter the investigation and that they can withdraw at any time during the Investigation, without having to give a reason.
No clinical investigation procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into investigation. A copy of the signed informed consent document will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

A.9 Schedule of assessments and interventions by visit (see also Appendix 1)

Baseline (visit one): See section 7.6 for details of the procedure
Patients in the intervention group will be in telephone or email contact with the BP-monitoring team in Oxford throughout the trial. Completion of baseline eCRF and all enrolled participants will attend their local hospital clinic for one in person follow-up visit at 3 months and a final follow-up visit and a

research MRI scan/clinical MRI scan (where a baseline research/clinical MRI scan were performed) at 12-24 months).

3 month follow-up (visit two): Completion of 3 month eCRF, BP recorded and completion of modified Montreal Cognitive assessment (appendix 2), EQ-5D questionnaire (appendix 3) and home blood pressure acceptability questionnaire (appendix 4). 24-hour ABPM to be performed at the time of the 3 month follow-up assessment.

12-24 month follow-up (final visit): Completion of 12-24 month eCRF, BP recorded, and completion of modified Montreal Cognitive assessment (appendix 2) and EQ-5D questionnaire (appendix 3). 24-hour ABPM to be performed at the time of the 12-24 month follow-up visit.

A research MRI scan will be performed for some participants at baseline and the 12-24 month follow-up visit to identify markers of cerebral small vessel disease including (but not limited to):

- change in white matter hyperintensity volume
- change in white matter microstructure (DTI)
- change in the number of CMBs
- change in cerebral atrophy

Where a baseline clinical MRI scan was performed in lieu of a baseline research MRI scan, a similar routine clinical follow-up MRI scan should be performed on the same scanner for the 12-24-month visit. A schedule of all trial assessments and procedures is set-out in Appendix 1. Where an in-person visit is not possible, every effort will be made to assess the participant by other means, including telephone, postal, email, or home visit contact. In this instance, two test readings on the ABPM machine, performed by the patient or their carer for this purpose at the time of assessment, may be used instead of the two clinic readings at 3-month and/or 12-24-month follow-up. If the participant refuses to undergo ABPM or is not capable of fitting the machine at home, two readings on a conventional home BP monitor can be taken by the patient during the assessment. Hourly daytime home BP readings can be used in lieu of 24-hour ABPM in this scenario, with participants in the control group being sent a home telemetric BP monitor for this purpose only, if required. Cognitive assessment in this scenario will be performed using a 22-point Telephone Montreal Cognitive Assessment.

A.9.1 Laboratory Assessments and Procedures

Translational research samples

Blood will be collected at baseline by a trained member of staff at the site. As soon as blood is collected, the member of the research team at the site will be responsible for sending the sample in a Safebox to the coordinating office, UCL. Blood samples will be stored for future research. An appropriate SOP will be in place for each site.

Sample storage and transfer

About 5-10mls of blood in EDTA plasma sampling tube will be collected from patients in accordance with the patient consent form and patient information sheet. The EDTA blood samples will be

appropriately sent in a Safebox from the sites to Shahena Butt, the research coordinator; Stroke Research Centre, UCL Institute of Neurology, Russell Square House, 10-12 Russell Square, First Floor, London, WC1B 5EH for DNA extraction and storage.

The neurogenetics lab, UCL will process, store and dispose of EDTA blood samples in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereto.
The EDTA blood samples will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients' consent. At the co-ordinating centre, DNA will be extracted and stored at -70 degrees C in the UCL Institute of Neurology.

A.10 Device accountability

The BP equipment will be purchased by the monitoring team in Oxford. The telemetric BP readings will be checked every working day by this team. In the absence of any readings, the monitoring team will troubleshoot the most common equipment problems over the telephone where possible, or arrange a replacement where necessary. There will be a service contract in place to replace or mend any monitors that are not working.

A.11 Monitoring Plan

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.
The degree of monitoring will be proportionate to the risks associated with the trial.
A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

Low risk: central monitoring
Each site to email to the sponsor annually: delegation log, adverse event log, deviation log, minutes of Trial Steering Committee (or equivalent), annual progress report (lead site only) when sent to Ethics Committee.

a) Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.
The electronic CRFs (eCRF) will not bear the participant's name or other personal identifiable data. The participant's year of birth and trial identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.
The team will ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, and Research Ethics Committee Approval. All participant identifiable information will be

anonymised with regard to any report. The same standard will be followed if any patient information needs to be sent to a third party.

b) Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 years from the declaration of end of trial.
Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements. The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

A.12 Statistical Considerations

A.12.1 Primary Outcomes

(i) BP study:

1. The efficacy of telemetric BP monitoring to guide intensive BP treatment in ICH survivors; detection of a statistically significant reduction in assessment BP from baseline in the intervention arm compared to the control arm at 3 months. We expect a 10 mm Hg difference in systolic BP between the intervention and control arms at 3 months (based on assessment of mean assessment BP at 3 months), and will be able to estimate this difference to within +/- 8 mm Hg with 112 patients if the standard deviation of systolic BP does not exceed 20 mm Hg (in either arm).

2. The feasibility and safety of telemetric BP lowering in ICH survivors
Feasibility criteria are:
(a) ≥50% of eligible participants agree to participate;
(b) <30% dropout from the intervention arm (discontinuation of home BP monitoring against the advice of the BP monitoring centre) prior to 1 month;
(c) Patient approval of the monitoring process in ≥70% of those randomised to the intervention arm.

Safety is measured by serious adverse events related to reducing BP in the intervention arm, cognitive function change since baseline (modified Montreal Cognitive Assessment) and a composite of all recurrent major cerebrovascular and cardiovascular events.

(ii) Imaging study:

Previous studies have shown that WMH volume increases over time in both older community and hospital stroke populations.(38-42) Data of WMH progression in ICH are limited but one small study showed a progressive increase in white matter lesions in subjects with cererbral amyloid angiopathy over a year.(43) Because of the strong relationship between BP and WMH severity and

progression;(36, 44) we hypothesise that lowering BP might reduce the increase in volume of WMH over 1 year. However, a key concern regarding intensive BP lowering is that this might reduce white matter perfusion and cause an increase in ischaemic injury to the brain. The primary imaging outcome is therefore the change in WMH volume (measured on 3T FLAIR images) since baseline. We will develop and use an in-house automated volumetric lesion detection method,(45) but will also use validated progression scales including the Rotterdam and Schmidt progression scores; progression over 2 years has previously been demonstrated in only 20 scan pairs of patients with cerebral small vessel disease.(46) We will exclude WMH directly related to the index symptomatic ICH (i.e. close to the ICH in the ipsilateral hemisphere). We will investigate WMH progression in subgroups of ICH including lobar and deep categories, and probable or possible cerebral amyloid angiopathy.(47) WMH progression analyses will adjust for important predictors including baseline WMH and age.

A.12.2 Secondary outcomes

(i) BP study

1. Clinical outcomes including recurrent vascular events and cognition.
2. Number of BP-lowering drugs at 3 month and at 12-24 month follow-up visits.
3. The magnitude of difference in mean daytime BP measured on 3-month ABPM in the intervention arm versus the control arm compared with baseline ABPM.
4. The magnitude of difference in mean daytime BP measured on 12-month ABPM in the intervention arm versus the control arm compared with baseline ABPM.

(ii) Imaging study

1. We will quantify white matter structure integrity using change in mean diffusivity (MD), fractional anisotropy (FA) and other 3T DTI metrics including tract-based spatial statistics.(48)
2. We hypothesise that intensive BP lowering will reduce the development of new haemorrhagic SVD-related brain injury. We will measure the proportion of patients developing new CMBs since baseline (measured using a validated visual rating scale)(49) and the number of new CMBs in each participant. We will exclude CMBs adjacent to the index symptomatic ICH. A previous study showed that 48% (95% CI, 40–55) of 168 patients with ICH developed incident CMBs over a 3.4-year period.
3. Any new infarcts or intracerebral haemorrhage
4. Change in cerebral blood flow (CBF) on 3T PCASL since baseline
5. Change in total brain volume, white matter volume and grey matter volume on 3T T1 volumetric images since baseline
6. Composite neuroimaging measures (e.g summary SVD scores)(50)
7. We will investigate progression of neuroimaging markers in subgroups of ICH including lobar and deep ICH,(51) and probable or possible cerebral amyloid angiopathy.(47, 52)

A.12.3 Sample size calculation

(i) BP study

Our data will allow accurate sample size calculation for an adequately powered efficacy trial and the ability to estimate a difference in systolic BP between arms. We will assess 3-month BP based on both clinic measurements and separately on 3-month ABPM. Power will be least for the comparison of clinic BP measurements. If we expect an effect in one direction (i.e. BP lowering in the intervention group), sample size calculations based on a mean group difference in SBP of 10 mm Hg between the intervention and control arms (and standard deviations of 10 mm Hg and 15 mm Hg respectively) at 3 month gives:
One-tailed significance level = 0.05, power = 0.9, n in each group = 56. We will be able to estimate this difference to within +/- 8 mm Hg with 112 patients if the standard deviation of systolic BP does not exceed 20 mm Hg.

(ii) Imaging study

There are insufficient data on WMH progression in patients with ICH on which to base accurate power calculations, making formal sample size estimation challenging. One study in 26 patients (mean age 69.1) with probable or possible CAA scanned over about a year found a rapid median WMH growth of 0.5 mL per year (interquartile range 0.1-2.8 mL per year).(43) In a substudy of 192 participants in the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) trial the mean total volume of new WMHs was significantly reduced in the active treatment group (0.4 mm3 [SE=0.8]) compared with the placebo group (2.0 mm^3 [SE=0.7]; P=0.012).(53) This difference in WMH progression was greatest for patients with severe WMH at entry, 0.0 mm^3 (SE=0) in the active treatment group versus 7.6 mm^3 (SE=1.0) in the placebo group (P<0.0001). The BP reduction in the active arm compared with the placebo arm was 11.2 mm Hg for systolic BP and 4.3 mm Hg for diastolic BP. With 56 patients in each arm we would be able to estimate a similar difference in new WMH lesion volume (2.0mm^3 vs 0.4mm^3) (if the SD does not exceed 2.0 mm^3) to that shown overall in PROGRESS, with power 80% at an alpha significance level of P=0.05.

A.12.4 Planned recruitment rate

We plan a screening, randomisation and recruitment period of 12 months from beginning to last patient randomised. We will approach about 145 patients, given an expected consent rate for randomisation of 60%, hence achieving the goal of 112 patients), allowing the consent rate to be estimated to within +/- 7%.

Regarding dropouts from the intervention arm prior to 1 month, we expect less than 20% of individuals to drop out. With an intervention arm sample size of 56 the dropout rate can be estimated to within +/- 11%.

Regarding patient approval of intervention, we expect that 90% of individuals in the intervention arm will approve the monitoring process (based on a semi-structured questionnaire). With an intervention arm sample size of 56, this approval rate can be estimated to within +/- 8%.

Recruiting sites will be selected on their suitability to conduct the study and perform the necessary MR imaging, and site initiation visits will be completed by teleconference and online training tools with follow up by the study coordinators.

A.12.5 Randomisation methods

Patients will be randomised in a 1:1 group assignment ratio to intensive BP lowering or standard care using an online randomisation service (Sealed Envelope), available 24 hours a day. There will be equal allocation between treatment arms; a sample size of 112 will consist of patients randomised equally to the intervention and control groups (56 each).

We will use a web-based randomisation service with the following pre-specified features:

- Web-based randomisation is by random permuted blocks to active or control treatment in a 1:1 ratio
- The system is accessed via a secure internet connection (SSL). This connection encrypts data between the user's internet browser and the server
- Online randomisation is achieved by the user entering a patient identifier (text field - must be unique) and stratification information, confirming eligibility
- The patient is randomised to the next treatment or code and the chosen treatment group or code shown or texted to the user
- An email notification is generated displaying the chosen treatment group or code and sent to the email address given by the user randomising and the administrator email address. The administrator email address is the one provided when the system is set up (usually a trial coordinator or central trial email address)
- A list of all randomisations performed to date may be sent to the administrator email address by entering the password
- The randomisation list cannot be viewed through the system
- There is only one password and anyone with knowledge of the password can perform a randomisation
- Sealed Envelope will not edit or delete any data held by the system

A.12.6 Statistical analysis

In general, the most suitable statistical analysis consistent with the form of data will be used and the underlying assumptions of the statistical method will be verified. Baseline BP, modified MoCA and EQ5D will also be compared between randomised groups. Descriptive statistics, as appropriate (e.g. means and standard deviations for continuous variables; proportions for categorical variables), will be reported for variables measured at baseline. A consort flow diagram will be included.

A.12.6.1 Summary of baseline data and flow of participants

Age (SD), sex, vascular risk factors and other medical history, and 24-hour ABPM will be used for baseline comparability of the randomised groups.

A.12.6.2 Primary outcome analysis

Analysis will be performed according to the intention to treat and the per protocol principles.
Efficacy: The difference in assessment BP (and the difference in change from baseline BP) between randomised groups at 3 months will be compared using t-tests. The change in white matter hyperintensity volume in the intervention and control groups will be compared using appropriate tests (e.g. t-tests or nonparametric tests) depending on whether the values are normally distributed. Automated analysis pipelines for WMH segmentation and quantification will be used to measure change.(45)

Feasibility: Proportions for the consent rate, drop-out rate and patient approval at 3 months will be calculated to determine if the required feasibility criteria were met.

Safety: Proportions of adverse events and recurrent events between randomised groups will be compared using Fisher's exact test. Randomised groups will be compared for cognitive impairment based on (1) the modified MoCA score as a continuous variable using the Mann-Whitney U-test and (2) numbers below cut-off thresholds of the modified MoCA score using Fisher's exact test. The change in modified MoCA score from baseline will also be compared between randomised groups similarly.

A.12.6.3 Secondary outcome analysis

Randomised groups will be compared for recurrent vascular events using Fisher's exact test and for the number of BP-lowering drugs at 3 month and at 1 year follow-up visits using the Chi-squared test. The change in mean daytime BP from baseline to 3-month and 12-month follow-up on 24-hour ABPM will be analysed using t-tests to compare the intervention and control groups.

Changes in all neuroimaging measures (CMBs,(49) DTI measures,(48) atrophy, etc., measured using validated methods) will be compared between the intervention and control arms using appropriate statistical tests. Specific automated analysis pipelines will be developed for each measure.
The study sample size has been based on the primary efficacy outcome of a reduction in BP and may lack power for the secondary outcomes; therefore results will be interpreted in the light of these limitations.

A12.6.4 Sensitivity and other planned analyses

It may be necessary to address potential imbalances between randomised groups for influencing risk factors.

A.13 Data Management

When a person agrees to participate, demographic, contact and medical history information necessary to conduct the study will be recorded in accordance with the patient consent form, patient information sheet and section 7 of this protocol. Each participant will be allocated a unique trial number. This data will be collected on an eCRF, on a secure server; sealed envelope. Access to this data, will be granted to authorized research staff and representatives from the sponsor, host institution and regulatory authorities, by arrangement with the CI, to permit trial-related activities, monitoring and audit. All records will be kept securely and confidentially and the data will be pseudo-anonymised for analysis.
All records are the responsibility of the investigators and will be kept in secure conditions. They will ensure that patients' identities are protected from any unauthorised parties. Participants' information will be kept confidential and managed in accordance with the Data Protection Act and Research Ethics Committee Approval.

For BP data acquired via the Bluetooth-enabled telemetric BP monitors (A&D UA-767 BT), anonymised measures are transmitted securely to a server hosting a password-protected website for daily review (t+ Medical, Abingdon, UK). BP data are acquired from the secure server and are exported in .mat (Matlab) format before being stored for offline analysis within the Centre for Prevention of Stroke and Dementia (CPSD) along with the data securely downloaded from all 24-hour ABPM. All BP data will be stored only at the University of Oxford site in accordance to the data governance policy of the University of Oxford, and will be the responsibility of Professor Rothwell.

Neuroimaging data will be transferred from participating sites in an anonymised form, and then stored on secure servers within UCL accessible to the Stroke Research Centre. Any patient related documents will not be transferred to any unauthorised party and are will not be processed and/or transferred other than in accordance with the patients' consent.
All baseline, follow up data will be entered on an electronic CRF. The CI will manage and maintain the study database throughout the investigation. Information on the eCRF will, where relevant, be accepted as source data and transferred, in part, and as appropriate, to a sealed envelope database, password protected to defined users and with an audit trial managed from the study coordinating site at UCL. Direct access to data, source data and documents will be granted to authorized representatives, host institution and regulatory authorities, by arrangement with the CI, to permit trial-related monitoring and audit.

A.13.1 Procedures for data review, database cleaning, and issuing and resolving data queries.

Data entered on the eCRFs will be 100 % source verified by a sponsor representative trained on the CIP and who has current GCP training. Data Clarification Forms (DCF) will be issued to the investigator should a discrepancy be found between the source and eCRF. The investigator will be required to verify and correct all errors or provide an explanation for the discrepant data. Sponsor representatives will re-verify the corrected data and mark the clarification as resolved at the next monitoring visit.

A.13.2 Procedures for verification, validation and securing of electronic clinical data systems

All data from the examinations and investigations listed in Appendix 1 will be transferred to media provided by the sponsor and collected at the time of eCRF collection.

The CI will manage and maintain the study database throughout the investigation. At the conclusion of the investigation, the database will then be locked and data transferred for analysis. A final copy of the database will be provided to the study site. Where data is transferred electronically, this will be in accordance with the UK Data Protection Act 1998 as well as Trust Information Governance Policy. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer.

The database maintained by the CI, shall be validated and secured according to the sponsor standard operating procedures. Access to the data shall be limited to sponsor representatives directly involved in

the collection, analysis, maintenance or safety monitoring of the data. Any study data released shall be done according to the publication policy and in accordance with the UK Data Protection Act 1998.

A.13.3 Data retention

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 years from the declaration of end of trial.
Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements. The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

A.13.4 Clinical quality assurance

The clinical investigators will meet every fortnight to discuss any issues with data quality and any concerns will be discussed with the sponsor.

A.13.5 Completion of electronic Case Report Forms

The local research team will be responsible for completion of an eCRF for each participant. This will be maintained by the local PI or delegated research staff. The eCRF will include participant's year of birth and unique trial number), medical history, visit details and dates, questionnaires and any related AEs and details of withdrawal from the study if appropriate.

The principal investigator will be responsible for the timing, accuracy and completeness of eCRF for each individual subject. All the data should be entered into sealed envelope, on the eCRF; access to this secure serve will be granted only to secure personnel. The personal data recorded on all documents will be regarded as confidential.

The principal investigator must record the subject's participation in this clinical investigation in the subject's hospital notes. In addition, the principal investigator must keep a separate list of all subjects entered into the clinical investigation showing each subject's name, date of birth and assigned subject number (for identification purposes). A subject identification log will also be provided in the investigation site file to record the subject's initials and assigned subject number.
All data will be handled in accordance with the UK Data Protection Act 1998.

A.13.6 Retention of Documentation

The principal investigator will retain all copies of the records for a period of 20 years from the discontinuation of the clinical investigation. In all cases, the principal investigator must contact the sponsor prior to disposing of any records related to the clinical investigation. Included in records to be maintained are the signed clinical investigation plan, , signed consent forms, ethics committee approval letters, product accountability records, correspondence concerning the clinical and any other documents to identify the subjects.

In addition, if the principal investigator moves/retires, etc., he should provide University College London with the name and address of the person who will look after and be responsible for the clinical investigation related records.

A.13.7 Training

During the initiation of the investigation site, the sponsor will ensure the investigators and the site study staff are trained on the device. The investigator is then responsible for ensuring that the investigation staff uses the device in the same way. All training will be documented in a Site Training Log.

The monitor will also ensure that the investigator and investigation site team have received and understood the requirements and content of:

* CIP (Clinical Investigation Plan)
* IB (Investigators Brochure)
* The informed consent forms
* eCRFs (electronic Case Report Forms)
* IFUs (Instructions For Use)
* All written clinical investigation agreements as appropriate

A.14 Amendments to the CIP

Amendments to this CIP may be necessary to protect the safety of the patients and integrity of the data. In collaboration with the Investigator(s), the CIP amendments will be documented and submitted for ethical and regulatory approval (as required) prior to implementation. All changes will be evaluated for impact per sponsor SOPs. Amendments will be considered implemented after all ethical and regulatory approvals (as required) are received and all key sponsor and site staff has been trained. This process does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

A.15 Deviations from clinical investigation plan

A deviation is considered a departure from the conditions and principles of GCP in connection with that investigation; or the CIP relating to that Investigation, as amended from time to time.

The investigator shall not deviate from this CIP except in situations that affect the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

A.15.1 Procedures for recording, reporting and analysing CIP deviations

If possible, prior approval from the sponsor and REC, if appropriate, shall be obtained by the investigator. All spontaneous CIP deviations shall be recorded and reported to the sponsor as agreed. A deviation log shall be maintained by the study site. Deviations shall be reported to the REC and the regulatory authorities if required by national regulations. All deviations will be included, as required in the final study report.

Notification requirements and time frames.

Requests for deviations by the investigator will be responded to within 48 hours of receipt.

Corrective and preventive actions and principal investigator disqualification criteria.

Refer to the Monitoring Plan (as applicable) for corrective and preventative actions and principal investigator disqualification criteria.

A.15.2 Procedure for reporting any protocol deviations

Any deviation from the protocol that has not been previously approved by the sponsor (JRO at University College London), must be reported to the sponsor within 2 working days of the deviation occurrence. Any deviations from the clinical investigation plan that are identified during routine monitoring visits will be reported to the sponsor (JRO, University College London) within 24 hours of being identified.A.16 Statements of compliance

The clinical investigation shall be conducted in accordance with the ethical principles of the Declaration of Helsinki, ISO standard 14155 and all other applicable device and UK regulations.

The clinical investigation shall not commence recruitment until all REC, regulatory (if applicable) and local (NHS permission) is received. All additional requirements imposed by the REC or regulatory authority will be followed.

A.16 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

A.17 Adverse events, adverse device effects and device deficiencies

a-c) Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. **Note 1:** This definition includes events related to the investigational medical device or the comparator **Note 2:** This definition includes events related to the procedures involved **Note 3:** For users or other persons, this definition is restricted to events related to investigational medical devices
Adverse Device Effect (ADE)	Adverse Event related to the use of an investigational device. **Note 1:** This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device **Note 2:** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device
Serious Adverse Event (SAE)	Any adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in • a life-threatening illness or injury, or

	• a permanent impairment of a body structure or a body function, or • in-patient or prolonged hospitalisation, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, • Led to foetal distress, foetal death or a congenital anomaly or birth defect

Serious Adverse Device Effect (SADE)	An ADE that has resulted in any of the consequences characteristic of an SAE
Unanticipated Serious Adverse Device Effect (USADE)	An SADE, which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report.
Device Deficiency (DD)	Inadequately of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **Note 1:** this includes malfunctions, use errors, and inadequate labeling

An adverse event does not include:

- Medical or surgical procedures; the condition that leads to the procedure is an adverse event.
- Pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);
- The disease being studied or signs/symptoms associated with the disease unless more severe than expected for the subject's condition.
- Expected post-operative course (see section x)

d) Reporting requirements and timelines

AEs and ADEs are not considered reportable.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Adverse Event (AE)	Investigator	Sponsor	As agreed with sponsor. CI to record fully all AEs.
Adverse Device Effect (ADE)	Investigator	Sponsor/Manufacturer	As agreed with sponsor. CI to record fully all ADEs.

The following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of DIRECTIVES 90/385/EEC AND 93/42/EEC respectively.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Serious Adverse Event (SAE)**/	Investigator	Sponsor	Immediately, but no more than 3 calendar days after becoming

Serious Adverse Device Effect (SADE)			aware of the event
	CI	MHRA aic@mhra.gsi.gov.uk	Immediately, but not later than 2* calendar days after awareness *For SAEs which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons All other events immediately but not later than 7 calendar days following date of awareness.
	CI	REC	N/A
Unanticipated Serious Adverse Device Effect (USADE)	Investigator	Sponsor	Immediately, but no more than 3 calendar days after becoming aware of the event
	CI	MHRA	Immediately, but not later than 2* calendar days after awareness *For SAEs which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons. All other events immediately but not later than 7 calendar days following date of awareness.
	CI	REC	Within 15 days of the chief investigator becoming aware of the event. Only reports of related and unexpected Serious Adverse Events (SAEs) should be submitted to the REC.

Term	**Reporter**	**Reported to**	**Reporting Timeline from awareness of the event**
Device Deficiency (DD)	Investigator	Sponsor	Immediately, no more than 24 hours of becoming aware of the event

	CI	MHRA	7 calendar days Only reportable if the event may have led to an SAE if; • suitable action had not taken • intervention had not been made • if circumstances had been less fortunate
Urgent Safety Measures	CI	REC	(i) Immediately-By telephone (ii) Within 3 days-Notice in writing setting out reasons for the USM and plan for further action

** **Note** Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

e) Assessments of adverse events

Each adverse event will be assessed for the following criteria:

Severity

Category	Definition
Mild	The adverse event does not interfere with the subjects daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the subjects routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health Note: A severity rating of severe does not necessarily categorise the event as an SAE.

Seriousness

Seriousness as defined for an SAE in section a) above. Causality

The assessment of relationship of adverse events to the study procedure and the investigational device will be a clinical decision based on all available information at the time of the completion of the eCRF. The following categories will be used to define the causality of the adverse event:

Category	Definition
Yes	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
No	There is no evidence of any causal relationship.

Expectedness

Category	Definition
Expected	An adverse event that is consistent with the information about the device listed in the Investigator Brochure or clearly defined in this CIP.
Unexpected	An adverse event that is not consistent with the information about the device listed in the Investigator Brochure

The reference document to be used to assess expectedness against the intervention is the IB. The CIP will be used as the reference document to assess disease related and/or procedural expected events.

f) Procedures for recording and reporting Adverse Events and Device Deficiencies

Investigator responsibilities:

All adverse events and SAEs will be recorded in the medical records and eCRF following consent.

All serious adverse events will need to be reported to the sponsor by completing the Incident Reporting Form found here: https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo unless stated in the CIP that some expected SAEs will not be reported to the sponsor, with a justification as to why they will not be reported.

For patients on the control arm of an Investigation, SAEs may not have to be reported to the sponsor but will be recorded in the eCRF and medical records.

The Chief or Principal Investigator will complete the serious adverse event form and the form will be emailed to the sponsor to add, within 3 working day of his/her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

The Investigator will report to the MHRA and REC (as applicable) all reportable events within the specified timeframes as per section d above.

"All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the device, or an unrelated event".

"Only deaths that are assessed to be caused by the device will be reported to the sponsor. This report will be immediate".

"All deaths, including deaths deemed unrelated to the device, if they occur earlier than expected will be reported to the sponsor".

All SAEs and UADEs should be reported to the following;
e-mail: research-incidents@ucl.ac.uk

Reporting of all Adverse Events and Device Deficiencies: Investigator and Sponsor responsibilities

Any adverse incident involving a medical device should be reported to the manufacturer of the device. This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious. Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.
All adverse incidents involving the telemetric medical device must be reported to the device co-ordination site in Oxford, John Radcliffe Hospital, Centre for Prevention of Stroke and Dementia.
Incidents will be reported as soon as possible (usually within 24 hours).
Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and trial site team to ensure they are aware of any specific local requirements for reporting device incidents.

Progress reports

Progress reports will be submitted to the REC as per the REC requirements. The chief investigator will prepare the annual progress reports.

A.18 Oversight Committees

Trial Management Group (TMG)
The TMG will include the Co-Chief Investigators and co-ordinating site trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly [approximately every month] in person, or by teleconference, and will send updates to local PIs and their teams. The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals. A Data Monitoring Committee (DMC) will regularly monitor outcome events including adverse events and will report to the TMG.

Trial Steering Committee (TSC)
The role of the TSC will provide overall supervision of the trial. The TSC will review the on-going of the trial and recommend any appropriate amendments/actions for the trial as necessary. The TSC will be determined by the TMG team, and will include members of the original grant application and other invitees with expertise relevant to the trial. The TSC is expected to meet either in person or by teleconference 1-2 times per year.

Independent Data Monitoring Committee (IDMC)
N/A

A.19 Vulnerable population

N/A

A.20 Suspension or premature termination of the clinical investigation

Both the Sponsor and the Principal investigator reserve the right to terminate the clinical investigation at any time. Should this be necessary, the procedures will be arranged on an individual basis after review and consultation by both parties. In terminating the clinical investigation, the JRO at University College London and the Principal investigator will assure that adequate consideration is given to the protection of the subject's interests.

A.20.1 Subject Withdrawals and Discontinuation

Participants who have consented to intervention, assessments, follow-up and data collection, their participation is voluntary and they are free to withdraw at any time and without their medical care or legal rights being affected. A participant may be withdrawn from trial whenever continued participation is no longer in the participant's best interests, and the reason for withdrawal will be recorded. Reasons for discontinuing the trial may include:

- intercurrent illness
- patients withdrawing consent
- persistent non-compliance to protocol requirements

The decision to withdraw a participant from treatment will be recorded in the eCRF and medical notes. If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the eCRF and medical notes.

A.21 Definition of End of Trial

The expected duration of the trial is 36 months from recruitment of the first participant.
The end of trial is the date of the last follow up of the last participant.

A.22 Publication policy

We plan to present the results of the study at scientific meetings and publish the results in scientific journals. All participant data will be anonymised for this purpose. Authorship of publications will be determined by the ICMJE criteria.

A.23 Bibliography

1. Wilson D, Adams ME, Robertson F, Murphy M, Werring DJ. Investigating intracerebral haemorrhage. BMJ. 2015;350:h2484.
2. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010;9(2):167-76.
3. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2014;85(6):660-7.
4. Cox AM, McKevitt C, Rudd AG, Wolfe CD. Socioeconomic status and stroke. Lancet Neurol. 2006;5(2):181-8.
5. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. Neurology. 1997;48(4):891-5.
6. Moulin S, Labreuche J, Bombois S, Rossi C, Boulouis G, Henon H, et al. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. Lancet Neurol. 2016;15(8):820-9.
7. Hanger HC, Wilkinson TJ, Fayez-Iskander N, Sainsbury R. The risk of recurrent stroke after intracerebral haemorrhage. J Neurol Neurosurg Psychiatry. 2007;78(8):836-40.
8. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke. 2004;35(6):1415-20.
9. O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med. 2000;342(4):240-5.
10. Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004;141(10):745-52.
11. Biffi A, Anderson CD, Battey TW, Ayres AM, Greenberg SM, Viswanathan A, et al. Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage. JAMA. 2015;314(9):904-12.
12. Inagawa T. Recurrent primary intracerebral hemorrhage in Izumo City, Japan. Surg Neurol. 2005;64(1):28-35; discussion -6.
13. Casolla B, Dequatre-Ponchelle N, Rossi C, Henon H, Leys D, Cordonnier C. Heavy alcohol intake and intracerebral hemorrhage: characteristics and effect on outcome. Neurology. 2012;79(11):1109-15.
14. Feldmann E, Broderick JP, Kernan WN, Viscoli CM, Brass LM, Brott T, et al. Major risk factors for intracerebral hemorrhage in the young are modifiable. Stroke. 2005;36(9):1881-5.
15. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006;66(8):1175-81.
16. Dandapani BK, Suzuki S, Kelley RE, Reyes-Iglesias Y, Duncan RC. Relation between blood pressure and outcome in intracerebral hemorrhage. Stroke. 1995;26(1):21-4.
17. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355-65.
18. Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, et al. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. Lancet Neurol. 2014;13(4):374-84.
19. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. Lancet Neurol. 2014;13(4):364-73.
20. Group PC. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358(9287):1033-41.

21. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. Stroke. 2004;35(1):116-21.
22. Group SPSS, Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet. 2013;382(9891):507-15.
23. Birns J, Markus H, Kalra L. Blood pressure reduction for vascular risk: is there a price to be paid? Stroke. 2005;36(6):1308-13.
24. Lager KE, Wilson A, Khunti K, Mistri AK. Quality of secondary prevention measures in TIA patients: a retrospective cohort study. Postgrad Med J. 2012;88(1040):305-11.
25. Ovbiagele B, Diener HC, Yusuf S, Martin RH, Cotton D, Vinisko R, et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. JAMA. 2011;306(19):2137-44.
26. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke. 2010;41(2):397-401.
27. Herttua K, Tabak AG, Martikainen P, Vahtera J, Kivimaki M. Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study. Eur Heart J. 2013;34(38):2933-9.
28. De Simoni A, Hardeman W, Mant J, Farmer AJ, Kinmonth AL. Trials to improve blood pressure through adherence to antihypertensives in stroke/TIA: systematic review and meta-analysis. J Am Heart Assoc. 2013;2(4):e000251.
29. Boan AD, Lackland DT, Ovbiagele B. Lowering of blood pressure for recurrent stroke prevention. Stroke. 2014;45(8):2506-13.
30. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12(8):822-38.
31. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009;8(2):165-74.
32. Gregoire SM, Brown MM, Kallis C, Jager HR, Yousry TA, Werring DJ. MRI detection of new microbleeds in patients with ischemic stroke: five-year cohort follow-up study. Stroke. 2010;41(1):184-6.
33. Kimberly WT, Gilson A, Rost NS, Rosand J, Viswanathan A, Smith EE, et al. Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy. Neurology. 2009;72(14):1230-5.
34. Gregoire SM, Charidimou A, Gadapa N, Dolan E, Antoun N, Peeters A, et al. Acute ischaemic brain lesions in intracerebral haemorrhage: multicentre cross-sectional magnetic resonance imaging study. Brain. 2011;134(Pt 8):2376-86.
35. Menon RS, Burgess RE, Wing JJ, Gibbons MC, Shara NM, Fernandez S, et al. Predictors of highly prevalent brain ischemia in intracerebral hemorrhage. Ann Neurol. 2012;71(2):199-205.
36. Benjamin P, Zeestraten E, Lambert C, Ster IC, Williams OA, Lawrence AJ, et al. Progression of MRI markers in cerebral small vessel disease: Sample size considerations for clinical trials. J Cereb Blood Flow Metab. 2016;36(1):228-40.
37. Greenberg SM, Al-Shahi Salman R, Biessels GJ, van Buchem M, Cordonnier C, Lee JM, et al. Outcome markers for clinical trials in cerebral amyloid angiopathy. Lancet Neurol. 2014;13(4):419-28.
38. Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. Stroke. 2008;39(5):1414-20.
39. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. Stroke. 2008;39(10):2712-9.

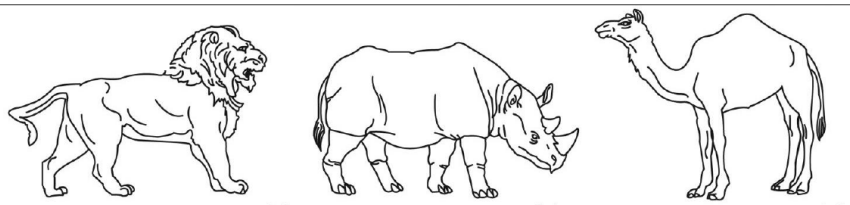
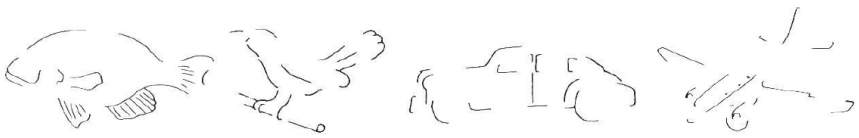
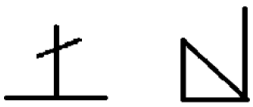
40. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F, Austrian Stroke Prevention S. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. Lancet. 2003;361(9374):2046-8.
41. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. Neurology. 1999;53(1):132-9.
42. Chappell FM, Del Carmen Valdes Hernandez M, Makin SD, Shuler K, Sakka E, Dennis MS, et al. Sample size considerations for trials using cerebral white matter hyperintensity progression as an intermediate outcome at 1 year after mild stroke: results of a prospective cohort study. Trials. 2017;18(1):78.
43. Chen YW, Gurol ME, Rosand J, Viswanathan A, Rakich SM, Groover TR, et al. Progression of white matter lesions and hemorrhages in cerebral amyloid angiopathy. Neurology. 2006;67(1):83-7.
44. Mok V, Kim JS. Prevention and Management of Cerebral Small Vessel Disease. J Stroke. 2015;17(2):111-22.
45. Sudre CH, Cardoso MJ, Ourselin S, Alzheimer's Disease Neuroimaging I. Longitudinal segmentation of age-related white matter hyperintensities. Med Image Anal. 2017;38:50-64.
46. Gouw AA, van der Flier WM, van Straaten EC, Pantoni L, Bastos-Leite AJ, Inzitari D, et al. Reliability and sensitivity of visual scales versus volumetry for evaluating white matter hyperintensity progression. Cerebrovasc Dis. 2008;25(3):247-53.
47. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology. 2001;56(4):537-9.
48. Baykara E, Gesierich B, Adam R, Tuladhar AM, Biesbroek JM, Koek HL, et al. A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of White Matter Tracts and Diffusion Histograms. Ann Neurol. 2016;80(4):581-92.
49. Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jager HR, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Neurology. 2009;73(21):1759-66.
50. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. Neurology. 2014;83(14):1228-34.
51. Charidimou A, Schmitt A, Wilson D, Yakushiji Y, Gregoire SM, Fox Z, et al. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): Development and assessment of reliability. J Neurol Sci. 2017;372:178-83.
52. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology. 2010;74(17):1346-50.
53. Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, et al. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. Circulation. 2005;112(11):1644-50.

Appendix 1 - Schedule of assessments

	Screening (Pre-treatment assessment)	Intervention phase and Follow-ups	
	Baseline	3 Month follow-up	12 Month follow-up
Visit No:	1	2	Final Visit
Window of flexibility for timing of visits:		e.g. +/- 2 days	Allow up to 12 months from their expected 12-month visit
Informed Consent	X		
Medical History	X		
Eligibility confirmation	X		
Blood test	X		
Research or clinical MRI scan or clinical CT scan (before randomisation)	X		X
Blood Pressure	X	X	X
24-hour ABPM	X	X	X
Cognitive assessment	X	X	X
Quality of life assessment (EQ-5D)	X	X	X
BP acceptability questionnaire		X	
Randomisation	X		
Adverse Events review	X	X	X

Appendix 2 - Cognitive functional change Assessment (modified Montreal Cognitive Assessment)

Name: DOB (Age): Hospital Number:
Place of Birth: Handedness: L / R Completion date:
Years of Education: Occupation:

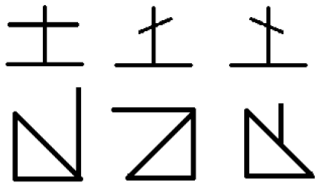
Orientation	[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City	**/6**
Attention + Executive functions	**Forward:** [ ] 3 2 9 7 **Backwards:** [ ] 2 5 **Forward:** [ ] 2 1 8 5 4 **Backwards:** [ ] 7 4 2 **Forward:** [ ] 7 2 9 5 8 4 **Backwards:** [ ] 4 9 7 5 **Tap A:** [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B **Motor tapping:** 1 2 1 1 2 2 2 1 2 1 Congruent [ ] Incongruent [ ] **Three step Luria task:** Copy [ ] ≤ 2 trials [ ] > 2 trials [ ]	/2 **/2** /2 **/1** /2 /3
Language	**Repeat:** No ifs, ands or buts [ ] I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ] **Command:** Touch your nose then open your mouth	/1 **/1** **/1** /1
Naming	 [ ] [ ] [ ]	**/3**
Perception		/4
Visual Memory -Immediate	 **COPY**	**RECALL** /2 /2
Verbal Memory -Immediate		/5 /5

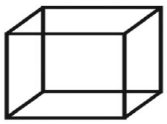
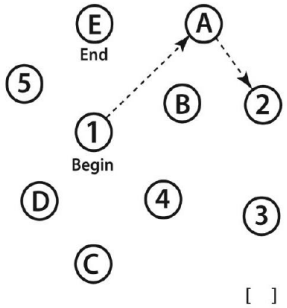
	Face	Velvet	Church	Daisy	Red
1st trial					
2nd trial					

<table>
<tr><td>Processing Speed</td><td>Count Backwards: 30 – 1 [ ] (Time ≤ 25secs, 0 errors)
Months backwards: December – January [ ] (Time ≤ 24secs, 1 error)</td><td>/1
/1</td></tr>
<tr><td>Working memory</td><td>Subtract 7: [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0pt</td><td><u>/3</u></td></tr>
<tr><td>Executive functions</td><td>Fluency F: [ ] (N ≥ 11 Words)

Similarities: e.g. Banana – Orange = Fruit [ ] Train – Bicycle [ ] Watch – Ruler</td><td><u>/1</u>

<u>/2</u></td></tr>
<tr><td rowspan="2">Memory -Delayed</td><td>Verbal Recall:
<table>
<tr><th></th><th>Face</th><th>Velvet</th><th>Church</th><th>Daisy</th><th>Red</th></tr>
<tr><td>Free Recall</td><td>[ ]</td><td>[ ]</td><td>[ ]</td><td>[ ]</td><td>[ ]</td></tr>
<tr><td>Category Cue</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Multiple Choice</td><td></td><td></td><td></td><td></td><td></td></tr>
</table></td><td><u>/5</u>
/5
/5</td></tr>
<tr><td>Visual Recall:

Visual recognition:
</td><td>/2
/2</td></tr>
<tr><td>Visuo-Executive</td><td>Draw Clock (Ten past eleven)

Copy cube 


[ ] Contour [ ] Numbers [ ] Hands [ ] [ ]</td><td><u>/5</u></td></tr>
<tr><td></td><td>[ ] <12yrs Education: +1 ORIGINAL MoCA TOTAL:</td><td>/30</td></tr>
</table>

NOTES: e.g. dominant hand weakness? visual impairments? English 2nd language?

COMPLETED BY: _____

Appendix 3 – EQ-5D Questionnaire Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

We would like to know how good or bad your health is TODAY

This scale is numbered from 0 to 100

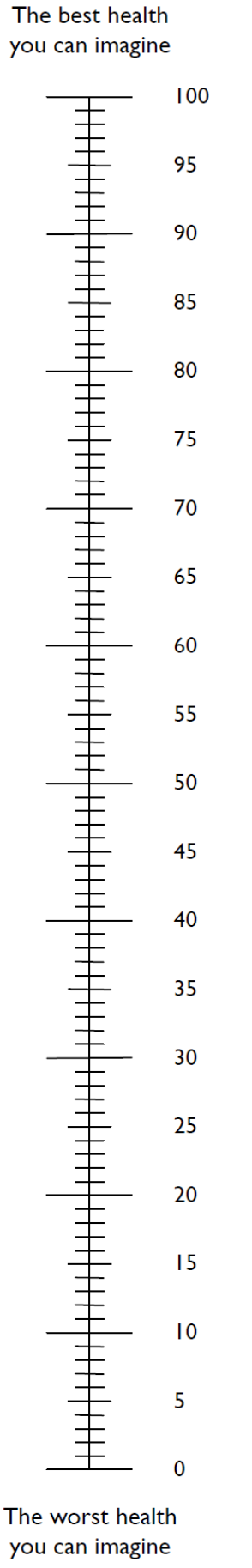
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 4 – Home BP monitoring participant acceptability questionnaire

HOME BLOOD PRESSURE MONITORING QUESTIONNAIRE

We would be very grateful if you could help us by answering some short questions about your experience using the home blood pressure monitor as part of the PROHIBIT-ICH study. Please tick the box that most closely matches your level of agreement with each of the following statements. Please give only one answer per line.

		Definitely agree	Moderately agree	Neither agree nor disagree	Moderately disagree	Definitely disagree
1	I liked the fact that the regular readings would provide better information about my blood pressure	☐	☐	☐	☐	☐
2	It reassured me to know that the equipment would transmit my readings directly to the hospital	☐	☐	☐	☐	☐
3	It was helpful to have a telephone number that I could call to discuss my blood pressure readings and treatment	☐	☐	☐	☐	☐
Measuring my blood pressure at home:						
4	was not uncomfortable	☐	☐	☐	☐	☐
5	was not too time consuming	☐	☐	☐	☐	☐
6	caused me no anxiety	☐	☐	☐	☐	☐
7	I found it very easy to remember to do it regularly	☐	☐	☐	☐	☐

Please rate your overall satisfaction with monitoring your blood pressure at home by marking a cross on the following line

0 25 50 75 100

Extremely satisfied ---------- **Extremely dissatisfied**

Has anyone helped you to fill in the questionnaire? (Please circle) **YES** or **NO**

Thank you very much for taking the time to complete this questionnaire.
Please return it to us in the attached prepaid envelope.

If you would like to make any additional comments please use the space provided below:

Appendix 2.2

Baseline Patient Information

Patient Initials: ☐☐☐

Year of Birth: ☐☐☐☐

Sex:

Male ☐

Female ☐

Hand Preference:

Right ☐

Left ☐

Ethnicity:

White or White British ☐

Asian or Asian British: Indian ☐

Asian or Asian British: Pakistani ☐

Asian or Asian British: Bangladeshi ☐

Asian or Asian British: Chinese ☐

Asian or Asian British: Other Asian ☐

Black or Black British ☐

Mixed ☐

Other ☐

Unknown ☐

Baseline Patient Consent

Has written consent from patient been obtained?

Yes ☐

No ☐

If No: Has Consultee consent been obtained?

Yes ☐

No ☐

Date of consent given: __ __ / __ __ / __ __ __ __

Name of person completing this form: _____

Position: _____

Baseline Blood Pressure Measurements:

Please take patient's blood pressure BEFORE randomisation

Date blood pressure readings taken:

__ __ / __ __ / __ __ __ __

1st Reading - Arm used:

Left ☐

Right ☐

1st Reading - Systolic BP: ☐

1st Reading - Diastolic BP: ☐

1st Reading - Time taken: __ __ : __ __

2nd Reading - Arm used:

Left ☐

Right ☐

2nd Reading - Systolic BP: ☐

2nd Reading - Diastolic BP: ☐

2nd Reading - Time taken: __ __ : __ __

Standing Reading - Arm used:

Left ☐

Right ☐

Standing Reading - Systolic BP: ☐

Standing Reading - Diastolic BP: ☐

Standing Reading - Time taken: __ __ : __ __

ICH details at Baseline

Details of ICH

Date of ICH: __ __ / __ __ / __ __ __ __

Is this the first ever symptomatic ICH?

Yes ☐

No ☐

Unknown ☐

If No: Please provide details of previous ICH:

Location of Most Recent (Qualifying) ICH

Type of ICH:

Lobar ☐

Non Lobar ☐

Location of ICH:

Right ☐

Left ☐

Specify number of ICHs: ☐

If Non Lobar ICH, specify the sub-region:

Deep (basal ganglia and thalamus) or brain stem ☐

Cerebellar ☐

Uncertain ☐

Additional Information Prior to Randomisation

Is there known sensitivity or contraindication to BP treatments (e.g. symptomatic postural hypotension)?

Yes ☐

No ☐

If required please provide more information:

Is the patient participating in another CTIMP or device trial?

Yes ☐

No ☐

If required please provide more information:

Patient Eligibility and Randomisation

Inclusion Criteria

	Yes	No
Is the patient 40 years old or above?	☐	☐
Does the patient have spontaneous primary ICH? (i.e. without known underlying structural or macrovascular cause)	☐	☐
Is it the opinion of the clinical team that the patient's BP control since the ICH is inadequate, AND the measured systolic BP prior to randomisation is ≥130 mm Hg?	☐	☐
Is the patient planned for home discharge (not including nursing/care home) after their inpatient stay?	☐	☐
Is the patient willing and can demonstrate an ability to undertake home BP measurements, either unassisted or with the help of a relative, friend or carer?	☐	☐
Is the patient able and willing to complete an MRI scan?	☐	☐
Is the patient able and willing to attend and complete study assessments including cognitive tests?	☐	☐
Is the patient able and willing to provide informed consent themselves, or with a suitable consultee available?	☐	☐

If any of the above are checked "No", the patient is NOT eligible for the study - STOP

Exclusion Criteria

Is there evidence of a macrovascular or structural cause for ICH (e.g. arteriovenous malformation or tumour)?	☐	☐
Has the patient been diagnosed with dementia (DSM IV criteria, self-reported or documented in medical records)?	☐	☐
Is there evidence of frailty or low functional status (MRS ≥4) before or after ICH likely to make participation in follow-up difficult for the patient?	☐	☐
Does the patient have a life expectancy of less than 2 years?	☐	☐
Is the patient taking 3 or more BP-lowering medications at the time of consent?	☐	☐
Does the patient have known flow-restricting intracranial/extracranial large arterial stenosis? (note this does not need additional investigations above standard care)	☐	☐
Is there a known absence of mobile phone coverage from all network operators and home internet at the participant's home?	☐	☐

If any of the above are checked "Yes", the patient is NOT eligible for the study – STOP

Patient Eligibility and Randomisation

Location of ICH: Stratification Question

Where is the location of the patient's most recent ICH?

Lobar ☐

Non Lobar ☐

Baseline MRI Scan

Has the patient completed the baseline study MRI scan:

Yes ☐

No ☐

*If **no** then please complete MRI scan before randomisation*

Modified Rankin Score at Baseline

Patient Functional Status modified Rankin Score

Was a pre-stroke mRS score taken?

Yes ☐

No ☐

If yes, date on which pre-stroke mRS score was taken:

__ __ / __ __ / __ __ __ __

Pre-stroke mRS Score: ☐

0 = no symptoms at all
1 = no significant disability despite symptoms: able to carry out all usual duties and activities
2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 = moderate disability: requiring some help, but able to walk without assistance
4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 = death

Was a baseline mRS score taken?

Yes ☐

No ☐

If yes, date on which baseline mRS score was taken:

__ __ / __ __ / __ __ __ __

Baseline mRS Score: ☐

0 = no symptoms at all
1 = no significant disability despite symptoms
2 = slight disability
3 = moderate disability
4 = moderately severe disability
5 = severe disability
6 = death

Past Medical History

Hypertension (on antihypertensive treatment pre-ICH or ≥ 140/90 mmHg on two or more occasions before the ICH):

Yes ☐
No ☐
Unknown ☐

If yes, what was the year of diagnosis: __ __ __ __

Hypercholesterolemia (on treatment pre-ICH or total cholesterol ≥5.2 mmol/L after):

Yes ☐
No ☐
Unknown ☐

Diabetes type I/II (pre-ICH diagnosis or ≥2 measurement random ≥11.1mmol/L or fasting ≥7 mmol/L after ICH):

Yes ☐
No ☐
Unknown ☐

Smoking status:

Current smoker ☐
Former smoker ☐
Never smoked ☐

Alcohol: current drinker:

Yes ☐
No ☐
Unknown ☐

If current drinker, record number of units consumed per week: ☐

Recreational drug use:

Yes ☐
No ☐
Unknown ☐

If yes, please record which drugs are used:

Cocaine ☐ Opiates ☐
Cannabis ☐ Other drugs ☐ If other drugs used, please describe: ☐

Myocardial Infarction (MI):

Yes ☐
No ☐
Unknown ☐

Past Medical History

Revascularisation (Percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)):

Yes ☐
No ☐
Unknown ☐

History of congestive heart failure:

Yes ☐
No ☐
Unknown ☐

History of atrial fibrillation:

Yes ☐
No ☐
Unknown ☐

History of peripheral arterial disease:

Yes ☐
No ☐
Unknown ☐

History of known dementia/cognitive impairment:

Yes ☐
No ☐
Unknown ☐

If yes, please provide details of the diagnosis:

History of seizures prior to ICH:

Yes ☐
No ☐
Unknown ☐

If yes, type of seizure:

Partial ☐ Generalised ☐
Both ☐ Unknown ☐

Past Medical Treatments

On antiplatelet therapy pre-ICH:

Yes ☐ No ☐ Unknown ☐

If on antiplatelet medication, please state whether the patient is taking any of the following medications:

Aspirin

Yes ☐ No ☐ Unknown ☐

Dipyridamole:

Yes ☐ No ☐ Unknown ☐

Clopidogrel:

Yes ☐ No ☐ Unknown ☐

Other antiplatelet therapy (please specify):

Yes ☐ No ☐ Unknown ☐

Please specify, other antiplatelet therapy taken: ☐

On anticoagulant therapy pre-ICH:

Yes No Unknown

If on anticoagulant medication, please state whether the patient is taking any of the following medications:

Warfarin:

Yes ☐ No ☐ Unknown ☐

Direct Thrombin Inhibitors:

Yes ☐ No ☐ Unknown ☐

If taking a Direct Thrombin Inhibitor, please specify:

Dabigatran 150mg ☐ Dabigatran 110mg ☐ Other ☐ Unknown ☐

On Factor Xa inhibitors:

Yes ☐ No ☐ Unknown ☐

If taking Factor Xa inhibitors, please state whether the patient is taking any of the following medications:

Rivaroxaban:

Yes ☐ No ☐ Unknown ☐

Apixaban:

Yes ☐ No ☐ Unknown ☐

Edoxaban:

Yes ☐ No ☐ Unknown ☐

Other Factor Xa inhibitors, (please specify):

Yes ☐ No ☐ Unknown ☐

Please specify, other Factor Xa inhibitors taken: ☐

Family History (Genetic Sub-study)

Family History

Reliable family history available?

Yes ☐ No ☐ Unknown ☐

Patient is a twin?

Yes ☐ No ☐ Unknown ☐

Total number of siblings (including the patient): ☐

Family History of Stroke - Parents

Is there any history of ischaemic stroke - **Father**:

Yes ☐ No ☐ Unknown ☐

If yes, age of **father** at the time of the stroke: ☐

Is there any history of intracerebral haemorrhage - **Father**:

Yes ☐ No ☐ Unknown ☐

If yes, age of **father** at the time of haemorrhage: ☐

Is there any history of ischaemic stroke - **Mother**:

Yes ☐ No ☐ Unknown ☐

If yes, age of **mother** at the time of the stroke: ☐

Is there any history of intracerebral haemorrhage - **Mother**

Yes ☐ No ☐ Unknown ☐

If yes, age of **mother** at the time of the haemorrhage: ☐

Family History of Stroke - Siblings

In other siblings is there any history of stroke? Please list siblings from OLDEST to YOUNGEST

Is there any history of ischaemic stroke - Sibling:

Yes ☐ No ☐ Unknown ☐

If yes, age of sibling at the time of the stroke: ☐

Is there any history of intracerebral haemorrhage - Sibling:

Yes ☐ No ☐ Unknown ☐

If yes, age of sibling at the time of haemorrhage: ☐

To add more siblings use back of page and enter into eCRF

Antihypertensive Drugs at Enrolment

Antihypertensive Drugs

Is the patient taking any antihypertensive drugs?

Yes ☐ No ☐

Antihypertensive drug 1 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Antihypertensive drug 2 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Frequency: OD BD TDS QDS Nocte PRN Other Units: Mg mcg units % other

Full list below:

Ca+2 channel blockers:

Amlodipine | Felodipine | Lercanidipine | Nicardipine | Lacidipine | Diltiazem | Verapamil

ACE inhibitors:

Ramipril | Enalapril | Lisinopril | Perindopril | Captopril

Beta Blocker:

Atenolol | Bisoprolol | Metoprolol | Nebivolol | Carvedilol | Propranolol

Angiotensin receptor antagonists:

Candersartan | Losartan | Valsartan | Irbesartan | Olmesartan | Telmisartan

Thiazide/thiazide-like diuretics:

Bendroflumethiazide | Hydrochlorothiazide | Indapamide

Loop diuretics:

Furosemide

Potassium-sparing diuretics:

Spironolactone

Alpha blockers:

Doxazosin | Doxazosin MR | Prazosin | Tamsulosin

Centrally acting agents:

Clonidine hydrochloride | Methyldopa | Moxonidine

Other
If Other please specify: ☐

Any Side Effects?

Has the patient previously had difficulty tolerating blood pressure medications?
Yes ☐ No ☐ Unknown ☐

If so please list side effects that limited treatment: Dizziness/Faintness ☐ Postural Hypotension ☐ Falls ☐
Other ☐

If Other, please specify: ☐

Antithrombotic Drugs at Enrolment

Is the patient taking any antithrombotic drugs:

Yes ☐ No ☐

Please select drug(s) from list below:

Aspirin ☐

Dipyridamole ☐

Clopidogrel ☐

Warfarin ☐

Direct Thrombin Inhibitors: ☐

Dabigatran 150mg ☐ Dabigatran 110mg ☐ Other ☐

Factor Xa Inhibitors: ☐

Rivaroxaban ☐ Apixaban ☐ Edoxaban ☐ Other ☐

Low molecular weight heparin (LMWH) ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ PRN ☐ Other ☐

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one antithrombotic drug:

Antithrombotic drug 1 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antithrombotic drug 2 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antithrombotic drug 3 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**

Lipid Lowering Drugs at Enrolment

Is the patient taking any Lipid Lowering Drugs :

Yes ☐ No ☐

Please select drug(s) from list below:

Atorvastatin ☐

Fluvastatin ☐

Pravastatin ☐

Rosuvastatin ☐

Simvastatin ☐

Other ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ PRN ☐ Other ☐

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one lipid lowering drug:

Lipid lowering drug 1 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Lipid lowering drug 2 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Lipid Lowering drug 3 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Other Relevant Drugs at Enrolment

Is the patient taking any Other Relevant Drugs :

Yes ☐ No ☐

Does the patient regularly use NSAIDs (>1/wk)? (e.g. Ibuprofen, Naproxen, Diclofenac and selective COX-2 inhibitors (e.g. celecoxib, etoricoxib, parecoxib))

Yes ☐ No ☐

Does the patient use decongestants/vasoconstrictor drugs? (e.g. ephedrine, pseudoephedrine)

Yes ☐ No ☐

Does the patient use any health preparations? (e.g. fish oil, gingko biloba)

Yes ☐ No ☐

Other ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ PRN ☐ Other ☐

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one other relevant drug:

Other relevant drug 1 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Other relevant drug 2 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Other relevant drug 3 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**

Baseline Cognitive Assessment

Cognition – assessment completed?

Yes ☐ No ☐ If yes, date Cognitive Assessment completed: __ __/ __ __ / __ __ __ __

Assessment scores:

Cognitive Assessment subscale: Orientation

Cognitive Assessment subscale: Attention - (A) ☐

Cognitive Assessment subscale: Attention - (B) ☐

Cognitive Assessment subscale: Attention - (C) ☐

Cognitive Assessment subscale: Executive - (A) ☐

Cognitive Assessment subscale: Executive - (B) ☐

Cognitive Assessment subscale: Executive - (C) ☐

Cognitive Assessment subscale: Language: Repeat - (A) ☐

Cognitive Assessment subscale: Language: Repeat - (B) ☐

Cognitive Assessment subscale: Language: Repeat - (C) ☐

Cognitive Assessment subscale: Language: Command ☐

Cognitive Assessment subscale: Naming ☐

Cognitive Assessment subscale: Perception ☐

Cognitive Assessment subscale: Visual Memory-intermediate: Copy: ☐

Cognitive Assessment subscale: Visual Memory-intermediate: Recall: ☐

Cognitive Assessment subscale: Verbal Memory-intermediate: 1st Trial: ☐

Cognitive Assessment subscale: Verbal Memory-intermediate: 2nd Trial: ☐

Cognitive Assessment subscale: Processing speed: Count backwards: ☐

Cognitive Assessment subscale: Processing speed: Months backwards: ☐

Cognitive Assessment subscale: Working Memory: ☐

Cognitive Assessment subscale: Executive functions: Fluency: ☐

Cognitive Assessment subscale: Executive functions: Similarities: ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Free Recall ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Category Cue: ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Multiple choice: ☐

Cognitive Assessment subscale: Memory-Delayed: Visual recall: ☐

Cognitive Assessment subscale: Memory-Delayed: Visual recognition: ☐

Cognitive Assessment subscale: Visuo-Executive: ☐

Does the patient have less than 12 years of education? Yes ☐ No ☐

Baseline IQ Code

IQ Code – assessment completed?

Yes ☐ No ☐ If yes, date IQ Code completed: __ __/ __ __ / __ __ __ __

IQ Code (Pre-ICH versus 10 years ago						
		1	2	3	4	5
	Remembering things about family and friends, e.g. occupations, birthdays and addresses					
	Remembering things that have happened recently					
	Recalling conversations a few days later					
	Remembering her/his address and telephone number					
	Remembering what day and month it is					
	Remembering where things are usually kept					
	Remembering where to find things which have been put in a different place from usual					
	Knowing how to work familiar machines around the house					
	Learning to use a new gadget or machine around the house					
	Learning new things in general					
	Following a story in a book or on TV					
	Making decisions on every day matters					
	Handling money for shopping					
	Handling financial matters, e.g. the pension, dealing with the bank					
	Handling other everyday arithmetic problems, e.g. knowing how much food to buy, knowing how long between visits from family or friends					
	Using his/her intelligence to understand what's going on and to reason things through					

1 = Much Improved

2 = A Bit Improved

3 = Not much changed

4 = A bit worse

5 = Much worse

Baseline EQ-5D Questionnaire

Baseline EQ-5D questionnaire completed?

Yes ☐ No ☐ If yes, date EQ-5D questionnaire completed: __ __/ __ __ / __ __ __ __

EQ-5D Questionnaire

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

Your health today: ☐

Baseline Procedures

Blood Sample

EDTA blood sample taken? Yes ☐ No ☐

If no, give reason sample not taken: _____

Blood sample sent to coordinating centre? Yes ☐ No ☐

Date sample sent to coordinating centre: __ __ / __ __ / __ __ __ __

Imaging

MRI date of completion: __ __ / __ __ / __ __ __ __

Confirmed correct sequences?

3D T1: Yes ☐ No ☐ 3D FLAIR: Yes ☐ No ☐ DTI: Yes ☐ No ☐

3D AWI: Yes ☐ No ☐ Axial T2: Yes ☐ No ☐

Optional: Arterial Spin labelling: Yes ☐ No ☐

Please send the MRI scan by clicking this web upload link: http://qsmscentre.org.uk

MRI Image sent to coordinating centre? Yes ☐ No ☐

If yes, date MRI Image sent to coordinating centre: __ __ / __ __ / __ __ __ __

MRI Transmittal form emailed to UCL? Yes ☐ No ☐

If yes, date MRI transmittal form sent to UCL: __ __ / __ __ / __ __ __ __

Baseline 24 Hour ABPM

24 hour BP applied: Yes ☐ No ☐ If yes, date 24 hour BP applied: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP applied: __ __ : __ __ If not applied please provide reason: _____

24 hour BP removed: Yes ☐ No ☐ If yes, date 24 hour BP removed: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP removed: __ __ : __ __ If not removed please provide reason: _____

24 hour BP received: Yes ☐ No ☐ If yes, date 24 hour BP received: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP received: __ __:__ __ If not received please provide reason: _____

24 hour BP downloaded: Yes ☐ No ☐ If yes, date 24 hour BP downloaded:__ __/__ __/__ __ __ __

If yes, time 24 hour BP downloaded and collected: __ __ :__ __

If BP not downloaded and collected please provide reason: _____

Baseline Bluetooth

Randomised to Intensive BP monitoring Yes ☐ No ☐

If yes, Bluetooth issued: Yes ☐ No ☐ If yes, date issued: __ __/__ __/__ __ __ __

If yes, Bluetooth ID: _____

If not issued, please provide reason:_____

CRF Sign Off

Date form completed:

__ __ / __ __ / __ __ __ __

Name of person completing form:

_____

Job title of person completing form:

_____

3 Month Follow Up

Date of 3 month follow-up assessment:

__ __/__ __/__ __ __ __

Please take patient's blood pressure BEFORE completing the form

Date blood pressure readings taken:

__ __/ __ __/ __ __ __ __

Arm used:

Left ☐

Right ☐

Systolic BP: ☐

Diastolic BP: ☐

taken: __ __ : __ __

Follow-up Questionnaire

Since enrolment into PROHIBIT-ICH has the participant experienced any of the following?

Ischaemic Stroke or TIA	Yes ☐	No ☐
Intracerebral Haemorrhage (ICH)	Yes ☐	No ☐
Diagnosis of Dementia	Yes ☐	No ☐
Death	Yes ☐	No ☐

IF THE ANSWER TO ANY OF THESE QUESTIONS IS YED PLEASE PROVIDE ALL MEDICAL DOCUMENTATION OF THE EVENT (E.G. HOSPITAL RECORDS (PATIENT'S DISCHARGE LETTER CLINIC LETTERS, BRAIN SCAN REPORTS, ETC.) AND COMPLETE THE STROKE EVENT FOR OR THE DEATH NOTIFICATION FORM. MANY THANKS!

Please send us any brain scans related to these events ('unscheduled events') by clicking this web scan upload link: http://qsmscentre.org.uk

Medical records including discharge letter sent to co-ordinating site?

Yes ☐ No ☐

Brain scans sent to co-ordinating site?

Yes ☐ No ☐

Completed event form sent to co-ordinating site?

Yes ☐ No ☐

If No: Please provide reason:

Antihypertensive Drugs at 3 Month Follow Up

Antihypertensive Drugs

Is the patient taking any antihypertensive drugs?

Yes ☐ No ☐

Antihypertensive drug 1 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antihypertensive drug 2 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antihypertensive drug 3 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antihypertensive drug 4 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antihypertensive drug 5 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**

Frequency: OD BD TDS QDS Nocte PRN Other Units: Mg mcg units % other

Full list below:

Ca+2 channel blockers:

Amlodipine | Felodipine | Lercanidipine | Nicardipine | Lacidipine | Diltiazem | Verapamil

ACE inhibitors:

Ramipril | Enalapril | Lisinopril | Perindopril | Captopril

Beta Blocker:

Atenolol | Bisoprolol | Metoprolol | Nebivolol | Carvedilol | Propranolol

Angiotensin receptor antagonists:

Candersartan | Losartan | Valsartan | Irbesartan | Olmesartan | Telmisartan

Thiazide/thiazide-like diuretics:

Bendroflumethiazide | Hydrochlorothiazide | Indapamide

Loop diuretics:

Furosemide

Potassium-sparing diuretics:

Spironolactone

Alpha blockers:

Doxazosin | Doxazosin MR | Prazosin | Tamsulosin

Centrally acting agents:

Clonidine hydrochloride | Methyldopa | Moxonidine

Other

If Other please specify: ☐

Any Side Effects?

Has the patient previously had difficulty tolerating blood pressure medications?

Yes ☐ No ☐ Unknown ☐

If so please list side effects that limited treatment: Dizziness/Faintness ☐ Postural Hypotension ☐ Falls ☐ Other ☐

If Other, please specify: ☐

Antithrombotic Drugs at 3 Month Follow Up

Is the patient taking any antithrombotic drugs:

Yes ☐ No ☐

Please select drug(s) from list below:

Aspirin ☐

Dipyridamole ☐

Clopidogrel ☐

Warfarin ☐

Direct Thrombin Inhibitors: ☐

Dabigatran 150mg ☐ Dabigatran 110mg ☐ Other ☐

Factor Xa Inhibitors: ☐

Rivaroxaban ☐ Apixaban ☐ Edoxaban ☐ Other ☐

Low molecular weight heparin (LMWH) ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ ☐ PRN ☐ Other

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one antithrombotic drug:

Antithrombotic drug 1 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antithrombotic drug 2 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antithrombotic drug 3 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**

Lipid Lowering Drugs at 3 Month Follow Up

Is the patient taking any Lipid Lowering Drugs :

Yes ☐ No ☐

Please select drug(s) from list below:

Atorvastatin ☐

Fluvastatin ☐

Pravastatin ☐

Rosuvastatin ☐

Simvastatin ☐

Other ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ PRN ☐ Other ☐

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one lipid lowering drug:

Lipid lowering drug 1 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Lipid lowering drug 2 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Lipid Lowering drug 3 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Other Relevant Drugs at 3 Month Follow Up

Is the patient taking any Other Relevant Drugs :

Yes ☐ No ☐

Does the patient regularly use NSAIDs (>1/wk)? (e.g. Ibuprofen, Naproxen, Diclofenac and selective COX-2 inhibitors (e.g. celecoxib, etoricoxib, parecoxib))

Yes ☐ No ☐

Does the patient use decongestants/vasoconstrictor drugs? (e.g. ephedrine, pseudoephedrine)

Yes ☐ No ☐

Does the patient use any health preparations? (e.g. fish oil, gingko biloba)

Yes ☐ No ☐

Other ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ PRN ☐ Other ☐

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one other relevant drug:

Other relevant drug 1 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Other relevant drug 2 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Other relevant drug 3 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**

3 Month Cognitive Assessment

Cognition – assessment completed?

Yes ☐ No ☐ If yes, date Cognitive Assessment completed: __ __/ __ __ / __ __ __ __

Assessment scores:

Cognitive Assessment subscale: Orientation

Cognitive Assessment subscale: Attention - (A) ☐

Cognitive Assessment subscale: Attention - (B) ☐

Cognitive Assessment subscale: Attention - (C) ☐

Cognitive Assessment subscale: Executive - (A) ☐

Cognitive Assessment subscale: Executive - (B) ☐

Cognitive Assessment subscale: Executive - (C) ☐

Cognitive Assessment subscale: Language: Repeat - (A) ☐

Cognitive Assessment subscale: Language: Repeat - (B) ☐

Cognitive Assessment subscale: Language: Repeat - (C) ☐

Cognitive Assessment subscale: Language: Command ☐

Cognitive Assessment subscale: Naming ☐

Cognitive Assessment subscale: Perception ☐

Cognitive Assessment subscale: Visual Memory-intermediate: Copy: ☐

Cognitive Assessment subscale: Visual Memory-intermediate: Recall: ☐

Cognitive Assessment subscale: Verbal Memory-intermediate: 1st Trial: ☐

Cognitive Assessment subscale: Verbal Memory-intermediate: 2nd Trial: ☐

Cognitive Assessment subscale: Processing speed: Count backwards: ☐

Cognitive Assessment subscale: Processing speed: Months backwards: ☐

Cognitive Assessment subscale: Working Memory: ☐

Cognitive Assessment subscale: Executive functions: Fluency: ☐

Cognitive Assessment subscale: Executive functions: Similarities: ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Free Recall ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Category Cue: ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Multiple choice: ☐

Cognitive Assessment subscale: Memory-Delayed: Visual recall: ☐

Cognitive Assessment subscale: Memory-Delayed: Visual recognition: ☐

Cognitive Assessment subscale: Visuo-Executive: ☐

Does the patient have less than 12 years of education? Yes ☐ No ☐

3 Month EQ-5D Questionnaire

3 Month EQ-5D questionnaire completed?

Yes ☐ No ☐ If yes, date EQ-5D questionnaire completed: __ __/ __ __ / __ __ __ __

EQ-5D Questionnaire

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

Your health today: ☐

BP data collection at 3 Month Follow Up

3 Month 24 Hour ABPM

24 hour BP applied: Yes ☐ No ☐ If yes, date 24 hour BP applied: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP applied: __ __ : __ __ If not applied please provide reason: _____

24 hour BP removed: Yes ☐ No ☐ If yes, date 24 hour BP removed: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP removed: __ __ : __ __ If not removed please provide reason: _____

24 hour BP received: Yes ☐ No ☐ If yes, date 24 hour BP received: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP received: __ __:__ __ If not received please provide reason: _____

24 hour BP downloaded: Yes ☐ No ☐ If yes, date 24 hour BP downloaded:__ __/__ __/__ __ __ __

If yes, time 24 hour BP downloaded and collected: __ __ :__ __

If BP not downloaded and collected please provide reason: _____

3 Month Bluetooth data

Randomised to Intensive BP monitoring: Yes ☐ No ☐

If yes, was Bluetooth issued at Baseline: Yes ☐ No ☐

If not issued, please provide reason:_____

If yes, Bluetooth hub returned (patients will keep the monitor to use as a conventional monitor and return it at 12 months): Yes ☐ No ☐

Date Bluetooth hub returned: __ __ /__ __ / __ __ __ __

if not returned please give reason:_____

Blood Pressure measurement (last assessment 3 Month Follow Up)

Please take patient's blood pressure as the LAST follow-up assessment

Date blood pressure readings taken:

__ __ / __ __ / __ __ __ __

Arm used:

Left ☐

Right ☐

Systolic BP: ☐

Diastolic BP: ☐

taken: __ __ : __ __

CRF Sign Off

Date form completed:

__ __ / __ __ / __ __ __ __

Name of person completing form:

_____

Job title of person completing form:

_____

12 Month Follow Up

Date of 12 month follow-up assessment:

__ __/__ __ /__ __ __ __

Please take patient's blood pressure BEFORE completing the form

Date blood pressure readings taken:

__ __ / __ __ / __ __ __ __

Arm used:

Left ☐

Right ☐

Systolic BP: ☐

Diastolic BP: ☐

taken: __ __ : __ __

Follow-up Questionnaire

Since enrolment into PROHIBIT-ICH has the participant experienced any of the following?

Ischaemic Stroke or TIA	Yes ☐	No ☐
Intracerebral Haemorrhage (ICH)	Yes ☐	No ☐
Diagnosis of Dementia	Yes ☐	No ☐
Death	Yes ☐	No ☐

IF THE ANSWER TO ANY OF THESE QUESTIONS IS YED PLEASE PROVIDE ALL MEDICAL DOCUMENTATION OF THE EVENT (E.G. HOSPITAL RECORDS (PATIENT'S DISCHARGE LETTER CLINIC LETTERS, BRAIN SCAN REPORTS, ETC.) AND COMPLETE THE STROKE EVENT FOR OR THE DEATH NOTIFICATION FORM. MANY THANKS!

Please send us any brain scans related to these events ('unscheduled events') by clicking this web scan upload link: http://qsmscentre.org.uk

Medical records including discharge letter sent to co-ordinating site?

Yes ☐ No ☐

Brain scans sent to co-ordinating site?

Yes ☐ No ☐

Completed event form sent to co-ordinating site?

Yes ☐ No ☐

If No: Please provide reason:

Antihypertensive Drugs at 12 Month Follow Up

Antihypertensive Drugs

Is the patient taking any antihypertensive drugs?

Yes ☐ No ☐

Antihypertensive drug 1 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Antihypertensive drug 2 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Antihypertensive drug 3 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Antihypertensive drug 4 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Antihypertensive drug 5 details: **Drug name:** **Dose:** **Frequency:** **Units:**

Frequency: OD BD TDS QDS Nocte PRN Other Units: Mg mcg units % other

Full list below:

Ca+2 channel blockers:

Amlodipine | Felodipine | Lercanidipine | Nicardipine | Lacidipine | Diltiazem | Verapamil

ACE inhibitors:

Ramipril | Enalapril | Lisinopril | Perindopril | Captopril

Beta Blocker:

Atenolol | Bisoprolol | Metoprolol | Nebivolol | Carvedilol | Propranolol

Angiotensin receptor antagonists:

Candersartan | Losartan | Valsartan | Irbesartan | Olmesartan | Telmisartan

Thiazide/thiazide-like diuretics:

Bendroflumethiazide | Hydrochlorothiazide | Indapamide

Loop diuretics:

Furosemide

Potassium-sparing diuretics:

Spironolactone

Alpha blockers:

Doxazosin | Doxazosin MR | Prazosin | Tamsulosin

Centrally acting agents:

Clonidine hydrochloride | Methyldopa | Moxonidine

Other

If Other please specify: ☐

Any Side Effects?

Has the patient previously had difficulty tolerating blood pressure medications?

Yes ☐ No ☐ Unknown ☐

If so please list side effects that limited treatment: Dizziness/Faintness ☐ Postural Hypotension ☐ Falls ☐

Other ☐

If Other, please specify: ☐

Antithrombotic Drugs at 12 Month Follow Up

Is the patient taking any antithrombotic drugs:

Yes ☐ No ☐

Please select drug(s) from list below:

Aspirin ☐

Dipyridamole ☐

Clopidogrel ☐

Warfarin ☐

Direct Thrombin Inhibitors: ☐

Dabigatran 150mg ☐ Dabigatran 110mg ☐ Other ☐

Factor Xa Inhibitors: ☐

Rivaroxaban ☐ Apixaban ☐ Edoxaban ☐ Other ☐

Low molecular weight heparin (LMWH) ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ PRN ☐ Other ☐

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one antithrombotic drug:

Antithrombotic drug 1 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antithrombotic drug 2 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Antithrombotic drug 3 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**

Lipid Lowering Drugs at 12 Month Follow Up

Is the patient taking any Lipid Lowering Drugs :

Yes ☐ No ☐

Please select drug(s) from list below:

Atorvastatin ☐

Fluvastatin ☐

Pravastatin ☐

Rosuvastatin ☐

Simvastatin ☐

Other ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ PRN ☐ Other ☐

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one lipid lowering drug:

Lipid lowering drug 1 details: Drug name: Dose: Frequency: Units:

Lipid lowering drug 2 details: Drug name: Dose: Frequency: Units:

Lipid Lowering drug 3 details: Drug name: Dose: Frequency: Units:

Other Relevant Drugs at 12 Month Follow Up

Is the patient taking any Other Relevant Drugs :

Yes ☐ No ☐

Does the patient regularly use NSAIDs (>1/wk)? (e.g. Ibuprofen, Naproxen, Diclofenac and selective COX-2 inhibitors (e.g. celecoxib, etoricoxib, parecoxib))

Yes ☐ No ☐

Does the patient use decongestants/vasoconstrictor drugs? (e.g. ephedrine, pseudoephedrine)

Yes ☐ No ☐

Does the patient use any health preparations? (e.g. fish oil, gingko biloba)

Yes ☐ No ☐

Other ☐

If Other, Please specify: ☐

Frequency:

OD ☐ BD ☐ TDS ☐ QDS ☐ Nocte ☐ PRN ☐ Other ☐

Total daily dose: ☐

Units:

Mg ☐ mcg ☐ units ☐ % ☐ other ☐

For more than one other relevant drug:

Other relevant drug 1 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Other relevant drug 2 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**
Other relevant drug 3 details:	**Drug name:**	**Dose:**	**Frequency:**	**Units:**

12 Month Cognitive Assessment

Cognition – assessment completed?

Yes ☐ No ☐ If yes, date Cognitive Assessment completed: __ __/ __ __ / __ __ __ __

Assessment scores:

Cognitive Assessment subscale: Orientation

Cognitive Assessment subscale: Attention - (A) ☐

Cognitive Assessment subscale: Attention - (B) ☐

Cognitive Assessment subscale: Attention - (C) ☐

Cognitive Assessment subscale: Executive - (A) ☐

Cognitive Assessment subscale: Executive - (B) ☐

Cognitive Assessment subscale: Executive - (C) ☐

Cognitive Assessment subscale: Language: Repeat - (A) ☐

Cognitive Assessment subscale: Language: Repeat - (B) ☐

Cognitive Assessment subscale: Language: Repeat - (C) ☐

Cognitive Assessment subscale: Language: Command ☐

Cognitive Assessment subscale: Naming ☐

Cognitive Assessment subscale: Perception ☐

Cognitive Assessment subscale: Visual Memory-intermediate: Copy: ☐

Cognitive Assessment subscale: Visual Memory-intermediate: Recall: ☐

Cognitive Assessment subscale: Verbal Memory-intermediate: 1st Trial: ☐

Cognitive Assessment subscale: Verbal Memory-intermediate: 2nd Trial: ☐

Cognitive Assessment subscale: Processing speed: Count backwards: ☐

Cognitive Assessment subscale: Processing speed: Months backwards: ☐

Cognitive Assessment subscale: Working Memory: ☐

Cognitive Assessment subscale: Executive functions: Fluency: ☐

Cognitive Assessment subscale: Executive functions: Similarities: ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Free Recall ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Category Cue: ☐

Cognitive Assessment subscale: Memory-Delayed (Verbal): Multiple choice: ☐

Cognitive Assessment subscale: Memory-Delayed: Visual recall: ☐

Cognitive Assessment subscale: Memory-Delayed: Visual recognition: ☐

Cognitive Assessment subscale: Visuo-Executive: ☐

Does the patient have less than 12 years of education? Yes ☐ No ☐

12 Month EQ-5D Questionnaire

12 Month EQ-5D questionnaire completed?

Yes ☐ No ☐ If yes, date EQ-5D questionnaire completed: __ __/ __ __ / __ __ __ __

EQ-5D Questionnaire

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

Your health today: ☐

MRI and BP data collection at 12 Month Follow Up

Imaging

MRI booked date: __ __ / __ __ / __ __ __ __ MRI time booked: __ __: __ __

MRI date of completion: __ __ / __ __ / __ __ __ __ MRI time completed: __ __ : __ __

Confirmed correct sequences?

3D T1: Yes ☐ No ☐

3D FLAIR: Yes ☐ No ☐

DTI: Yes ☐ No ☐

3D AWI: Yes ☐ No ☐

Axial T2: Yes ☐ No ☐

Optional: Arterial Spin labelling: Yes ☐ No ☐

Please send the MRI scan by clicking this web upload link: http://qsmscentre.org.uk

MRI Image sent to coordinating centre? Yes ☐ No ☐

If yes, date MRI Image sent to coordinating centre: __ __ / __ __ / __ __ __ __

MRI Transmittal form emailed to UCL? Yes ☐ No ☐

If yes, date MRI transmittal form sent to UCL: __ __ / __ __ / __ __ __ __

12 Month 24 Hour ABPM

24 hour BP applied: Yes ☐ No ☐ If yes, date 24 hour BP applied: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP applied: __ __ : __ __ If not applied please provide reason: _____

24 hour BP removed: Yes ☐ No ☐ If yes, date 24 hour BP removed: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP removed: __ __ : __ __ If not removed please provide reason: _____

24 hour BP received: Yes ☐ No ☐ If yes, date 24 hour BP received: __ __ / __ __ / __ __ __ __

If yes, time 24 hour BP received: __ __:__ __ If not received please provide reason: _____

24 hour BP downloaded: Yes ☐ No ☐ If yes, date 24 hour BP downloaded:__ __/__ __/__ __ __ __

If yes, time 24 hour BP downloaded and collected: __ __ :__ __

If BP not downloaded and collected please provide reason: _____

12 Month Follow UP Bluetooth

Randomised to Intensive BP monitoring: Yes ☐ No ☐

If yes, Bluetooth issued at Baseline: Yes ☐ No ☐

If not issued, please provide reason: _____

If yes, Bluetooth monitor returned: Yes ☐ No ☐

Date Bluetooth monitor returned: __ __ / __ __ / __ __ __ __

if not returned please give reason: _____

Blood Pressure measurement (last assessment 12 Month Follow Up)

Please take patient's blood pressure as the LAST follow-up assessment

Date blood pressure readings taken:

__ __ / __ __ / __ __ __ __

Arm used:

Left ☐

Right ☐

Systolic BP: ☐

Diastolic BP: ☐

taken: __ __ : __ __

CRF Sign Off

Date form completed:

__ __ / __ __ / __ __ __ __

Name of person completing form:

_____

Job title of person completing form:

_____

Prevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment (PROHIBIT-ICH)

PATIENT INFORMATION SHEET

We'd like to invite you to take part in our research study. The aim of the study is to compare blood pressure (BP) treatment (to a target of 120/80mm Hg, guided by a special BP monitor linked to our research team by Bluetooth technology), versus standard care. The more intensive BP lowering treatment is promising, but is not yet proven. Our study will therefore assess the feasibility, safety and effectiveness of this intensive BP treatment strategy. Before you decide to take part, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please ask us.

What is the purpose of this study?

About 1 in 10 strokes are due to a bleed into the brain from a ruptured (burst) artery, called intracerebral haemorrhage (ICH). The symptoms of ICH are due to nerve cell damage or swelling, and depend on where in the brain the bleeding has occurred; they can include drowsiness, nausea and vomiting, headaches, weakness of one or more limbs, loss of vision or speech, or seizures. In some cases, ICH is caused by injury or surgery, in others it happens suddenly without warning (“spontaneous”).

Spontaneous ICH is sometimes the result of high BP which, over time, causes damage to the small blood vessels supplying the brain, making them more likely to rupture. The main cause of spontaneous ICH is called “small vessel disease” (SVD), this may be because of poor BP control. Magnetic Resonance Imaging (MRI) has improved our ability to see the effects of SVD on scans of the brain after ICH.

The aim of this research study is to determine whether frequent measurements of BP using a monitor that securely sends readings automatically to our research team by Bluetooth technology (called “telemetric” monitoring) can be used to safely guide medication changes to “intensively” lower BP (to a target of 120/80mmg Hg) to reduce damage to the small blood vessels in the brain after spontaneous ICH. At multiple sites in the UK, participants will be randomly allocated to either intensive BP treatment guided by telemetric home monitoring or standard care in adult ICH survivors. We will follow-up these two groups of participants to assess whether BP lowering using this home monitoring is feasible, safe and effective in reducing brain injury. We will measure BP control at 3 months. To measure its effectiveness in reducing brain injury, where possible MRI scans will be taken before starting monitoring and after a year. A sample of blood will also be collected to find out if there are any genetic variations associated with ICH or SVD.

Why have I been invited to take part in this study?

You have been invited to take part because you are over the age of 30 and have had a spontaneous ICH, most likely due to SVD, confirmed on a brain scan.

Do I have to take part?

No. Participation in this study is entirely voluntary. It is entirely up to you to decide if you would like to participate or not. If you agree to participate, you will be asked to read and sign a consent form. You are free to withdraw from the study at any time, without giving a reason. This will have no impact on your clinical care.

What will happen to me if I decide to take part?

You will meet a member of the research team at your hospital, who will be able to answer any questions you may have. If you are eligible and willing to participate in the study, you will be given a unique study number; we will collect information regarding your health status, memory and thinking (cognition), and quality of life. We will take a small blood sample (equivalent to one teaspoonful or 5-10 millilitres of blood). You will either have an MRI scan of the brain, or we will use the results of an MRI or CT scan you previously had. No identifiable information will be stored, only your year of birth will be used and stored on a secure server called sealed envelope. Your local team will send all of this information, and your blood sample, to our PROHIBIT-ICH study co-ordinator at UCL. Only the team in UCL (co-ordinating site) and the team in University of Oxford (device co-ordinating site) will use the

information collected and have access to your medical records in this study to facilitate blood pressure treatment recommendations and for analysis.

You will be invited back for follow up after 3 months and 1 year, where you will be asked about any medical problems or admissions to hospital since you joined the study and how you are recovering. You will also be asked to do some memory tests and be fitted for 24 hours with a BP monitor that records BP every 30 minutes during the day and hourly at night. If you had an MRI scan at your 1st visit, you will have an MRI of the brain at your final follow up.

Half of the participants recruited to the PROHIBIT-ICH study will be randomly (by chance) allocated to monitor their BP at home using a telemetric monitor, this is called randomisation. Randomisation will be carried out by using a computer, it will allocate at random half of the group to use the BP monitors and the other half without it. BP data will be automatically sent to our Oxford study centre to monitor and change medicine dose to reach an BP target of 120/80mm Hg. The other half of participants will receive usual clinical care including BP control monitored by their hospital stroke team and their General Practitioner.

If you are selected to monitor your blood pressure at home, you will be shown how to use the monitor and will be asked to measure your blood pressure in a seated position three times over ten minutes (in your non-dominant arm (the one that you don't usually use for things like writing) unless you have been told otherwise), when waking in the morning, in the early afternoon, and before going to bed. This will need to be done for at least one month, and possibly up to three months, depending on how quickly your blood pressure reaches the intensive target. These BP measurements will be transmitted to a co-ordinating centre in Oxford via Bluetooth technology and assessed daily by a dedicated research team of nurses and doctors who will contact you by phone if a change in medication is indicated. The GP will also be notified by the co-ordinating centre. After three months, you will be asked to take readings three times over ten minutes, once a week until you are seen again at one year.

What will happen to my blood samples?

Your blood sample will be stored at UCL and will be stored for 20 years (the standard length)

What are the possible benefits of taking part?

Participation in the study will allow you access to a team with expertise in ICH, providing you with more information regarding your disease, as well as its prognosis. If randomly selected to intensive treatment, monitoring your BP at home should allow you to understand and manage your own BP better. Many participants in the study, regardless of whether they have home monitoring, will receive a research quality brain scan and all will have careful follow-up of their progress after their ICH, and the opportunity to benefit from up to date information from a specialist stroke research team. Our study will increase understanding about whether more intensive lowering of BP in survivors of ICH is feasible, safe and effective in reducing brain injury on MRI scans. If successful, we hope that this trial will lead to a larger trial. Our research will benefit the ICH research community and ultimately improve care for ICH survivors.

Are there any possible disadvantages or risks from taking part?

The collection of a blood sample from your arm is a standard procedure that is usually very safe, though can cause slight discomfort. Very rarely, a blood test can cause bruising, fainting or light-headedness, but the risks will be minimised because the collection of blood is done only by experienced and trained practitioners.

The MRI scan is noisy and, rarely, may provoke claustrophobia. Noise is minimised using earplugs and anxiety and claustrophobia are reduced by continuous communication during the scan via intercom. The scanning team will be able to remove you from the scanner at any time at your request.

Taking blood pressure readings may be uncomfortable due to a squeezing sensation, but this will only last a few seconds. These readings will be performed by an experienced professional whilst you are in hospital and by you or your carer when you have been discharged form hospital.

All staff on the study will be fully trained in good clinical practice, and will always consider your well-being as their primary concern. You can withdraw from the study at any time without affecting your clinical care.

Will my General Practitioner/family doctor (GP) be informed of my participation?

Yes, they will be aware of your participation in the study. Should you be randomly selected to home BP monitoring, any advised adjustment of BP medications will also be

communicated to your GP. We will send your GP a letter to inform them about your blood pressure readings at your 3 month and final follow-up.

What will happen to the results of this study?

The information from all participants taking part in this study will be collected and stored at UCL and Oxford. After analysing the data, the results will be reported to the funder of the study and published in scientific journals. Following completion and publication, these results will be posted on a study website for participants to view.

With your consent; the UCL team may use the data collected in this study for future research.

What if something goes wrong?

The UCL Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

What will happen if I don't want to carry on with the study?

Participation is entirely voluntary and you may withdraw at any time, without providing a reason.

Will my taking part in this study be kept confidential?

All information relating to your blood tests, MRI scans and any of your medical records will be kept strictly confidential and will only be used for medical research. Patient identifiable information will be anonymised in any reports. The research teams will ensure that patient identities are protected from any unauthorized parties. The clinical data records will be kept securely at the Stroke Research Centre, UCL. Prof David Werring, the Chief Investigator, will be responsible for the security and access to the information. The blood pressure data will be kept securely at the Centre for Prevention of Stroke and Dementia at the University of Oxford. Prof Peter Rothwell will be responsible for the security and access to the information. Data from the PROHIBIT-ICH study may be used for future research on stroke by UCL, and other research institutions in the UK or worldwide, but your confidentiality will be maintained. Your medical records may be inspected by competent authorities and properly authorized persons, but if any information is released outside the trial office it will be transferred in a secure manner. The results of the study will be published in medical journals or other public sites. We keep research results strictly confidential.

Who is organising and funding the study?

The research is being organised Professor David Werring, Professor of Clinical Neurology, Stroke Research Centre, UCL Institute of Neurology, and Prof Peter Rothwell, Action Research Professor of Neurology and Director of the stroke prevention research unit, Centre for Prevention of Stroke and Dementia, University of Oxford.

The Stroke Association has funded this study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by London - Camden & Kings Cross Research Ethics Committee.

In summary, if you take part, you will have:

- A short initial assessment to determine eligibility
- Questionnaires (clinical, cognitive, quality of life) at the beginning of the study, at 3 months and the final visit
- A blood sample collected upon entering the study
- An MRI scan (where possible) upon entering the study and at final follow up
- Either be assigned to usual care or receive a telemetric blood pressure monitor to measure BP 3 times daily (early morning, early afternoon and evening), with each time taking 3 readings over 10 minutes, and accordingly, receive adjusted BP treatment
- A 24 hour blood pressure monitor at follow up at the beginning, 3 months and final follow-up.

Thank you for reading this information sheet and taking the time to consider participating in this study. If you agree to take part, you will be given a copy of this information sheet and a copy of the signed consent form.

Further information can be obtained from:

University College London (UCL)	
Professor David Werring Professor of Clinical Neurology Stroke Research Centre UCL institute of Neurology Russell Square House 10-12 Russell Square London WC1B 5EH d.werring@ucl.ac.uk Tel: 020 3108 7493	Shahena Butt PROHIBIT-ICH Study Co-ordinator Stroke Research Centre UCL Institute of Neurology Russell Square House 10-12 Russell Square London WC1B 5EH shahena.butt@ucl.ac.uk Tel: 0203 108 6181
University of Oxford	
Iain McGurgan BP Clinical Research Fellow Centre for Prevention of Stroke and Dementia University of Oxford Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU ian.mcgurgan@ndcn.ox.ac.uk Tel: 01865 231601	Michelle Wilson BP Clinical Research Therapist Centre for Prevention of Stroke and Dementia University of Oxford, Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU michelle.wilson@ndcn.ox.ac.uk Tel: 01865 231601

Appendix 2.6

PROHIBIT-ICH

Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

Short Information Sheet
V2 04 Jan 2021

<table>
<tr><td></td><td>What is this study about?
We would like you to take part in a research study to find out if using a home monitoring machine after a brain haemorrhage can improve blood pressure control and overall brain health.</td></tr>
<tr><td></td><td>Soon after your stroke:
We will ask you if you would like to take part.
We will then ask you (and maybe a family member) some extra questions about your thinking, mood and memory.
We will also collect information from your local hospital records, now and later.
You will be asked to have a blood test, blood pressure measurements and where possible, a brain scan.
If you belong to a group who needs the blood pressure machine, you will be given this machine to take home with you
Your blood pressure will be monitored 3 times a day
Your blood pressure results will be sent to the research team and they will let you know if your blood pressure medication needs changing</td></tr>
<tr><td></td><td>A short time after your haemorrhage (3 months):
We will measure your blood pressure and ask you some questions again, with more details.
This will occur in the hospital</td></tr>
<tr><td></td><td>Is there anything else?
Blood sample will be stored for future genetic DNA analysis
We would like you to fill out some questionnaires
All study information will be anonymised.</td></tr>
<tr><td></td><td>Follow up 1 year after your haemorrhage:
We will ask you some questions again, with more details.
This will occur in the hospital to see how you are, if you have had any problems, and how well you have recovered.
We would like to collect information about you from central NHS records about any new illnesses, hospital admissions, or other health problems.
We will measure your blood pressure and where possible, you will have another brain scan</td></tr>
<tr><td></td><td>Risks:
There are no extra treatments involved, so the risk is low.
All the questions are designed to stop if you get tired.</td></tr>
<tr><td></td><td>During the study:
If you have any questions, then please ask.
You may decide you do not want to take part any more. This will not affect any of your care now or in the future.
We would like to know if you are happy to stay in the study if you become unable to make decisions for yourself.
A person who knows you well may be able to answer questions for you.
The information we hold about you is kept in strictest confidence.</td></tr>
</table>

PROHIBIT-ICH

Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

ARE YOU OVER THE AGE OF 30 WITH A HISTORY OF A BRAIN HAEMORRHAGE?

If so you might be eligible to take part in our research study



We are doing a research study to determine whether frequent **home telemetric monitoring** of blood pressure can be used to safely guide medication changes to **intensively lower blood pressure** to reduce damage to small brain blood vessels after spontaneous brain haemorrhage

The main procedures in the trial are as follows:

- Questionnaires at the beginning of the study, at 3 months and 1 year
- Where possible we will obtain an MRI brain scan; a blood sample will also be collected
- You would be assigned to usual care or receive a telemetric blood pressure monitor to measure BP 3 times daily, and accordingly receive adjusted BP treatment to a target of 120mmHg systolic
- A 24-hour blood pressure monitoring at the beginning of the study, 3 months and 1 year

If you would like more information about taking part in the PROHIBIT-ICH study, please contact our research team

Research team contact name:

Research team contact telephone number:

Appendix 2.8

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Prevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment (PROHIBIT-ICH)

Name of Researcher:

	Please initial in box
1. I confirm that I have read the information sheet dated 15.12.2020 (version 5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University College London (UCL), regulatory authorities or from participating NHS Trusts, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records for this study and to use the data collected in this study for future research.	☐
4. I give permission for the University of Oxford team (blood pressure (BP) device co-ordinating centre) to have access my record for this study in order to facilitate BP monitoring and treatment recommendations.	☐
5. I agree to my General Practitioner or other care professional being informed of my participation in the study.	☐
6. I agree that my blood samples can be stored at UCL for subsequent genetic analysis in this study and for future research.	☐
7. I agree for my study data to be stored at UCL and the University of Oxford for this study and for future research.	☐
8. I agree to take part in the above study.	☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Prevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment (PROHIBIT-ICH)

CONSULTEE INFORMATION SHEET

Where people cannot take decisions for themselves, for example the decision to consent to be involved in a research project, a consultee must be appointed to advise on persons wishes or feelings. This could be friend, family member, court appointee, or medical professional not connected to the study. You have been nominated as a possible consultee for a patient recently admitted to our hospital or seen in clinic for a stroke due to bleeding in the brain, called intracerebral haemorrhage (ICH). As the patient has lost capacity to consent, we are asking you to advise on whether the patient should take part in the project, and if you feel that he/she would be content to take part. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and any other doctors if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you think it is appropriate for the patient to take part. Remember that your decision must be in the patient's best interests and should not reflect your personal views on the project.

What is the purpose of this study?

About 1 in 10 strokes are due to a bleed into the brain from a ruptured artery, called intracerebral haemorrhage (ICH). The symptoms of ICH are due to nerve cell damage or swelling, and depend on where in the brain the bleeding has occurred; they can include drowsiness, nausea and vomiting, headaches, weakness of one or more limbs, loss of vision or speech, or seizures. In some cases, ICH is caused by injury or surgery, in others it happens suddenly without warning ("spontaneous").

Spontaneous ICH is sometimes the result of high BP which, over time, causes damage to the small blood vessels supplying the brain, making them more likely to rupture. The main cause

of spontaneous ICH is called “small vessel disease” (SVD), a process which is likely to be accelerated by poorly controlled BP. Magnetic Resonance Imaging (MRI) has rapidly improved our ability to see the effects of SVD on scans of the brain after ICH.

The aim of this research study is to determine whether frequent measurements of BP using a monitor that securely transmits readings automatically to our research team by Bluetooth technology (called “telemetric” monitoring) can be used to safely guide medication changes to “intensively” lower BP (to a target of 120/80mmg Hg) to reduce damage to the small blood vessels in the brain after spontaneous ICH. At multiple sites in the UK, participants will be randomly allocated to either intensive BP treatment guided by telemetric home monitoring or standard care in adult ICH survivors. We will follow-up these two groups of participants to assess whether BP lowering using this home monitoring is feasible, safe and effective in reducing brain injury. We will measure BP control at 3 months. To measure its effectiveness in reducing brain injury, where possible MRI scans will be taken before starting monitoring and after a year. A sample of blood will also be collected to find out if there are any genetic variations associated with ICH or SVD.

Why have you been chosen as a consultee?

You have been chosen as a consultee because our clinical examination shows that the patient has impaired brain and mind function, meaning that they cannot give consent. You are not obliged to undertake the role of consultee if you do not wish to do so. We are asking you to advise on whether the patient should take part in the project, and if you feel that he/she would be content to take part. We would like to make sure that taking part would not distress him/her in any way.

Why has the patient been chosen?

They have been invited to take part because he/she is over the age of 30 and has had a spontaneous ICH, most likely due to SVD, confirmed on a brain scan.

Does the patient have to take part?

His/her participation in the study is entirely voluntary. It is up to you to decide whether or not he/she will take part. If you do decide to consent on his/her behalf, you will be given this information sheet to keep and be asked to sign a consent form. He/she will be free to stop

taking part at any time and without giving a reason. This will have no impact on his/her clinical care.

What will happen to him/her if he/she takes part?

You will meet a member of the research team at your hospital, who will be able to answer any questions you may have. If he/she is eligible and willing to participate in the study, he/she will be given a unique study number; we will collect information regarding his/her health status, memory and thinking (cognition), and quality of life. We will take a small blood sample from him/her (equivalent to one teaspoonful or 5-10 millilitres of blood). He/she will either have an MRI scan of the brain, or we will use the results of an MRI or CT scan he/she has previously had. The local team will send all of this information, and his/her blood sample, to our PROHIBIT-ICH study co-ordinator at UCL. No identifiable information will be stored, only year of birth will be used and stored on a secure server called sealed envelope. Your local team will send all of this information, and blood sample, to our PROHIBIT-ICH study co-ordinator at UCL. Only the team in UCL (co-ordinating site) and the team in University of Oxford (device co-ordinating site) will use the information collected and have access to your medical records in this study to facilitate blood pressure treatment recommendations and for analysis.

He/she will be invited back for follow up after 3 months and 1 year, where they will be asked about any medical problems or admissions to hospital since he/she joined the study and how they are recovering. He/she will also be asked to do some memory tests and be fitted for 24 hours with a BP monitor that records BP every 30 minutes during the day and hourly at night. If he/she had an MRI scan at his/her 1st visit, he/she will have an MRI of the brain at his/her final follow up.

Half of the participants recruited to the PROHIBIT-ICH study will be randomly (by chance) allocated to monitor their BP at home using a telemetric monitor. BP data will be automatically sent to our Oxford study centre to monitor and adjust their treatment to reach an intensive BP target of 120/80mm Hg. The other half of participants will receive usual clinical care including BP control supervised by their hospital stroke team and their General Practitioner.

If he/she is selected to monitor their blood pressure at home, you and the participant will be shown how to use the monitor and will be asked to measure his/her blood pressure in a

seated position three times over ten minutes (in your non-dominant arm (the one that you don't usually use for things like writing) unless you have been told otherwise), when waking in the morning, in the early afternoon, and before going to bed. This will need to be done for at least one month, and possibly up to three months, depending on how quickly your blood pressure reaches the intensive target. These BP measurements will be transmitted to a co-ordinating centre in Oxford via Bluetooth technology and assessed daily by a dedicated research team of nurses and doctors who will contact you by phone if a change in medication is indicated. The GP will also be notified by the coordinating centre. After three months, the participant will be required to take readings three times over ten minutes, once a week until you are seen again at one year.

What will happen to his/her blood samples?

His/her blood sample will be stored at UCL and will be stored for 20 years (the standard storage length).

What are the possible benefits of him/her taking part?

Participation in the study will allow him/her access to a team with expertise in ICH, providing him/her with more information regarding their disease, as well as its prognosis. If randomly selected to intensive treatment, monitoring his/her BP at home should allow more understanding and better BP management. Many participants in the study, regardless of whether they have home monitoring, will receive a research quality brain scan and all will have careful follow-up of their progress after their ICH, and the opportunity to benefit from up to date information from a specialist stroke research team. Our study will increase understanding about whether more intensive lowering of BP in survivors of ICH is feasible, safe and effective in reducing brain injury on MRI scans. If successful, we hope that this trial will lead to a larger definitive trial. Our research will benefit the ICH research community and ultimately improve care for ICH survivors.

Are there any possible disadvantages or risks from him/her taking part?

The collection of a blood sample from his/her arm is a standard procedure that is usually very safe, though can cause slight discomfort. Very rarely, a blood test can cause bruising, fainting or light-headedness, but the risks will be minimised because the collection of blood is done only by experienced and trained practitioners.

The MRI scan is noisy and, rarely, may provoke claustrophobia. Noise is minimised using earplugs and anxiety and claustrophobia are reduced by continuous communication during the scan via intercom. The scanning team will be able to remove you from the scanner at any time at your request.

Taking blood pressure readings may be uncomfortable due to a squeezing sensation, but this will only last a few seconds. These readings will be performed by an experienced professional whilst you are in hospital and by you or your carer when you have been discharged form hospital.

All staff on the study will be fully trained in good clinical practice, and will always consider the participant's well-being as their primary concern. He/she can withdraw from the study at any time without affecting your clinical care.

Will the patient's General Practitioner/family doctor (GP) be informed of their participation?

Yes, they will be aware of your participation in the study. Should he/she be randomly selected to home BP monitoring, any advised adjustment of BP medications will also be communicated to his/her GP. We will send his/her GP a letter to inform them about his/her blood pressure readings at his/her 3 month and final follow-up.

What will happen to the results of this study?

The information from all participants taking part in this study will be collected and stored at UCL and Oxford. After analysing the data, the results will be reported to the funder of the study and published in scientific journals. Following completion and publication, these results will be posted on a study website for participants to view.

With your consent; the UCL team may use the data collected in this study for future research.

What if something goes wrong?

The UCL Sponsor, has appropriate insurance in place in the unlikely event that he/she suffer any harm as a direct consequence of their participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

Can I request for the patient to be withdrawn from the study?

Yes. Participation is entirely voluntary and you may request he/she be withdrawn from the study at any time, without giving any reason.

Will the patient's taking part in this study be kept confidential?

All information relating to his/her blood tests, MRI scans and any of their medical records will be kept strictly confidential and will only be used for medical research. Patient identifiable information will be anonymised in any reports. The research teams will ensure that patient identities are protected from any unauthorized parties. The clinical data records will be kept securely at the Stroke Research Centre, UCL. Prof David Werring, the Chief Investigator, will be responsible for the security and access to the information. The blood pressure data will be kept securely at the Centre for Prevention of Stroke and Dementia at the University of Oxford. Prof Peter Rothwell will be responsible for the security and access to the information. Data from the PROHIBIT-ICH study may be used for future research on stroke by UCL, and other research institutions in the UK or worldwide, but his/her confidentiality will be maintained. The participant's medical records may be inspected by competent authorities and properly authorised persons, but if any information is released outside the trial office it will be transferred in a secure manner. The results of the study will be published in medical journals or other public sites. We keep research results strictly confidential.

Who is organising and funding the study?

The research is being organised Professor David Werring, Professor of Clinical Neurology, Stroke Research Centre, UCL Institute of Neurology, and Prof Peter Rothwell, Action Research Professor of Neurology and Director of the stroke prevention research unit, Centre for Prevention of Stroke and Dementia, University of Oxford.

The Stroke Association has funded this study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by London - Camden & Kings Cross Research Ethics Committee.

In summary, if you decide for the patient to take part, he/she will have:

- A short initial assessment to determine eligibility
- Questionnaires (clinical, cognitive, quality of life) at the beginning of the study, at 3 months and the final visit
- A blood sample collected upon entering the study
- An MRI scan (where possible) upon entering the study and at final follow up
- Either be assigned to usual care or receive a telemetric blood pressure monitor to measure BP 3 times daily (early morning, early afternoon and evening), with each time taking 3 readings over 10 minutes, and accordingly, receive adjusted BP treatment
- A 24 hour blood pressure monitor at follow up at the beginning, 3 months and final follow up.

Thank you for reading this information sheet and taking the time to consider participating in this study. If you agree to take part, you will be given a copy of this information sheet and a copy of the signed consent form.

Further information can be obtained from:

<table>
<tr><th colspan="2">University College London (UCL)</th></tr>
<tr><td>Professor David Werring
Professor of Clinical Neurology
Stroke Research Centre
UCL institute of Neurology
Russell Square House
10-12 Russell Square
London WC1B 5EH
d.werring@ucl.ac.uk
Tel: 020 3108 7493</td><td>Shahena Butt
PROHIBIT-ICH Study Co-ordinator
Stroke Research Centre
UCL Institute of Neurology
Russell Square House
10-12 Russell Square
London WC1B 5EH
shahena.butt@ucl.ac.uk
Tel: 0203 108 6181</td></tr>
<tr><th colspan="2">University of Oxford</th></tr>
<tr><td>Iain McGurgan
BP Clinical Research Fellow
Centre for Prevention of Stroke and Dementia
University of Oxford
Level 6, West Wing
John Radcliffe Hospital
Headley Way
Oxford OX3 9DU
ian.mcgurgan@ndcn.ox.ac.uk
Tel: 01865 231601</td><td>Michelle Wilson
BP Clinical Research Therapist
Centre for Prevention of Stroke and Dementia
University of Oxford,
Level 6, West Wing
John Radcliffe Hospital
Headley Way
Oxford OX3 9DU
michelle.wilson@ndcn.ox.ac.uk
Tel: 01865 231601</td></tr>
</table>

Centre Number: Study Number:

Participant Identification Number for this study:

CONSULTEE DECLARATION FORM

Title of Project: Title of Project: Prevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment (PROHIBIT-ICH)

Name of Researcher:

	Please initial in box
1. I [name of consultee] have been consulted about [name of potential participant]'s participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved.	☐
2. I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected.	☐
3. I understand that relevant sections of his/her medical notes and data collected during the study may be looked at by individuals from University College London (UCL) , regulatory authorities or from participating NHS Trusts, where it is relevant to their taking part in this research. I give permission for these individuals to have access to his/her records for this study and to use the data collected in this studyfor future research.	☐
4. I give permission for the University of Oxford team (blood pressure (BP) device co-ordinating centre) to have access to his/her records for this study in order to facilitate BP monitoring and treatment recommendations.	☐
5. I agree to their GP or other care professional being informed of their participation in the study.	☐
6. I agree that their blood samples can be stored at UCL for subsequent genetic analysis in this study and for future research.	☐
7. I agree for the participant's study data to be stored at UCL and the University of Oxford for this study and for future research.	☐
8. In my opinion he/she would have no objection to taking part in the above study.	☐

Name of Consultee Date Signature

Relationship to participant:

Person undertaking consultation (if different from researcher):

Name Date Signature

Researcher Date Signature

When completed: 1 (original) to be kept in care record, 1 for consultee; 1 for researcher site file

Appendix 2.11

PROHIBIT-ICH

Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

UCL

IMAGING MANUAL

Contents

	Page no
Quick Reference Guide	2
Section 1: Contact details	3
Section 2: Introduction and Study Overview	
2.1 Background	5
2.2 Study Objectives and Endpoints	6
2.3 Study MRI Requirements (Summary)	7
Section 3: MRI Technologist Instructions	8
3.1 General Introduction for MRI procedures	
Section 4: PROHIBIT-ICH MRI Flow Chart	9
Section 5: MRI scanning procedures	10
5.1 General processes	
Section 6: MRI scanning procedures – dummy scan	11
6.1 Performing the Scan	12
6.2 Guideline scan	
6.3 Guide tables with scan parameters for use in dummy run scan	
Section 7: Guide tables with scan parameters for the MRI scan	13
Section 8: Data upload instructions	15
Appendices	
Appendix 1: Transmittal form	20

PROHIBIT-ICH MRI MANUAL VERSION 1 APRIL 2018

Quick Reference Guide

- **PROHIBIT-ICH:** PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment
- A pilot multi-site randomised controlled trial in approximately 112 adult survivors of spontaneous (SVD-related) ICH
- A 'dummy run' scan is required from all MRI sites. No trial subjects can be scanned until the 'dummy run' scan has been approved.
- MRI visits are scheduled for baseline, month 6 and month 12.
- Scanning protocol (with approx. acquisition time), for all visits, consists of :
  - 3D T1 (5min)
  - 3D FLAIR (5min)
  - DTI (5min)
  - 3D SWI (5min)
  - Axial T2 (2min)

  Total: 22 mins

Optional: Arterial Spin labelling (5min)

Total: 27 mins

➢ MRI scans sent to the MS Centre, UCL Institute of Neurology, London, UK

Section 1: Contact Details

Central MRI Reader Facility Contact Details

Jo Hornby
PROHIBIT-ICH Study Co-ordinator
UCL Stroke Research Centre
UCL Institute of Neurology
Russell Square House
10-12 Russell Square
First Floor
London
WC1B 5EH
Tel: 020 7670 5718
Email: prohibit-ich@ucl.ac.uk

Chief Investigator and Trial Coordinator Contact Details for imaging section of the study

Chief Investigator (Imaging)	**Professor David Werring** **d.werring@ucl.ac.uk** **Tel: 020 3108 7493**
Trial Coordinator	**Dr Jo Hornby** **Prohibit-ich@ucl.ac.uk** **Tel: 020 7670 5718**
Imaging study co-lead (UCL)	**Professor Rolf Jager** **r.jager@ucl.ac.uk**
Imaging study co-lead (UCL)	**Professor Frederik Barkhof** **f.barkhof@ucl.ac.uk**
MR Physicist (UCL)	**Dr David Thomas** **d.thomas@ucl.ac.uk**

Section 2 - Introduction and Study Overview

2.1 Background

- Intracerebral hemorrhage (ICH) accounts for 10-15% of all strokes in the Western populations with high mortality, disability, recurrence and socioeconomic burden to society[1-3]
- Most ICH is caused by cerebral small vessel diseases (SVD): hypertensive arteriopathy and cerebral amyloid angiopathy (CAA)
- Previous studies strongly suggest that intensive and sustained BP lowering could improve secondary prevention of ICH, but there are no current trials to guide the optimum strategy or intensity for BP lowering after ICH.
- Telemetric home BP monitoring is a promising intervention to improve BP control, evaluated previously in Oxford Vascular (OXVASC) Study by the Centrally Observed home telemetric Monitoring of BP to Manage Intensive Treatment (COMMIT) Study.[4,5]
- Blood pressure control might reduce SVD progression after ICH, which can be monitored by MRI biomarkers, including white matter hyperintensities and cerebral micro-bleeds (CMBs). Use of MRI biomarkers might be useful in demonstrating treatment efficacy in a smaller sample size than clinical outcomes.

1. Wilson D, Adams ME, Robertson F, et al. Investigating intracerebral haemorrhage. BMJ 2015;350:h2484.
2. Van Asch CJ, Luitse MJ, Rinkel GJ, et al. Incidence, case fatality, and functional outcome of intrac erebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet neurology 2010;9(2):167-76.
3. Jorgensen HS, Nakayama H, Reith J, et al. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. Neurology 1997;48(4):891-5.
4. U. Fischer, M. Wilson, N.L.M. Paul, L. Bull, S. Welch, L. Tarassenko, P.M. Rothw ell. Bluetooth home BP-monitoring in patients w ith TIA and minor stroke: feasibility and BP control. Cerebrovasc Dis 2014;38:137.
5. A Webb, N Lovett, L Li, M Wilson, F Cuthbertson, U Fischer, L Tarrassenko, P M Rothw ell. Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT) Study: Maximum SBP AND variability on home versus ambulatory monitoring International Journal of Stroke 2015. Vol 10 (Suppl. 2); April 2015; 53.

2.2 Study Objectives and Endpoints

The trial will investigate whether intensive lowering of blood pressure (BP) using telemetric home monitoring in survivors of intracerebral haemorrhage (ICH) is feasible, safe and effective in reducing brain injury. If successful this study will be a precursor for a larger definitive trial. Our intervention should allow survivors of ICH to know, understand, and manage their own BP to prevent strokes and cognitive impairment, and improve outcomes.

Primary objectives:

- BP study. Does the use of centralised telemetric home BP monitoring in patients with spontaneous (non-traumatic) ICH achieve a reduction in 3 -month BP compared with standard care?
- Imaging study. Does intensive BP treatment using centralised telemetric home monitoring result in a reduction in progression of small vessel disease (SVD)-related brain injury assessed on MRI (including, but not limited to, white matter hyperintensities (WMH), white matter structural integrity, incident cerebral microbleeds (CMBs), and brain atrophy) compared with standard care?

Secondary objectives:

(i) BP study

1. Is it feasible in a multi-site setting to intensively lower BP using centralised telemetric home BP monitoring for an extended period of time following spontaneous ICH?
2. Is it safe to intensively lower BP for an extended period of time following spontaneous ICH, or are there adverse responses (including increased progression of cognitive decline)?
3. Is the intervention acceptable to participants, including measures of quality of life?

(ii) Imaging study

1. Does any reduction in recurrent vascular events (including ICH) or progression of cognitive decline on intensive BP treatment correlate with baseline measures of changes in quantitative and structural brain scan markers of small blood vessel health?
2. Are there any adverse effects on neuroimaging measures (e.g. increased white matter ischaemic injury) associated with intensive BP treatment?

2.3 Study MRI Requirements (Summary)

Two types of MRI studies will be obtained during the course of the study

1. Dummy (test) Scan

Before a site can enrol subjects into this study; a test scan must be submitted for review and approval to the UCL MRI Central Reader Centre, Russell Square, London UK.

2. Routine On-Study Scan

Digital MRI images in DICOM standard will be uploaded to the MRI Central Reader Centre, UCL Russell Square, where they will be analysed and then archived.

Study scans should be performed using the study-specific MRI sequence instructions (see below) at the following time points:

Baseline Visit, Month 12 scans

1. **3D T1**
2. **3D FLAIR**
3. **DTI**
4. **3D SWI**
5. **Axial T2**

Optional: Arterial Spin labelling

An archive copy of the local MRI Report **MUST** be kept at the study site in the subjects CRF binder.
A local archive copy of the MRI data must also be retained at the site for future possible inspection by the sponsor or relevant Regulatory Authorities.

Section 3 - MRI TECHNOLOGISTS INSTRUCTIONS

3.1 GENERAL INTRODUCTION FOR MRI PROCEDURES

1. The preferred method of image transfer to UCL is by direct electronic transfer. All sites will be contacted during the initial site start-up period to discuss the implementation of a direct transfer protocol for scan transfer

2. Prior to starting to scan subjects for the study, you must submit a 'Dummy' or test scan to the MRI Central Reader Centre for evaluation and acceptance. This process will also confirm the sequence parameters you should use for all study scans.

3. All information relating to subject's details will be provided to you by the PI/study coordinator at your site. This information will be used to log the subject in for an MRI Scan.

4. Perform the MRI scan using the agreed upon parameters for your scanner. Parameters for your site will be determined as part of the test scan procedure. Once agreed upon, the finalised MRI parameters for your site will be issued to you on the Scan Parameter Form and should be filed in Section 7 of this manual. These parameters should be used for all study scans.

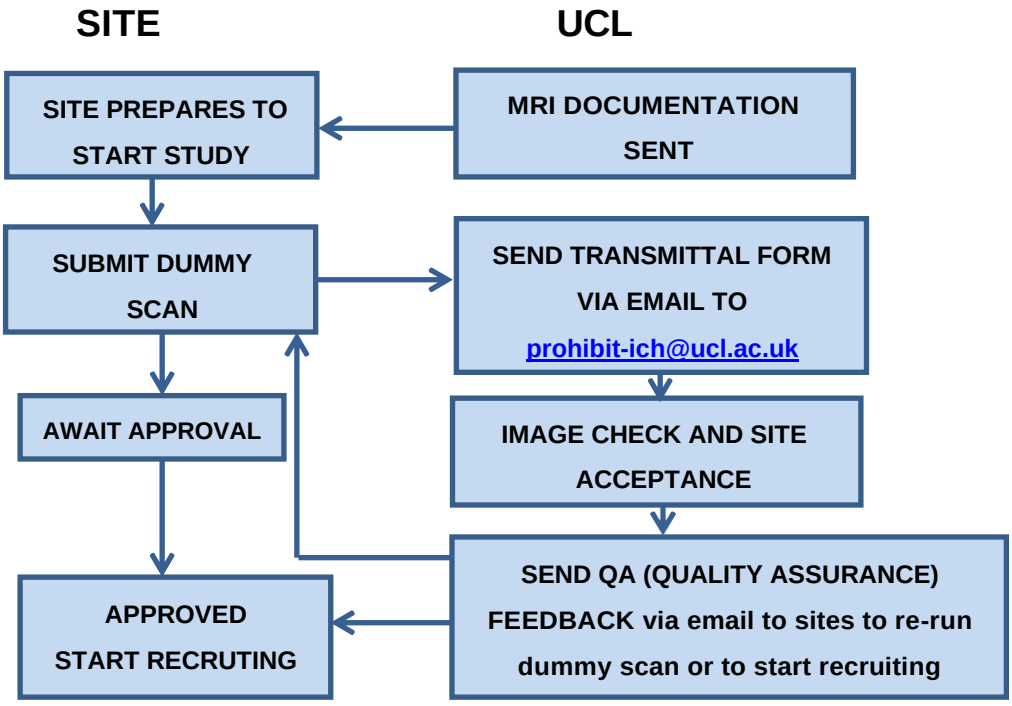
5. Remember, a subject should only be identified by the Subject Identification Number, date of scan and year of birth. The scan annotation must also include all scan parameters. The information recorded should be consistent with the information provided to you by your site PI/study coordinator.

6. Make a second copy of the MRI scan to be retained at your site for possible future data access (e.g. Regulatory Authority Inspection or routine study monitoring).

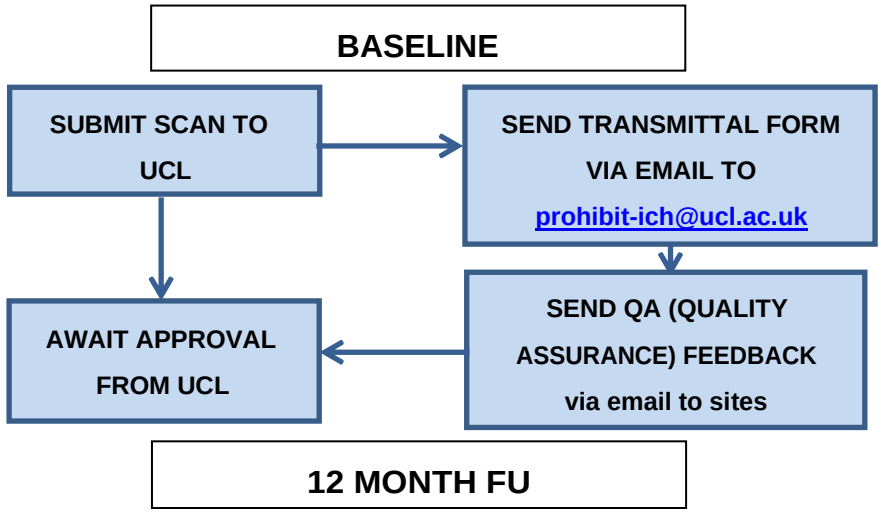
7. You should complete a Transmittal Form (attached in this manual) and send this to the UCL via email to prohibit-ich@ucl.ac.uk to notify of any scan that has been sent.

8. Following scan evaluation by the Reader Centre, you will receive a quality assurance report (QA Assessment Form) from the co-ordinator via e-mail which will indicate if each scan is acceptable or if problems have been identified. Please file these forms and all other correspondence with UCL.

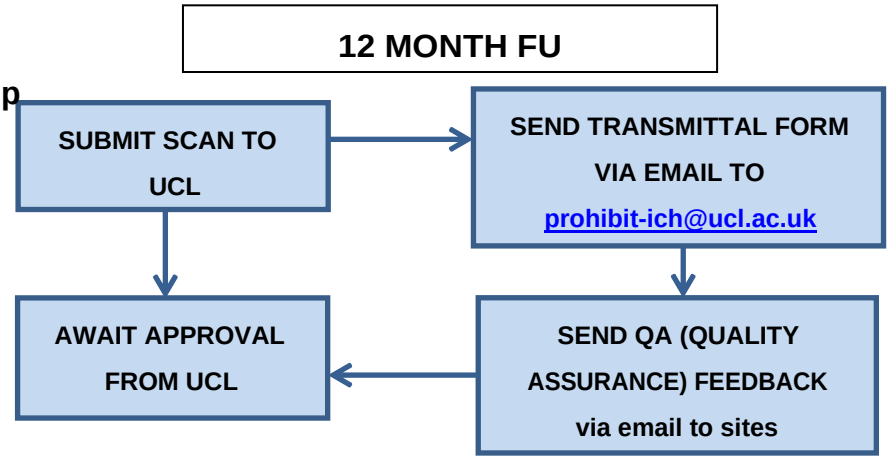
Section 4 - PROHIBIT-ICH MRI Flow Chart



Baseline



Month 12 Follow-up



Section 5 - MRI scanning procedures

5.1 General processes

Subject comfort during the scan is important. Adequate padding and neck support is recognised to be important, but no specific recommendations are made beyond the standard practice at your institution. Please provide ear plugs, eye masks, prism glasses or other items required for subject comfort as routinely used at your institution.

Minimising motion artefact is very important for study scan quality. Use of standard Velcro head straps and foam wedges is recommended. However, other methods of stabilising the head which are used routinely at your institution are acceptable.

The subject must be positioned appropriately so that the mid-line of the brain falls in the middle of the initial sagittal localising sequence. Follow the routine procedures at your institution for your type of scanner for placing subject in the machine and general positioning.

Please refer back to the previous timepoint study scans for study for each subject to enable exact repositioning between scans. This step is essential for the production of comparable scans and to enable effective evaluation by the Reader Centre.

The coil routinely used for research scans should be used. If possible, a high channel array coil (32 or 64 channels) should be used; otherwise an array coil with fewer channels is also acceptable. The coil information should be documented in the MRI Overview Form in Section 10 of the MRI Technologist Manual for future reference. The same coil must be used for all patients throughout the study – this is very important for longitudinal comparability.

Section 6 - MRI scanning procedures – dummy scan

As mentioned earlier, before each MRI centre is accepted into the trial, a test scan needs to be performed. This is often referred to as the "Dummy Scan". This procedure enables the Central MRI Reading Centre to determine the following:

- Scanner performance is within specification for entry into trial
- The MRI site's choice of scan sequence parameters give adequate tissue contrast for the purposes of the trial
- The MRI site can provide contiguous slices with adequate signal to noise ratio
- The MRI site is able to produce and transport the electronic data required for the study to the Central MRI Reader Centre at Queen Square

To facilitate the objectives listed above, each MRI site is required to perform an acceptable dummy (or test) scan as listed below **PRIOR** to any study scans being performed.

Your dummy scan will be reviewed by UCL after which you will be sent a **QA Assessment Feedback** telling you whether the scan is acceptable. You may be asked to resubmit a dummy scan to achieve acceptability, or the QA Assessment Feedback may make some recommendations for future scans.

When your dummy (or test) scan has been approved, you will be notified with an approval email by UCL that will confirm whether the MRI scan sequence parameters used for your centre are acceptable. These approved parameters **must** be used by your centre throughout the study for all scans.

ANY FUTURE DEVIATION FROM THESE APPROVED SCAN PARAMETERS MAY RESULT IN THE REQUIREMENT TO RECALL THE STUDY SUBJECT AND PERFORM A REPEAT MRI EXAMINATION.

It is therefore strongly advised that you store/save the approved scan protocol for the study on your scanner to avoid any mistakes being made when performing 'on study' MRI examinations for the trial.

6.1 Performing the Scan

It is the responsibility of the Principal Investigator (PI) and/or Study Coordinator (SC) at your site to arrange for a **suitable subject or normal volunteer** to be available for the 'dummy run' scan.

6.2 Guideline scan

1. Position the subject and perform 'localiser' scans in order to align the transverse slices for all scans to run parallel to the inferior points of the corpus callosum (see image below). We recommend that you use axial, coronal and sagittal planning scans to optimally position the subject



2. For all sequences, plan the scan to achieve as full converge of the entire brain as possible.

6.3 Guide tables with scan parameters for use in dummy run scan

The following table (section 7) contains a guide to the scan parameters to be used for the 'dummy run scan'. As parameters can change depending on scanner model and software level, some values are given as approximations.

7.0 Guide tables with scan parameters for the MRI scan

	PROHIBIT-ICH PARAMETERS GUIDE FOR GE 3T					
BRAIN	**3D T1**	**3D FLAIR**	**DTI**	**3D SWI**	**Axial T2**	**ASL (opt)**
slice orientation	Sagittal	Sagittal	Axial	Ob axial	Axial	Axial
TR (ms)	-	5000	8000	31	4000	-
TI (ms)	400	1540	-	-	-	2025
TE (ms)	Min Full	152	76.6	25	80	-
Number slices	200	192	80	48	44	-
slice thickness (mm)	1.2	1	2	3	4	4
slice gap (mm)	0	0	0	0	0	0
Field of View (cm)	27	25.6	22.4	25	24	24
Image matrix acquisition (frequency x phase)	256x256	256x240	112x112	384x384	256x256	512x8
Image matrix recon (frequency x phase)	256x256	256x240	112x112	384x384	256x256	512x8
Frequency encoding	S/I	S/I	R/L	R/L	A/P	R/L
Phase encoding	A/P	A/P	A/P	A/P	R/L	A/P
number of averages (excitations)	1	1	32 b=1000 4 b=0	1	1	3
Flip angle	11	-		15	150	-

	PROHIBIT-ICH PARAMETERS GUIDE FOR PHILIPS 3T					
BRAIN	**3D T1**	**3D FLAIR**	**DTI**	**3D SWI**	**Axial T2**	**ASL (opt)**
slice orientation	Sagittal	Sagittal	Axial	Axial	Axial	Axial
TR (ms)	6.8	5000	7500	28	3000	4800
TI (ms)	824	1650	-	-	-	2025
TE (ms)	3.1	395	91	25	80	10
Number slices	170	192	60	60	45	36
slice thickness (mm)	1.2	1	2	2	3	4.5
slice gap (mm)	0	0	0	0	4	0
Field of View (cm)	270x252	256x256	224x224	220x182	238x238	220x220
Image matrix acquisition (frequency x phase)	244x227	256x256	112x112	368x303	256x255	64x61
Image matrix recon (frequency x phase)	256x238	256x256	112x112	384x316	256x255	64x64
Frequency encoding	S/I	S/I	R/L	A/P	A/P	R/L
Phase encoding	A/P	A/P	A/P	R/L	R/L	A/P
number of averages (excitations)	1	1	32 b=1000 4 b=0	1	1	30
Flip angle	9	-	-	15	90/120	90

	PROHIBIT-ICH PARAMETERS GUIDE FOR SIEMENS 3T					
BRAIN	**3D T1**	**3D FLAIR**	**DTI**	**3D SWI**	**Axial T2**	**ASL (opt)**
slice orientation	Sagittal	Sagittal	Axial	Axial	Axial	Axial
TR (ms)	2300	5000	7200	28	4000	4000
TI (ms)	900	1650	-	-	-	2000
TE (ms)	2.95	395	56	25	78	20.26
Number slices	176	192	60	60	47	32
slice thickness (mm)	1.2	1	2	2	3	4.5
slice gap (mm)	0	0	0	0	0	0
Field of View (cm)	270x253	256x256	224x224	220x181	240x217	240x240
Image matrix acquisition (frequency x phase)	256x240	256x256	112x112	384x311	256x232	64x63
Image matrix recon (frequency x phase)	256x240	256x256	112x112	384x311	256x232	64x64
Frequency encoding	S/I	S/I	R/L	A/P	A/P	R/L
Phase encoding	A/P	A/P	A/P	R/L	R/L	A/P
number of averages (excitations)	1	1	32 b=1000 4 b=0	1	1	10
Flip angle	9	-	-	15	150	160

When your dummy (or test) scan has been approved by the imaging team at UCL, you will be provided with an email confirming that the sequence parameters used for the dummy MRI scan are suitable for your centre. These approved parameters must be used by your centre throughout the study for all scans.

Section 8 - Data upload instructions

File preparation:

Ensure your scans are compressed into a zip file before uploading.

Data upload:

Scans from your site should be sent to the Central Reading Facility at UCL by direct image transfer from your scanner or workstation/PC.

URL: http://qsmscentre.org.uk

We recommend you use web browser: Chrome, Firefox or Microsoft Edge
Internet Explorer 6 and 7 are NOT compatible!

Web Uploader Guide

This is a guide to sending images to the UCL Stroke Research Centre using the web upload service. To follow these instructions you will need a username and password for the web upload service. If you have not received these please request them by emailing prohibit-ich@ucl.ac.uk

1. Logging in

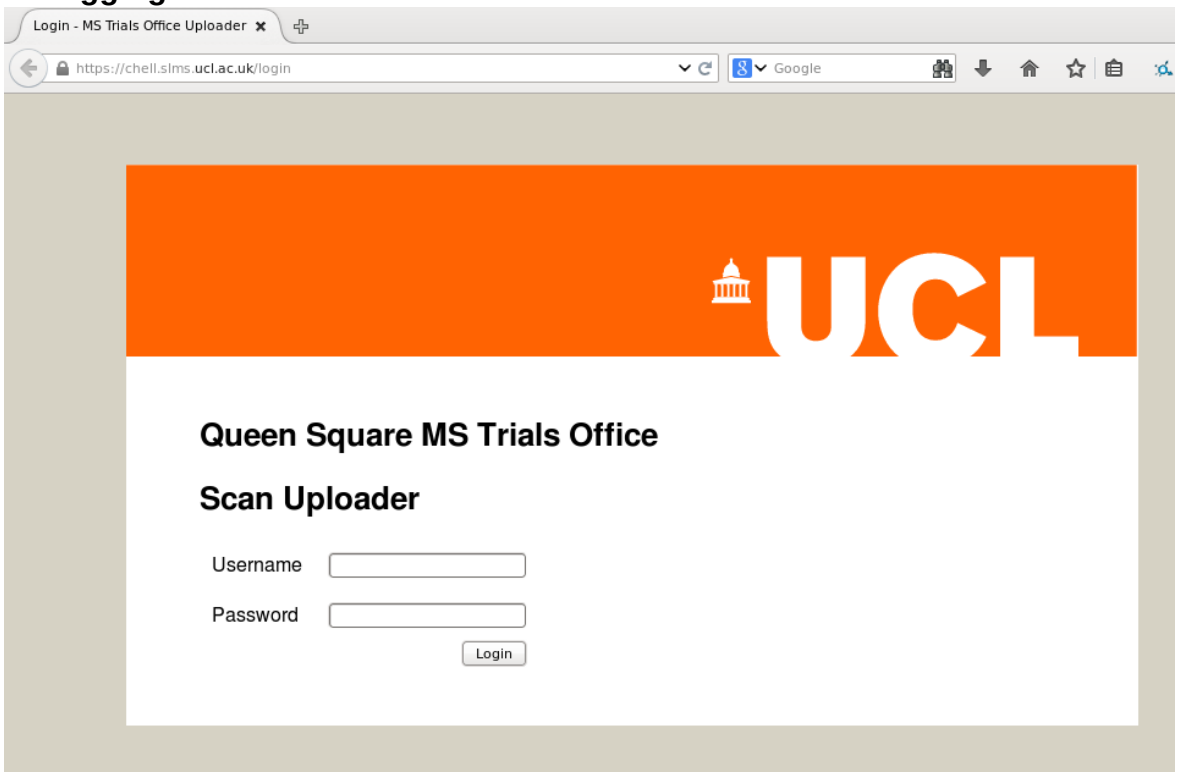


Figure 1: Login page

The URL for the web upload service is http://qsmscentre.org.uk. Most web browsers are compatible with the service but note that Internet Explorer 6 and 7 are *not* compatible.

On connecting you should make sure that you have a secure connection. Your web browser should show a lock symbol in the URL bar and the displayed web address should be https://chell.slms.ucl.ac.uk/login. If you're not sure that the connection is secure then you should **not** proceed as your login details and patient data may not be safe.

Once you have made sure you have a secure connection you should enter the username and password you have been provided with and click the login button.

2. Starting an upload

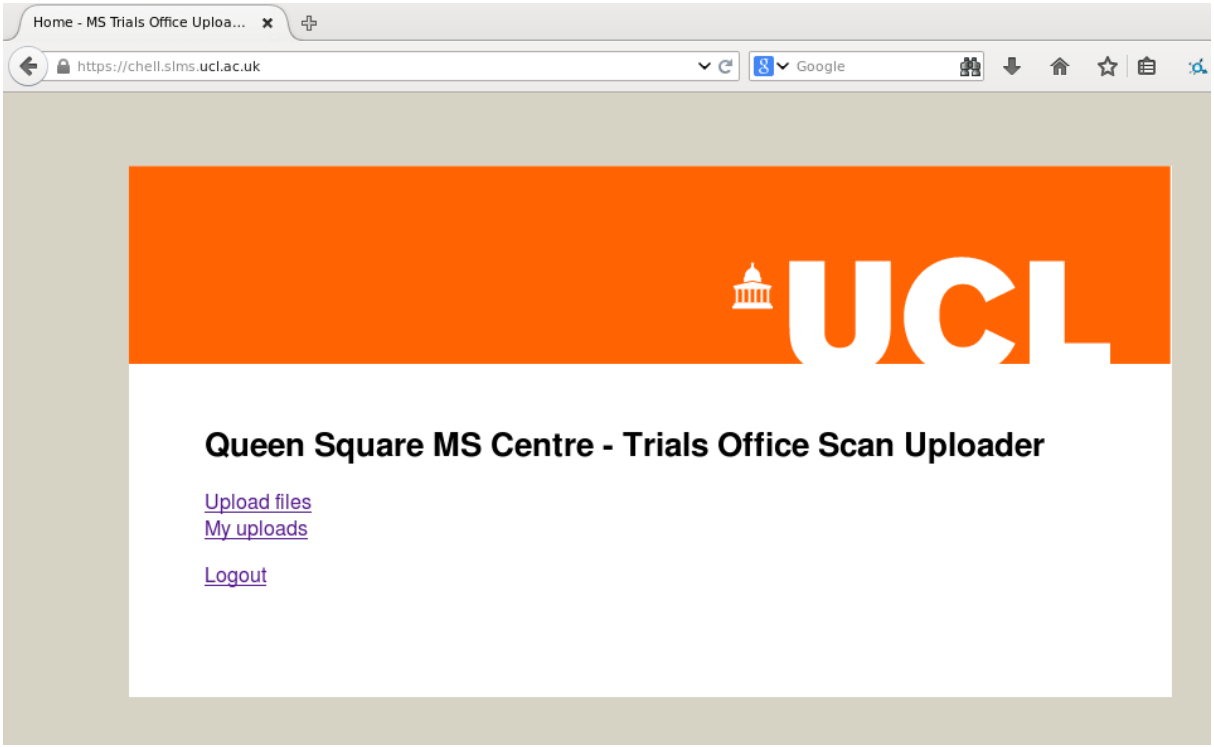


Figure 2: Home page

To begin the upload process click the 'Upload files' link.

3. Scan information

The next step is to enter information about which subject and timepoint you are uploading images for. The following fields must be filled in:

- Site
- Subject number
- Year of birth – ***enter 01/01/ [year of birth]****
- Scan date
- Visit

The comments field can be used for any other information that needs to be provided about the scan.

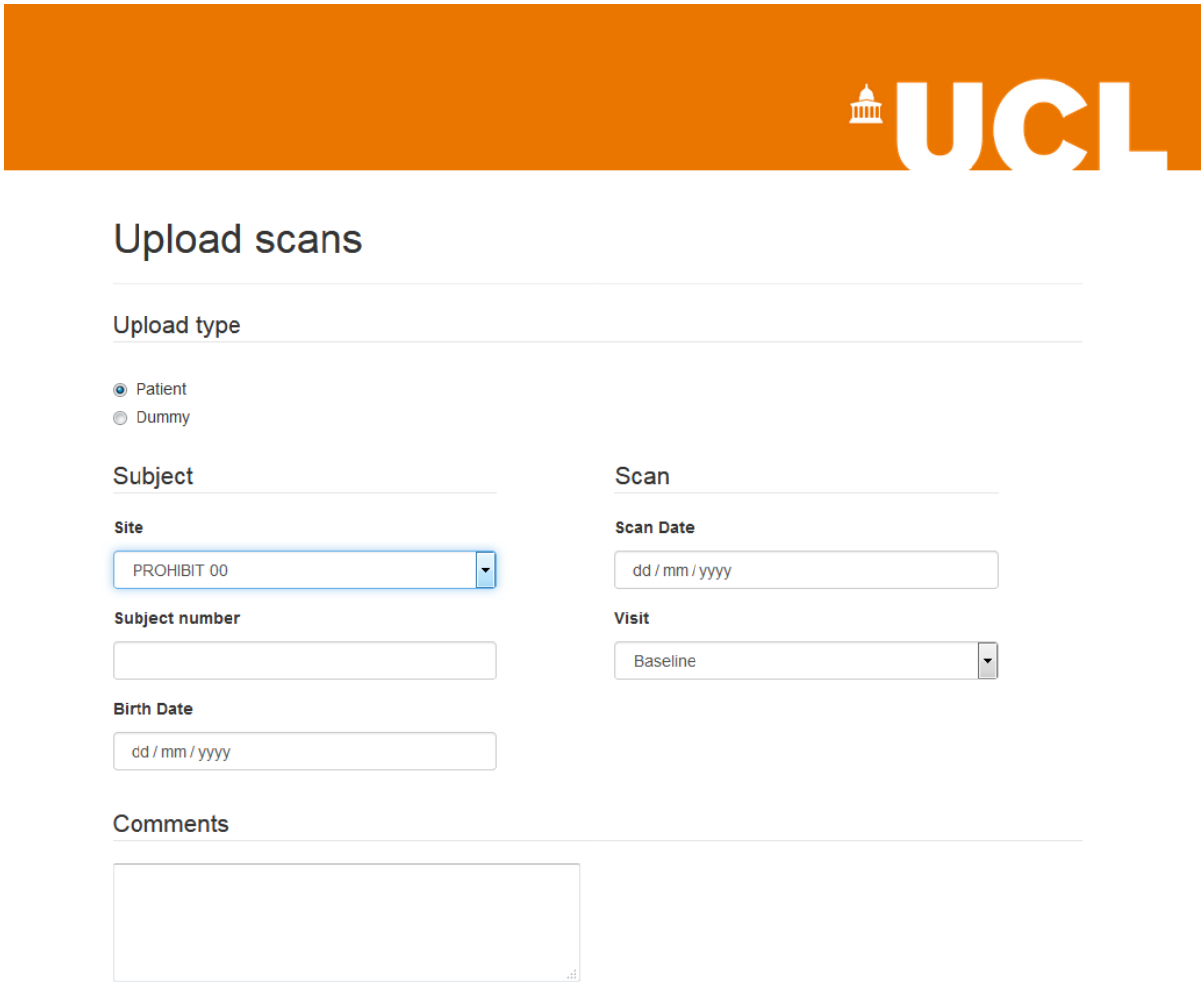


Figure 3: Prepare upload - patient scan

After completing the form please double-check the information you' ve entered and then scroll down and click the 'Select files' button.

4. Selecting files

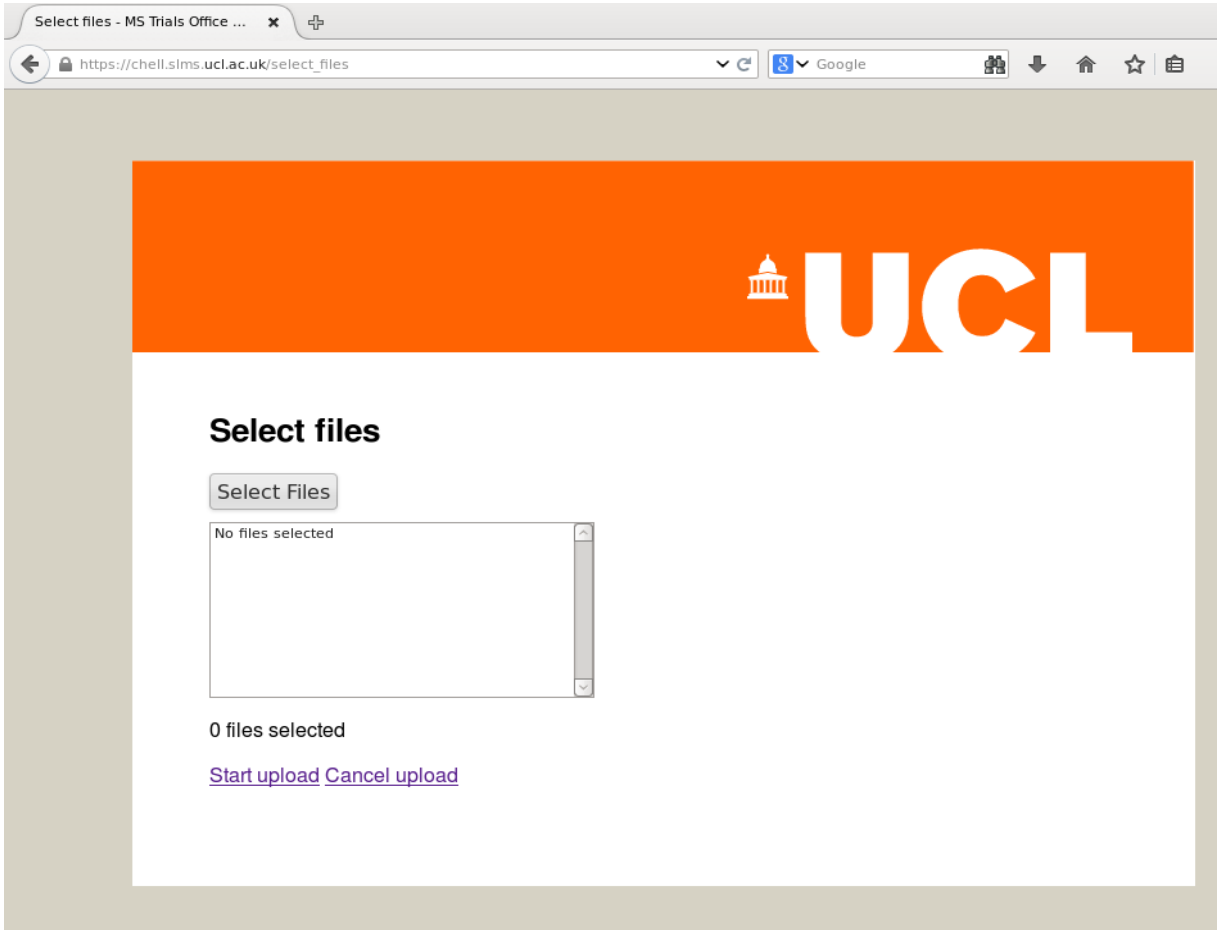


Figure 4: Select files

At this point you need to select the image files that you wish to upload.

We recommend compressing the DICOM image files into a zip format before sending the scans as this reduces the transfer time and assures that all the files are included.

To select files click the 'Select Files' button. Use the file selection window that appears to select your files - you can select multiple files at the same time. When you have selected the files to send, click the 'OK' button and check that the files are now listed in your web browser. Once the correct files are selected, click the 'Start upload' link. A progress bar will be displayed while the images are being transferred.

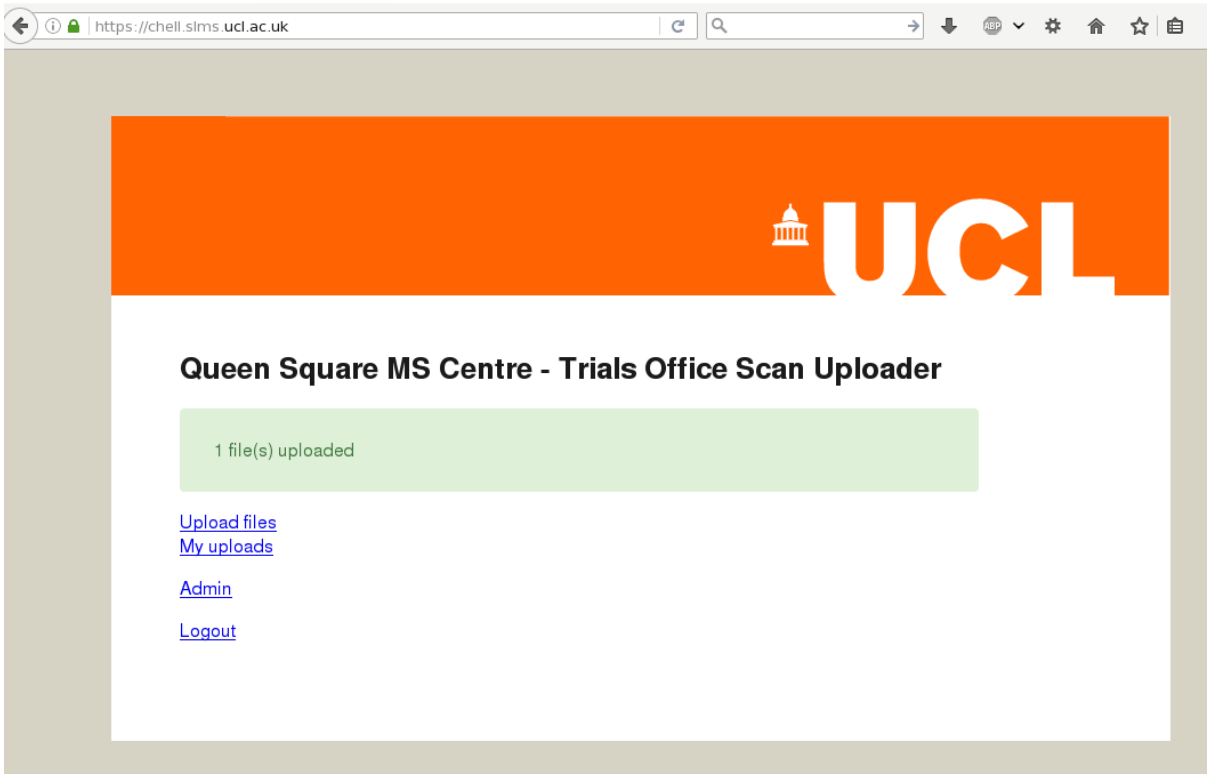


Figure 5: Transfer completed

When the transfer is complete you will be returned to the main page. You should see also a message saying the number of files that have been successfully upload.

After an upload you should use the 'My uploads' link to check that your transfer has been recorded.

Please email now your transmittal form to UCL (prohibit-ich@ucl.ac.uk). This would allow the imaging team to run a quality check on the scan promptly.

Example Transmittal form, including Quality Assurance feedback can be found in the appendix below.
This will be sent to you in a separate email also.

APPENDIX 1: TRANSMITTAL FORM

PROHIBIT-ICH TRANSMITTAL FORM

NOTIFICATION OF MRI SCANS SENT TO UCL

Email (prohibit-ich@ucl.ac.uk) this form to the PROHIBIT-ICH Trial Office

Senders name:	**Site number:**
MRI Centre name:	
Date sent:	**Sender's phone number/email address:**

Details of Scan sent

Subject number	Subject's Birth year (yyyy)	MRI Visit Baseline, month 12	Exam date (dd/mm/yyyy)

Comments:

For UCL MRI core lab use only:

PROHIBIT-ICH MRI QA FEEDBACK

Results of MRI QA Assessment

PASS ☐ Adequate image quality. **Scan has been accepted.** No repeat exam necessary

Results of MRI QA Assessment

FAIL ☐ Scan has been **rejected** - please see below for **instructions as to action required.**

Upon review of MRI data, the following Data Quality Issues were found:

	3D T1	3D FLAIR	DTI	3D SWI	Axial T2	ASL (opt)
Recall subject and rescan	☐	☐	☐	☐	☐	☐
Resend	☐	☐	☐	☐	☐	☐

Appendix 2.12

Process for changes to antihypertensive medications in the intervention arm of PROHIBIT-ICH

Date of Preparation: 12.07.2018	Date of next review:			
Prepared by: Iain McGurgan				
Signature: 	Date review takes place and initials			
Version number: 1				

STANDARD OPERATING PROCEDURE

SCOPE

This SOP applies to the process of initiating or changing antihypertensive medication in the intervention arm of the PROHIBIT-ICH trial.

Participants randomised to the intervention group will receive a telemetric Bluetooth home BP-monitoring device. It will facilitate the Oxford BP-monitoring team to closely monitor the participant's BP to keep to the target of <120/80 mm Hg. If this is not achieved then BP medication will be adjusted accordingly in order to achieve the target as soon as possible, and ideally by the 3 month follow-up visit.

The role of the Oxford BP-monitoring team is to use the detailed information about participants' BP to inform the patient about their BP, empower them with regard to their BP management and to provide recommendations to them and their GP about treatments to reduce their BP to the specified target.

PROCEDURE

P1 Decisions regarding BP treatment

Oxford BP-monitoring team

- All BP data will be automatically transmitted centrally in real time to the device coordination site in Oxford. A dedicated BP-monitoring research team will be responsible for checking all BP data daily.

- BP will be graphically presented, expressed in a “mean in last X days” and "% above target" form, among others, to inform treatment decisions.

- BP treatment decisions will be made on a per-patient basis, based on the latest British Hypertension Society guidelines, to ensure that BP is lowered to the intervention arm target.

- The following factors will be taken into account where thought to be significant to assess treatment decisions for clinical appropriateness:

    - Age of patient
    - Sex of patient
    - Ethnicity of patient
    - Severity of hypertension
    - Pregnant or breastfeeding
    - Relevant clinical condition
    - Patient medication record
    - Interactions with other drugs, foods, supplements or disease states
    - Dose and dose changes
    - Strength and strength changes
    - Formulation
    - Contra-indications
    - Previously-used agents, if relevant
    - Previous adverse effects

P2 Schedule of BP medication changes

Oxford BP-monitoring team

- For the treatment-naïve participant, first line treatment (in the absence of contraindications) will usually be either combination therapy with an ACE-inhibitor and thiazide-like diuretic, or a calcium channel blocker.

- Possible initial regimens, depending on local prescribing practices, will include perindopril arginine 5mg or perindopril erbumine 4mg and indapamide 2.5mg or indapamide MR 1.5mg per day, or amlodipine 5mg, increased to 10mg if needed.

- Subsequent treatment will be decided on a patient-specific basis, taking into account previous treatment trials and treatment responses, but will be likely to include the addition of spironolactone 25mg per day, doxasozin 4mg per day and nebivolol 2.5-5mg per day, alone or in combination.

P3 Communication and implementation of proposed BP medication changes

Oxford BP-monitoring team

- All recommended medication changes will be notified to the local research team and GP, with the GP providing prescriptions to participants based on correspondence from the Oxford BP-monitoring team.

- The Oxford BP-monitoring team will notify patients directly by phone should their BP be above target and of our proposed management plan.

- This management plan will incorporate general recommendations about starting particular medications or adjusting existing medications, and the rationale for those changes.

- Additional contact information from participants will be sought at randomisation including a mobile phone number, email address, and phone numbers and email addresses for the patient's nominated next of kin(s) in case they are not contactable by phone.

- The patient's GP will be contacted by letter, email and by phone (where possible, depending on the study site) by the Oxford BP-monitoring team to inform them of the proposed prescription changes, which will be recommended over and above standard BP care provided by the GP.

- The patient will also be advised to contact their GP practice to ensure such changes are made as soon as possible, so that they can collect an updated prescription. It is envisaged that such prescription changes should be made and collected by the patient within a week.

- The local study centre will also be informed of all such treatment recommendations.

Local study centre

- The local study centre may wish to directly initiate additional contact with the GP to help ensure these recommended changes are made; this is encouraged if it is a possibility.

- In some cases, if challenges are encountered in reaching the patient's GP to recommend treatment changes, then the local study centre may and would be encouraged to issue the prescription for the recommended treatment

should it have the ability to do this, and the GP has agreed in advance for changes to be made directly.

General Practitioner

- Prescriptions will be issued by the patient's GP based on communication from the Oxford BP-monitoring team, in the majorty of cases, according to local prescribing guidelines / practices.

- The responsibility for BP management will return to the GP after 3 months of follow-up.

- Participants will also be asked to record a weekly BP reading on a sheet which will be returned with the monitor at the end of the 12 month follow-up period.

Appendix 2.13

PLEASE NOTE

For your safety, the blood pressure machine should not be switched on whilst driving.

During the 24 hours: you should not do any vigorous sport or use machinery
you are asked not to shower or bath

The recorder is programmed to take your blood pressure automatically half-hourly during the day and hourly at night (2300-0700). Once switched on you do not need to do anything else to it.

You should be seated and remain QUIET and STILL while the recorder is taking your blood pressure and avoid any sudden movement.

When the recorder starts to take a measurement SIT DOWN if possible. Rest the arm with the cuff on it on the chair arm or table, with the hand relaxed and the palm facing upwards. If you cannot sit down, rest your arm on your midriff until you feel the cuff deflate.

The measurement process may take 20-30 seconds. Do not worry if the cuff inflates again – this is perfectly normal.

When the machine is switched off only the current time is displayed
To switch the machine on press and hold the black button marked AUTO ON/OFF
A small A will appear in the top left hand corner
The machine will now automatically take your blood pressure

To switch the machine off press and hold the black button marked AUTO ON/OFF. The small A will then disappear.

Please switch the machine off after you have completed the 24 hours and remove the cuff.

If a 'B' is displayed on the screen this indicates the batteries are low. In the unlikely event of this happening, or if there are any other problems, please contact us. In an emergency the machine can be switched off and the cuff removed.

Have a normal day. Do not spend the day relaxing!

PROHIBIT-ICH
Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

Stroke association | NHS | University of Oxford | UCL Stroke Research Centre | UCL

Patient Details and Diary

Visit: Baseline ☐ **3 month** ☐ **12 month** ☐

Monitor Number:

Date recording commenced:

Test reading (mmHg):

Full name:

Study ID: **Site:**

The following questions will be useful in the analysis of your recording:

Today were you at work? ☐ at home? ☐

What sort of day did you have?

Average ☐ Unusually quiet ☐ Unusually busy ☐ Unusually stressful ☐

How well did you sleep?

What time did you go to bed? What time did you get up?

Were you awake during the night?

Appendix 2.14

BLOOD PRESSURE MONITORING

Now that you have completed the intensive phase of blood pressure monitoring (daily readings and 24-hour monitor) we would like to make sure that your blood pressure remains well controlled. We would like you to use the blood pressure monitor **once a week** (3 consecutive readings at one sitting please) and record it on the chart. You can choose which day of the week you do it. **Please take your readings shortly after breakfast.** We would be grateful if you could try to take your readings at a similar time each week.

For the best results, please try to:

- rest for a couple of minutes before and between each reading
- sit quietly and still, with your arm supported and your legs uncrossed
- ensure that the cuff is on properly (high up your arm, tight enough, over bare skin, wearing loose clothing, with the tube going down the inside of your arm) and well connected to the blood pressure monitor (not loose or obstructed)
- place the blood pressure monitor on a level surface e.g. a table.

Week	Date	Day of Week	Reading 1		Reading 2		Reading 3		Comments
			Top Number (Systolic)	2nd number (Diastolic)	Top Number (Systolic)	2nd number (Diastolic)	Top Number (Systolic)	2nd number (Diastolic)	
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									

PROHIBIT-ICH ID: Date collected/received:
Name: Arm used Left / Right:

Week	Date	Day of Week	Reading 1		Reading 2		Reading 3		Comments
			Top Number (Systolic)	2nd number (Diastolic)	Top Number (Systolic)	2nd number (Diastolic)	Top Number (Systolic)	2nd number (Diastolic)	
19									
20									
21									
22									
23									
24									
25									
26									
27									
28									
29									
30									
31									
32									
33									
34									
35									
36									
37									
38									
39									
40									
41									
42									
43									
44									
45									

Please note the bottom number on the blood pressure monitor screen is your pulse, and this does not need to be recorded.

PROHIBIT-ICH ID:
Name:

Date collected/received:
Arm used Left / Right:

<Patient title> <Patient forename> <Patient surname>
<Patient address 1>
<Patient address 2>
<Patient city>
<Patient post code>

<date>

Dear <Patient title> <Patient surname>,

Invitation to an outpatient appointment to discuss a research study

Our hospital [hospital name] is taking part in a research study called PROHIBIT-ICH. We want to assess the feasibility, safety and effectiveness of intensive Blood Pressure (BP) treatment compared to standard care. Our records indicate that you may be eligible for this as you are over the age of 30 and have had a brain haemorrhage. Further details are available in the summary attached and also in the enclosed Patient Information Sheet. We would like to invite you to consider taking part in this study.

We have enclosed a short form for you to complete to respond to this letter. If you are interested in hearing more about the PROHIBIT-ICH study, we will arrange an outpatient appointment to review your health and treatment and to discuss whether you could participate. We will provide you with more information at the appointment.

Please let us know if you are interested, or not, by following the instructions attached by email, telephone or post.

Yours sincerely,

Signature of PI

[Hospital site address]

[Hospital site Telephone number]

Background to research	• About 1 in 10 strokes are due to a bleed into the brain from a ruptured (burst) artery, called intracerebral haemorrhage (ICH). • In some cases, ICH is caused by injury or surgery, in others it happens suddenly without warning ("spontaneous"). • Spontaneous ICH is sometimes the result of high blood pressure (BP) which, over time, causes damage to the small blood vessels supplying the brain, making them more likely to rupture. • The main cause of spontaneous ICH is called "small vessel disease" (SVD), which may be related to poor BP control. • BP lowering is the most promising preventive strategy, but adherence and BP control in clinical practice remain poor. • There is an urgent need to improve ICH secondary prevention through improved long term BP control
Aims of the research	• The trial will investigate whether intensive lowering of blood pressure (BP) using telemetric home monitoring in survivors of intracerebral haemorrhage (ICH) is feasible, safe and effective in reducing brain injury. • If successful we hope this study will be a precursor for a larger trial. • Telemetric home monitoring is a promising strategy to facilitate home BP monitoring after stroke, which should improve adherence and optimize medication to better control BP. • Telemetry allows patients with hypertension to monitor their own BP and automatically send the information to a secure website, available to

	their clinicians to monitor and adjust their treatment. • The intervention should allow survivors of ICH to know, understand, and manage their own BP to prevent strokes and cognitive impairment, and improve outcomes.
Design and methods used	• Eligible patients will be identified by the research practitioner or member of research/ clinical teams, from acute stroke units or high dependency units at participating hospitals, outpatient clinics (stroke, neurology, geriatric, neurosurgical), primary care centres and from site databases • Staff will provide the patient, their legal representative, or their nearest relative with information leaflets about this trial • After consent is given, trial staff will take some details from the participants and carry out some tests, BP test and where possible an MRI scan • Participants will be randomly allocated to either intensive BP treatment guided by telemetric home monitoring or standard care in adult ICH survivors • We will follow-up these two groups of participants to assess whether BP lowering using this home monitoring is feasible, safe and effective in reducing brain injury. • There will be 2 follow ups: one at 3 months and one at 12 months • A sample of blood will also be collected to find out if there are any genetic variations associated with ICH or SVD.
Participants	• Participants invited will be over the age of 30 and have had a spontaneous ICH, most likely due to SVD, confirmed on a brain scan

Dissemination	• The results of the study will be reported to the funder of the study and published in scientific journals. Following completion and publication, these results will be posted on a study website for participants to view.

Please reply to this invitation, using one of the methods below:



Email us at ****@***

Or



Telephone us on: ***** ******

Or



Provide your details below, tick the relevant box, and return this slip in the enclosed envelope.

Print your name	
Date of birth	
Your address, including post code	
Phone number (and best time to call)	

Tick one box:

☐ **I would like to know more about PROHIBIT-ICH.** Please contact me.

I realise that this is not a commitment to taking part in the study.

☐ **I do not wish to be considered for PROHIBIT-ICH**. We will assume that you do not want to take part in the study and we will make no further contact if we do not hear from you. However, you are still welcome to tick the 'No' box above and provide feedback if you wish.

Appendix 2.16

PROHIBIT-ICH COVID-19 Contingency Plan

Version: 1.0 Date: 08/04/2020

Approved by: Professor David Werring, Professor Peter Rothwell

Purpose: This document provides guidance to all PROHIBIT-ICH research sites about how to manage trial-specific research activities during the COVID-19 pandemic.

Recruitment of new participants: <u>suspended until further notice</u>

- Please keep a screening log of potentially eligible patients for later recruitment.
- Once UK Government restrictions are lifted and there are MRI scanning facilities available for the baseline visit, recruitment can recommence.

3-month follow-up (Visit 2): <u>to be performed remotely by each site</u>

- 24-hour ABPM should still be performed by each participant; fitting can be performed by the participant or carer by following the video instructions on the PROHIBIT-ICH website www.prohibit-ich.org.uk and with telephone or video call guidance (if the participant has facilities available) from the Oxford BP Monitoring Team.
- Participants should continue to use pre-paid envelopes to return the 24-hour ABPM equipment to the Oxford team. This may require individual solutions for individual participants; please contact the Oxford team by email for guidance in advance. If participants show signs of fever or cough/shortness of breath, please instruct them to place the equipment into two bags prior to sending in the pre-paid envelope.
- Cognitive assessment is to be performed using a 22-point Telephone-MoCA (i.e. the MoCA items not requiring the use of a pencil and paper and/or visual stimulus).

12-month follow-up (Visit 3): <u>postponed</u>

- The 12-month follow-up visit should be performed as close as possible to the scheduled date, once restrictions are lifted. The MRI scan and 24-hour ABPM should happen on the same date, with the e-CRF completed at that time.

Participant Safety

- Please continue to report SAE's as outlined in the protocol.
- Where capacity issues may prevent timely reporting of SAE's, they should be reported as soon as possible after the issue is resolved and the delay recorded as a protocol deviation.

Relevant Guidance

- Guidance about COVID-19 for sponsors, sites and researchers has been provided by the HRA. Section 3.2 is relevant to sites: <u>https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/</u>

Appendix 2.17

PROHIBIT-ICH Trial Management Group's proposal to continue the study taking into account The Stroke Association's recommendations from Thursday 12th November

Tuesday 17th November

Baseline Visits:

- The recruitment of a new PROHIBIT-ICH participant should not be delayed if a site is unable to obtain an MRI scan; in this case they should be recruited with a routine clinical acute CT scan. We will explore methods of measuring small vessel disease markers on CT scans instead of MRI.

- We will also request all routine clinical MRI scans (within 6 months of randomisation) as these can also be used to measure the key markers of cerebral small vessel disease

12 month follow up visits:

- We would like to include the option for new participants to have a CT or MRI scan at the 12 month follow up visit, depending on the imaging modality provided at baseline (CT or MRI).

Target of 60 participants for the MRI study:

Where possible we would like to give sites the opportunity to obtain research MRI scans (which follow the PROHIBIT-ICH Imaging Manual protocol) from new participants at baseline, until we reach a target of 60 participants with MRI. We aim to fund these additional 17 sets of MRI scans (total ~£8500) using Oxford and UCL internal funds. We anticipate that this sample size will still be useful to see if we can detect changes in small vessel disease markers over time.

Delayed 12 month follow up visits:

- We would like to continue postponing the 12 month follow up visit until sites can obtain MRI scans i.e. we would prefer that the 12 month follow up BP data is not collected before the MRI scan but rather that both BP monitoring and the MRI scan are collected on the same visit date.

- We are happy for the MRI scans from the 12 month follow up visits to be delayed by up to approximately 2 years i.e. these can happen up to approximately 24 months from the baseline visit. Longer follow-up will not compromise the aims of the study (and might help detect MRI changes)

Set-up of new sites:

- We would like to recruit new sites (aiming for up to 8 new sites to bring the total to 20 sites) that would recruit with CT only. However, we need to clarify what the capacity of the BP equipment is if many more participants are recruited than expected.

PROHIBIT-ICH
Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

Paper 1

PROHIBIT-ICH Steering Committee Progress Report

Contents

1. Progress and study update
2. Summary of site start-up progress
3. Strategies to increase recruitment
4. Study timelines
5. Budget

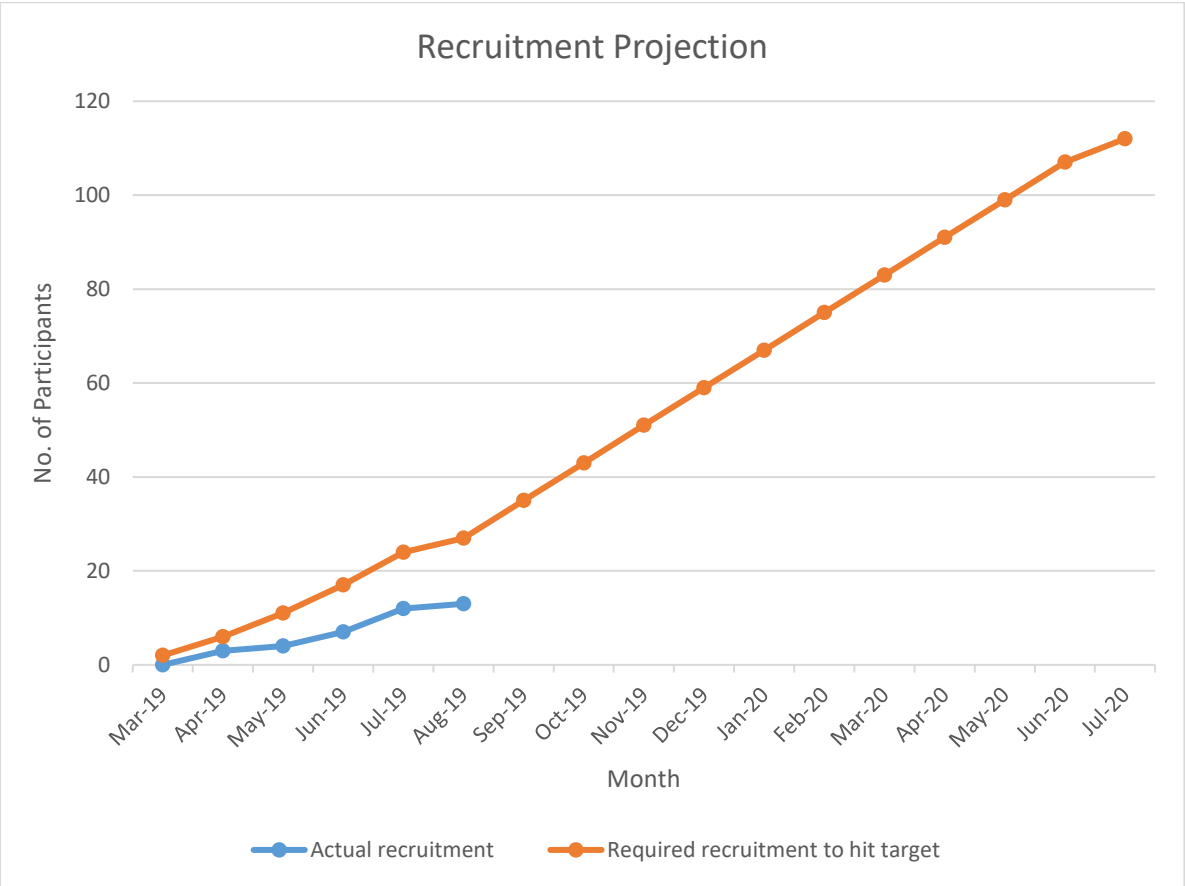
1. Progress and study update

Table 1: Recruitment summary

Date recruitment started	11th March 2019
Planned recruitment end date	September 2020
Target recruitment	112
Number of participants recruited	13

a). Recruitment Projection

Figure 1: Recruitment projection graph



b). Site league table

Table 2: Site Recruitment league table

Sites	Recruitment number	Number of months site open	Recruitment rate per month
University College Hospital, London	**4**	**5**	**0.8**
Charing Cross Hospital, London	**2**	**5**	**0.4**
St George's Hospital, London	**1**	**5**	**0.2**
John Radcliffe Hospital, Oxford	**1**	**5**	**0.2**
Queen Elizabeth University Hospital, Glasgow	**1**	**5**	**0.2**
Sheffield Teaching Hospitals NHS Foundation Trust	**1**	**5**	**0.2**
Royal Infirmary of Edinburgh	**1**	**5**	**0.2**
Salford Royal Hospital, Manchester	**1**	**5**	**0.2**
Nottingham University Hospitals NHS Trust	**1**	**4**	**0.3**
Royal Preston Hospital	**0**	**5**	**0**
Addenbrookes Hospital, Cambridge	**0**	**5**	**0**
Kings College Hospital, London	**0**	**2**	**0**
Total:	**13**		**Mean=0.2**

Target: if study end date is September 2020 = 0.7 patients per month

Or if study end date is November 2020 = 0.6 patients per month

2. Summary of site start-up progress

Table 3: Site initiation start-up

Site	PI	Status	SIV	Site R&D approval	Green light
University College Hospital, London	Professor David Werring	Active	24/07/2018	15/10/2018	11/03/2019
John Radcliffe Hospital, Oxford	Professor Peter Rothwell	Active	24/07/2018	09/11/2018	11/03/2019
Charing Cross Hospital, London	Dr Soma Banerjee	Active	24/07/2018	18/03/2019	18/03/2019
Royal Infirmary of Edinburgh	Professor Rustam Al-Shahi Salman	Active	18/09/2018	28/11/2018	11/03/2019
Salford Royal Hospital, Manchester	Dr Adrian Parry-Jones	Active	10/09/2018	15/10/2018	11/03/2019
Royal Preston Hospital	Prof Hedley Emsley	Active	24/09/2018	20/03/2019	20/03/2019
Kings College Hospital, London	Dr Laszlo Sztriha	Active	25/07/2018	13/06/2019	13/06/2019
Addenbrookes Hospital, Cambridge	Dr Michele Pellizzaro Venti	Active	07/08/2018	19/10/2018	11/03/2019
Nottingham University Hospitals NHS Trust	Dr Kailash Krishnan	Active	24/07/2018	12/04/2019	12/04/2019
Queen Elizabeth University Hospital, Glasgow	Dr Keith Muir	Active	25/09/2018	15/03/2019	18/03/2019
St George's Hospital, London	Dr Liqun Zhang	Active	25/09/2018	09/11/2018	11/03/2019
Sheffield Teaching Hospitals NHS Foundation Trust	Dr Kirsty Harkness	Active	14/09/2018	17/10/2018	11/03/2019

3. Strategies to increase recruitment

a). Teleconference with Principle Investigators at each site:

Table 4: Teleconference calls with PI schedule

Site	Teleconference Date
Royal Preston Hospital	01/07/2019
Addenbrookes Hospital, Cambridge	15/07/2019
Nottingham University Hospitals NHS Trust	17/07/2019
Sheffield Teaching Hospitals NHS Foundation Trust	23/07/2019

Remaining sites have been scheduled for a teleconference this month and next. Outcome from teleconferences so far - factors limiting recruitment (see paper 2): the main themes are summarised below:

i. Low BP
ii. More than 3 BP drugs
iii. Discharged to rehab unit or nursing care
iv. Too unwell to recruit
v. Patient's discharged/referred out of area and cannot follow-up
vi. Elderly patients, trouble using technology

Reminders:

i. There is no time limit to recruit after ICH, allowing the use of follow-up clinics and databases
ii. We can co-enrol with SoStart (trial run by Professor Rustam Al-Shahi Salman (RASS)
iii. RASS has given permission to recruit the patient that were enrolled in the RESTART trial

b). Regulatory update / amendments to improve recruitment

Table 5: List of amendments

Substantial Amendment 1	Date approved
1. Removal of inclusion criteria number 4 from protocol: 'For patients recruited in hospital there should be a plan for home discharge (not to a nursing or care home) after their inpatient stay, or living at home at the time of recruitment' 2. Patients can also be identified from site databases.	Pending

3. We will provide posters which gives information on the study, to be displayed at participating sites (see appendix). 4. Patient Identification Centre (PIC) sites will be included in the study. These sites will be NHS sites; the staff at these sites will identify potential patients and inform the study team at local PROHIBIT-ICH recruiting sites.	

For discussion: how to optimise PIC/additional sites:

Question 1: Could additional sites recruit and carry out scans at existing sites?

Question 2: Should the timing of imaging be changed to after randomisation?

4. Study timelines

a) Timelines

Original timeline was to start in 2015 when the funding was granted in July 2015, due to administrative delays to post for the study co-ordinator position, the study co-ordinator started in February 2017. We expected the set-up of the study to take at least 6-12 months, allowing 1 year for recruitment (2018) and 1 year for follow-up (2019) and expected end date was March 2020. Due to unforeseen circumstances the study was delayed and a revised timeline was planned.

Revised timeline (due to various delays in post approvals, CRF finalisation, etc.) was recruitment over 1 year (starting March 2019, ending March 2020) – 112 patients at 12 sites = **0.8 patients per site per month.**

The rate for recruitment per month has varied across sites from **0 to 0.8 patients per month**. Recruitment to date for the whole study (assuming all 12 sites opened in March 2019) has been at a rate of approximately **0.2 patients per site per month**.

b) Current timelines required to meet recruitment target:

We applied for a no cost extension until December 2021, and this was approved. Current recruitment is 13, leaving 99 patients to recruit.

The current end date of PROHIBIT-ICH is 31st December 2021, allowing follow-up to be completed by September 2021 and 3 months for study close-out.

Unfortunately, recruitment is currently slowly progressing but we hope to finish recruitment by September 2020 (a 1 year period). With this end date we would need to recruit **0.7 patients per site per site per month**.

If we extend recruitment to November 2020 this would give a required recruitment rate of **0.6 patients per site per month**.

5. Budget

So far with some reallocation of budget categories, we have sufficient funding to cover the UCL study co-ordinator salary until August 2021; we will seek alternative sources of funding to December 2021 in due course. All other costs for the Oxford site are covered until December 2021.

APPENDIX: Posters

NIHR | National Institute for Health Research

PROHIBIT-ICH

Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

HAVE YOU SEEN A PATIENT WITH SPONTANEOUS INTRACEREBRAL HAEMORRHAGE (ICH)?

If so they might be eligible to take part in our study



We are doing a research study to determine whether frequent **home telemetric monitoring** of blood pressure can be used to safely guide medication changes to **intensively lower blood pressure** to reduce damage to the cerebral small blood vessels after spontaneous ICH

The key inclusion criteria are:

- Over the age of 40
- Blood Pressure: ≥130 mm Hg
- Taking less than 3 BP lowering medications
- presumed to have cerebral small vessel disease (hypertensive arteriopathy or cerebral amyloid angiopathy, or both)

If you see a patient who might be eligible please speak to your research team!

Research team contact name:

Research team contact telephone number

NIHR | National Institute for Health Research

PROHIBIT-ICH

Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

ARE YOU OVER THE AGE OF 40 WITH A HISTORY OF A BRAIN HAEMORRHAGE?

If so you might be eligible to take part in our study



We are doing a research study to determine whether frequent **home telemetric monitoring** of blood pressure can be used to safely guide medication changes to **intensively lower blood pressure** to reduce damage to small brain blood vessels after spontaneous brain haemorrhage

The main procedures in the trial are as follows:

- Questionnaires at the beginning of the study, at 3 months and 1 year
- A blood sample collected upon entering the study
- An MRI scan upon entering the study and at 1 year follow up
- You would be assigned to usual care or receive a telemetric blood pressure monitor to measure BP 3 times daily, and accordingly receive adjusted BP treatment to a target of 120mmHg systolic
- A 24-hour blood pressure monitoring at the beginning of the study, 3 months and 1 year

If you would like more information about taking part in the PROHIBIT-ICH study, please contact our research team

Research team contact name:

Research team contact telephone number:

Paper 2

PROHIBIT-ICH Eligibility Screening Report

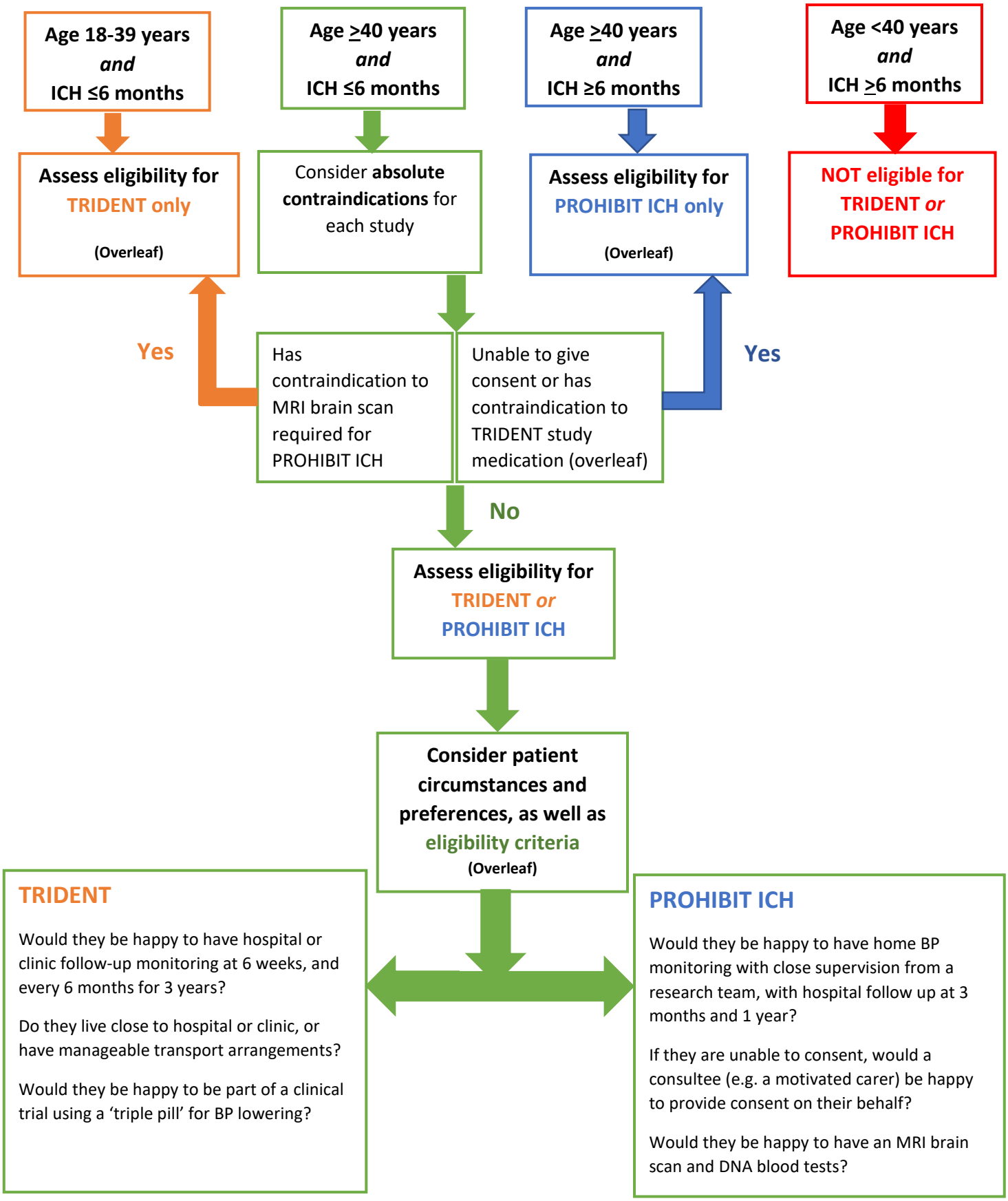
Table 1: Screening numbers from PROHIBIT-ICH sites

Site	No. of patients screened	No. of eligible patients	Why not eligible following screening?	Final no. approached	No. agreed	Reasons unable to recruit to study
UCLH	1153	29	- Not had ICH - Patients have died - mRS > 4 - Patient has dementia - Under age limit	11	4	- BP consistently <130mmHg - Patient taking ≥3 antihypertensive agents. - Not approached all eligible patients
Imperial	753	25	- Not had ICH - Bleed post thrombolysis - Patients have died - Patients have been repatriated - cavernous/ aneurysm - mRS > 4 - Patient has dementia - Under age limit -Low GCS	12	2	- Unable to speak English - BP consistently <130mmHg - Patient taking ≥3 antihypertensive agents. - Patient overseas, unable to follow-up
St George's	1150	26	- Not had ICH - Patients have died - Patients have been repatriated - mRS > 4: palliative care - Patients have dementia - Under age limit	5	2	- Unable to speak English - BP consistently <130mmHg - Patient taking ≥3 BP drugs - Declined: not interested - some not yet approached
King's	357	21	- Not had ICH - mRS of 5 before ICH - cannot have MRI due to aneurysm clips – mRS 4 before ICH - Palliative care: mRS6	4	1	- taking > 2 anti-hypertensive meds - refused: prefers natural remedies and would not comply with taking anti-hypertensive medication
Sheffield	127	24	- Not had ICH - Too sick with poor survival	5	1	- Non English speakers - Older patients are put off by technology aspect of the study - Not approached eligible patients yet

Nottingham	30 ICH	5	- Too Unwell - Below age requirement - discharged to rehab unit or nursing care	5	1	- Not interested - Low BP
Addenbrookes (Cambridge)	43 ICH	10	- Patients have died - Patients have been repatriated (discharged out of area) - Have co-morbid conditions	10	0	- Low BP - More than 3 BP drugs - Discharged to nursing care home or Rehab unit
Royal Preston	22 ICH	12	- Patients have dementia - Patients have died - Below age limit	12	0	- Controlled BP - More than 3 BP drugs - Discharged to nursing care home or Rehab unit
Edinburgh	20 ICH	8	- Died in hospital - Too unwell - Have a guarded prognosis	8	1	- Have systolic BP levels <130 mmHg - Taking 4 agents for BP control already - Has a history of alcohol excess and ongoing behavioural issues on the ward - Russian speaker (no English) who has bilateral carotid disease - Declined as they was not interested
Glasgow	15 ICH	12	- Essential thrombocytopenia - Complex medical history - Cognitive impairment	12	1	- Non-English speaking - Recruitment to competing trial (1-TRIDENT) - Patient declined - Systolic blood pressure <130mmhg
Oxford	36 ICH	12	- Re-bleed of AVM - Palliative - Severe Dementia - Haemorrhagic transformation - Died - Seizures in the context of CAA - mRS too high - Too frail	12	1	- Nursing Home Pathway - Low BP - Declining to take part in research - Side effect to BP medication -Pacemaker in situ

			- Too young			
Salford, Manchester	93 ICH	25	- Patients have died - Patients have been repatriated -Too young - Not suitable for follow-ups	5	1	- BP consistently <130mmHg - Patient taking ≥3 BP drugs - Declined: not interested - Recruited into TRIDENT

Paper 3 ELIGIBILITY: TRIDENT Vs PROHIBIT-ICH



TRIDENT

Would they be happy to have hospital or clinic follow-up monitoring at 6 weeks, and every 6 months for 3 years?

Do they live close to hospital or clinic, or have manageable transport arrangements?

Would they be happy to be part of a clinical trial using a 'triple pill' for BP lowering?

PROHIBIT ICH

Would they be happy to have home BP monitoring with close supervision from a research team, with hospital follow up at 3 months and 1 year?

If they are unable to consent, would a consultee (e.g. a motivated carer) be happy to provide consent on their behalf?

Would they be happy to have an MRI brain scan and DNA blood tests?

Paper 3 ELIGIBILITY: TRIDENT Vs PROHIBIT-ICH

TRIDENT

Inclusion Criteria:

- **Adults (≥18 years)** with a history of **up to 6 months after symptom onset of primary ICH** confirmed by brain imaging
- Clinically stable, as judged by investigator
- Two resting SBP levels, measured 5 minutes apart in the range **130-160mmHg** recorded in a seated position
- Geographical **proximity** to the recruiting hospital and/or follow-up medical clinic site to allow ready access for in-person clinic visits during follow-up
- No major contraindication to any of the study treatments
- Provision of **written informed consent**

Exclusion Criteria:

- **Taking an ACE-I that cannot be switched** to:
  - telmisartan 20 or 40mg, amlodipine 2.5 *or* 5mg, indapamide 1.25 or 2.5mg, *or* an equivalent class (ARB, CCB or thiazide-like diuretic), *or* a beta-blocker
- **Taking more than half dose of any study medications:**
  - telmisartan > 40mg
  - amlodipine > 5mg
  - indapamide > 1.25mg
- **Contraindication to any of the study medications**, in the context of currently prescribed BP lowering medication
- Unable to complete the study procedures and/or follow-up
- Females of child bearing age and capability, who are pregnant or breast-feeding, or those not using adequate birth control
- Significant hyperkalaemia and/or hyponatremia, in the opinion of the responsible physician
- Estimated glomerular filtration rate <30 mL/min
- Severe hepatic impairment (ALT or AST >3x the upper limit of normal)
- Any other conditions that in the opinion of the responsible physician or investigator that renders the patient unsuitable for the study (e.g. severe disability [i.e. smRS of 4-5] or significant memory or behavioural disorder)

PROHIBIT ICH

Inclusion Criteria:

- **Adults (≥40 years) with spontaneous primary ICH** including participants presumed to have cerebral small vessel disease (both hypertensive arteriopathy and cerebral amyloid angiopathy)
- **SBP 130-160 mm Hg** at the time of randomisation
- For patients recruited in hospital there should be a plan for home discharge (not to a nursing or care home)
- Able and willing to demonstrate the ability to **undertake home BP measurements**, either unassisted or with the help of a relative, friend or carer
- Able and **willing to complete an MRI scan**
- Able and willing to attend and complete study assessments including cognitive screen
- Able and willing to provide **informed consent**, and able to participate in the intervention (with suitable consultee and/or motivated carer if required)

Exclusion Criteria:

- Inability to provide informed consent or lack of suitable consultee
- Evidence of a macrovascular or structural cause for ICH (e.g. AVM or tumour)
- Diagnosis of dementia (DSM IV criteria, or self-reported or documented in medical records)
- Low Functional status (MRS ≥4) before or after ICH or frailty likely to make participation in 1 year follow-up difficult for the participant
- Life expectancy <2 years
- Taking more than 2 BP-lowering medications at entry
- Consistently good BP control (below target of 130/80 mm Hg) prior to planned recruitment, judged not to require more intensive treatment
- Known sensitivity or contra-indication to BP treatments (e.g. symptomatic postural hypotension)
- Known flow-restricting intracranial/extracranial large arterial stenosis
- **Known contraindication to MRI**
- Known absence of mobile phone coverage from all network operators and home internet at the participant's home
- Participation in other CTIMP or device trial

Flow Chart provided by: Professor Rustam Al-Shahi Salman

Professor of clinical neurology, University of Edinburgh

Paper 3 ELIGIBILITY: TRIDENT Vs PROHIBIT-ICH

TRIDENT Enrolment figures:

UK sites have enrolled 26 participants at 9 sites:

Site no.	Site Name	No. Enrolled
44041	RIE *	5
44044	Vic, Fife	5
44050	Stoke	5
44051	Morriston	3
44042	Nottingham *	2
44045	RDE	2
44053	Salford *	2
44046	QE Glasgow *	1
44052	Royal Hallamshire	1
44043	Calderdale	0

*** = PROHIBIT-ICH sites**

Figures provided by:

Ruth Freed
Senior Project Manager, Academic Project Operations

Paper 3 ELIGIBILITY: TRIDENT Vs PROHIBIT-ICH

Paper 4

PROHIBIT-ICH Imaging Report

Contents

1. **Quality Assurance imaging check process**
2. **Imaging Upload and Storage**

1. Quality Assurance (QA) imaging check process

Table 1: List of sites that have recruited and scans sent

Site	Scan no.	Scans Received?	QA check 1 (SB)						QA check 2 (DT)					
			3D T1	3D FLAIR	DTI	3D SWI	Axial T2	ASL	3D T1	3D FLAIR	DTI	3D SWI	Axial T2	ASL
UCLH	1	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	2	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	3	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	4	No												
Imperial	1	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	2	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
St George's	1	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Oxford	1	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glasgow	1	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sheffield	1	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Edinburgh	1	No												
Salford, Manchester	1	No												
Nottingham	1	No												

✓ = QA Pass

✘ = QA Fail

2. Imaging Upload and Storage

Scans from sites are sent to the Central Reading Facility at UCL by direct image transfer from your scanner or workstation/PC.

URL: http://qsmscentre.org.uk

We recommend you use web browser: Chrome, Firefox or Microsoft Edge Internet Explorer is NOT compatible! (As mentioned in the PROHBIT-ICH imaging manual)

Table 2: MRI Scan upload and storage

Site	Scan No.	Upload problems?	Stored?
UCLH	1	No	UCL server
	2	No	UCL server
	3	No	UCL server
Imperial	1	Yes – Attempting to upload via Internet explorer	UCL server
	2	No	UCL server
St George's	1	Yes - Attempting to upload via Internet explorer	UCL server
Oxford	1	No	UCL server
Glasgow	1	Yes - Attempting to upload via Internet explorer	UCL server
Sheffield	1	Yes – was unable to upload, central reading facility server at UCL storage was full. Made space and then the site was able to upload	UCL server

1st Report to the Trial Steering Committee from the Oxford Blood Pressure Monitoring Centre

Iain McGurgan, Clinical Research Fellow, 30.08.2019

Baseline characteristics of participants randomised to date, unstratified by treatment allocation, are displayed in Table 1. Baseline blood pressure data is presented in Table 2. Six (54.5%) participants were randomised to the intensive monitoring and treatment group. No participants have withdrawn from the study.

Some feasibility issues have been encountered in baseline assessments, particularly relating to ambulatory blood pressure monitoring. These issues are summarised in Table 3, along with the resulting delays to randomisation where relevant. The malfunctioning of ambulatory blood pressure monitors was attributed to a loss of their pre-programmed settings during postage without batteries, as is recommended by Royal Mail, or due to prolonged storage at trial sites. These problems have not been encountered in Oxford where the monitors are used soon after programming. One participant declined to be re-fitted with the baseline 24-hour ambulatory blood pressure monitor after failure of the initial recording period. Another participant removed the ambulatory blood pressure monitor due to discomfort, but the 17 daytime readings returned were considered valid for analysis.

Table 4 outlines a list of feasibility issues encountered in the intensive blood pressure monitoring group.

Table 1: Baseline characteristics of randomised participants

		Mean (SD) or frequency (%)
N		11
Age, years		67.2 (10.5)
Gender	**Male**	8 (72.7%)
Ethnicity	**White-British**	7 (63.6%)
Smoking	**Never smoked**	6 (54.5%)
	Ex-smoker	4 (36.4%)
	Current smoker	1 (9.1%)
Alcohol, units/week		12.7 (17.1)
ICH	**Lobar location**	6 (54.5%)
	Time from ICH to randomisation, days	123.3 (185.1)
Past medical history	**Hypertension**	5 (45.4%)
	Ischaemic heart disease	0 (0.0%)
	Diabetes	0 (0.0%)
	Atrial fibrillation	2 (18.2%)
Antihypertensive therapy at baseline	**Receiving treatment**	11 (100.0%)
	Number of agents	1.5 (0.5)

SD, standard deviation; ICH, intracerebral haemorrhage.

Table 2: Baseline blood pressure of randomised participants

		Baseline clinic measurements	Daytime ABPM*
Mean (SD) BP, mm Hg	**Systolic**	146.5 (19.9)	145.1 (21.1)
	Diastolic	85.5 (8.3)	83.4 (9.0)

SD, standard deviation; BP, blood pressure; ABPM, ambulatory blood pressure measurement.

*ABPM performed in 10 of 11 participants.

Table 3: Feasibility issues encountered in baseline assessments and current/future actions taken to address these

Issue encountered	Number (%) of participants	Mean attributable delay to randomisation from baseline assessment, days	Action proposed
Baseline MRI scan delay	2 (18.2%)	14	(i) MRI scans requested earlier in the recruitment process at trial sites (ii) Consideration of a protocol amendment including an acceptable time period post-randomisation for the baseline MRI to be performed, if this is an ongoing problem
ABPM malfunction	4 (36.4%)	4*	(i) Trial sites to ensure ABPM is still functional prior to issue to participants (ii) Reminders from Oxford centre to trial sites to test monitors intermittently (iii) Postage of monitors to sites with batteries inserted
Expiry of prepaid postage for ABPM return	3 (27.3%)	-	(i) Participant reimbursed for their personal expenses (ii) Prepaid enveloped sent in closer proximity to the time of use
Incomplete ABPM	2 (18.1%)	-	(i) Trial sites to ensure ABPM is functional prior to issue

ABPM, ambulatory blood pressure monitor. *In 3 cases, ABPM was performed after randomisation due to a malfunction of the initial test, a protocol violation in theory, which led to delays in starting telemetric monitoring in the treatment group.

Table 4: Feasibility issues encountered in one or more participant in the intensive monitoring and treatment group, and current/future actions taken to address these

Issue encountered	Action proposed
Delays in securing contact with the participant's GP by phone and/or delays in patient appointments to receive an updated prescription	(i) Participant seeks an appointment with an alternative GP at the practice (ii) Seek email addresses for GPs from practice administrators
Pharmacy stock issues of amlodipine causing delays in starting treatment	(i) Encourage participants to attend alternative pharmacies
Nationwide shortage of nifedipine requiring an alternative formulation to be prescribed and a temporary dose reduction	(i) Trial site hospital pharmacy contacted for emergency supply (ii) Avoid new prescriptions of nifedipine
Medication side effects prompting self-discontinuation of treatment	(i) Highlight the need for participants to contact the Oxford BP monitoring centre before discontinuing treatment
Lapses in telemetric BP monitoring due to trips overseas	(i) Participants encouraged to use the BP monitor (without the telemetric hub) when abroad where possible

GP, general practitioner; BP, blood pressure

PROHIBIT-ICH
Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

Paper 2

PROHIBIT-ICH Steering Committee Progress Report

Contents

1. **Background**
2. **Recruitment**
3. **Impact of COVID 19 on follow up visits**
4. **Study timelines**
5. **Strategies to increase recruitment and Amendments**
6. **Budget and Staffing**

Appendix 1: Summary list of the substantial amendment

Appendix 2: Timeline of events since last year's TSC meeting on 5th September 2019

Appendix 3: PROHIBIT-ICH COVID-19 Contingency Plan

Appendix 4: Site Teleconference minutes 13 October 2020

1. Background

Aims and Objectives:
PROHIBIT-ICH is a trial that investigates whether intensive lowering of blood pressure (BP) using telemetric home monitoring in survivors of intracerebral haemorrhage (ICH) is feasible, safe and effective in reducing brain injury. If successful, this study will be a precursor for a larger definitive trial. Our intervention should allow survivors of ICH to know, understand, and manage their own BP to prevent strokes and cognitive impairment, and improve outcomes.

Population studied:
Patients aged 30 years or more with spontaneous primary ICH (i.e. without known underlying structural, macrovascular or other cause), presumed to have cerebral Small Vessel Disease (SVD), who have a measured systolic blood pressure (SBP) of ≥130 mm Hg prior to randomisation and are able and willing (either unassisted or with the help of a relative, friend or carer) to complete the study assessments including BP measurements, cognitive screen and MRI scan.

Trial design:
PROHIBIT-ICH is a pilot multi-site randomized controlled trial comparing a strategy of intensive BP treatment (target <120/80mm Hg) guided by telemetric home monitoring (intervention group), versus standard care (current RCP guideline is 130/80 mm Hg, control group), in 112 adult survivors of SVD-related ICH. We will establish the feasibility and safety of the intervention, the efficacy of BP reduction, and explore whether it reduces the progression of SVD-related injury on brain MRI.

Primary outcomes:
(a) BP study
- Efficacy: the magnitude of difference in assessment BP at 3 months in the intervention arm versus the control arm compared with baseline measures
- Feasibility: consent rate; dropout rate from the intervention prior to 1 month; patient approval of the monitoring process
- Safety: serious adverse event related to reducing BP in intervention arm

(b) Imaging study
- Efficacy: the progression in MRI white matter hyperintensity (WMH) volume over 1 year

Secondary outcomes:
(a) BP study: Clinical outcomes including recurrent vascular events and cognition; number of BP lowering drugs at 3 months and at 1 year follow-up visits; the magnitude of difference in mean daytime BP measured on 3-month and 12-month ABPM in the intervention arm versus the control arm compared with baseline ABPM

(b) Imaging study: Neuroimaging outcomes including (but not limited to):
- the proportion of patients who develop new cerebral microbleeds (CMBs) over 1 year;
- number of new CMBs at 1 year;
- new infarcts or intracerebral haemorrhages at 1 year; change in mean diffusivity (MD), fractional anisotropy (FA) and other 3T DTI metrics;
- change in cerebral blood flow (CBF) on 3T PCASL;
- change in total brain volume, white matter volume and grey matter volume on 3T T1 volumetric images;
- composite neuroimaging measures (e.g summary SVD scores)

2. Recruitment

Table 1: Summary details of recruitment

Total number of participants recruited to date	*43 participants (38% of recruitment target)*	**Total target number of participants for trial**	*112 participants*
Total duration of recruitment to date	*15 months*[1] *(50% of recruitment duration)*	**Planned duration of recruitment (revised)**[2]	*30 months*[1]
Start date of recruitment[3]	*11 March 2019*	**Current predicted recruitment end date**[1]	*31 December 2021*
Date of start of COVID-19 lockdown pause for PROHIBIT-ICH	*20 March 2020*	**Date of end of COVID-19 lockdown pause for PROHIBIT-ICH**[4]	*8 July 2020*

The current recruitment is **0.3 patients per month per site**. With 12 sites being involved in recruitment, this leads to a current mean recruitment rate of approximately **3 patients per month in total.**

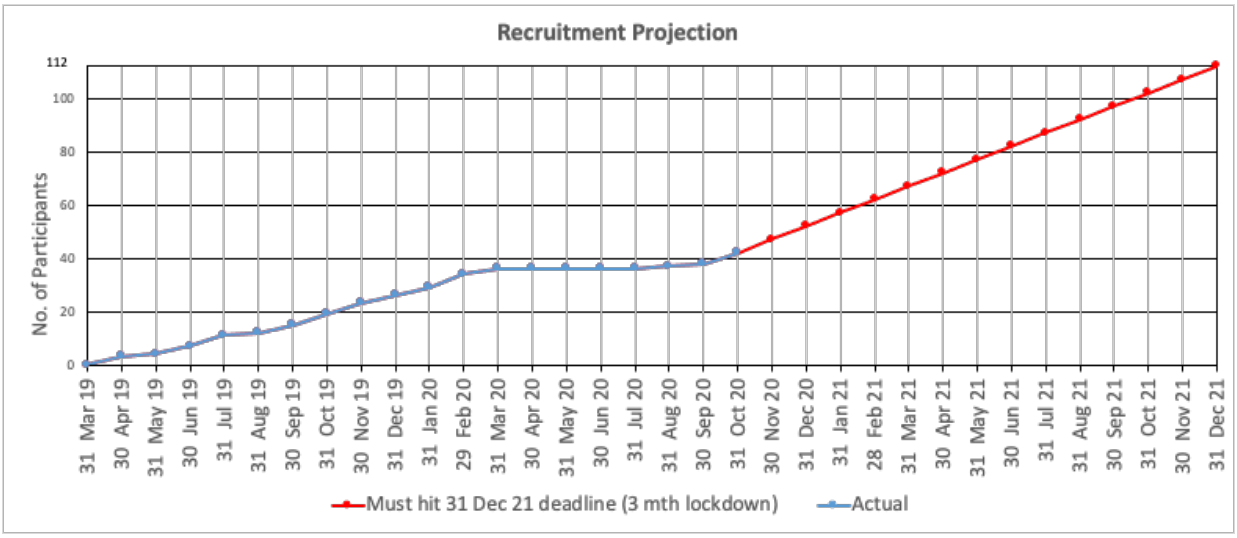
Unfortunately, despite excellent recruitment in early 2020, recruitment is currently slow (due to the effects of COVID-19) but we hope to finish recruitment by December 2021. With this end date we would need to recruit a realistic level of **0.4 patients per month per site (with 12 sites)**.

We held a site teleconference on 13th October 2020. The minutes are provided in **Appendix 4**, with full details of challenges and the response of sites to the pandemic. The themes discussed included:

- Staff shortages from redeployment to COVID-19 activities (NHS or prioritised trials)
- Access to MRI scanners
- Lack of outpatient clinics to recruit
- Challenges with providing and managing blood pressure monitoring equipment
- Difficulties with 12-month follow-up (requires MRI)

[1] Excludes four months of COVID-19 pause for PROHIBIT-ICH.
[2] The originally planned recruitment duration was 12 months.
[3] The originally planned recruitment start date (as at application) was 10/12/2018 with a planned recruitment end date 10/12/2019.
[4] Date of sponsor confirmation of restart after COVID-19 pause for PROHIBIT-ICH.

Chart 1: Recruitment projection chart



Shaded area = pause due to COVID-19

The revised target recruitment rate of 5 new participants per month is based on a revised per site recruitment rate of 0.4 participants per month which itself is based on a modest increase on the pre-COVID-19 recruitment rate from 0.3. new participants per site per month to 0.4. Using this revised recruitment rate, we have revised the target date for completing recruitment to 31st Dec 2021. The reason for this is:

- Individual site recruitment rates (0.3 per month per site) is slightly below the desired recruitment rate (0.4 per month per site).
- The number of sites re-opened has been delayed due pending R&D department and MRI department restart approvals (modelling assumption - one site a month re-opens).

Since the confirmation of restart email was issued on July 8th, we have recruited 7 (seven) participants (x2 Cambridge, x2 Edinburgh, x1 Oxford, Imperial, King's)

Table 2: Recruitment by site

Sites	Recruitment number	Number of months site open (less COVID pause)	Recruitment per month
University College Hospital, London	5	15	0.33
Kings College Hospital, London	7	11	0.66
St George's Hospital, London	4	12	0.32
Charing Cross Hospital, London	3	12	0.25
Sheffield Teaching Hospitals NHS Foundation Trust	3	12	0.24
Queen Elizabeth University Hospital, Glasgow	3	16	0.19
Royal Infirmary of Edinburgh	4	16	0.24
Salford Royal Hospital, Manchester	1	12	0.08
Nottingham University Hospitals NHS Trust	3	12	0.25
John Radcliffe Hospital, Oxford	3	16	0.19
Royal Preston Hospital	0	12	0
Addenbrookes Hospital, Cambridge	7	16	0.43
TOTAL	**43**	**13.55**	**3.2**

3. Impact of COVID 19 on follow up visits

Leading up to the lockdown announcement by the government, the Trial Management Group (TMG) held an emergency meeting to discuss the impact of COVID-19 on the trial. A contingency plan was sent to the TSC for approval prior to being sent out to sites on April 17th. (**See Appendix 3**)

3 month follow up visits

Fortunately, at the time of lockdown (March 20th 2020) almost all of the 3 month follow up visits of participants that had recently been recruited from January 2020 were able to be completed remotely.

For the 3 month follow up visits to occur remotely the following modifications to trial procedures were required:
- Two test readings could be used on ABPM machines posted to participants instead of the two clinic readings at 3-month follow up.
- If the participant refused to undergo ABPM or was not capable of fitting the machine at home, two readings on a conventional home BP monitor could be taken by the patient during the assessment.
- Hourly daytime home BP readings could be used in lieu of 24-hour ABPM in this scenario, with participants in the control group being sent a home telemetric BP monitor for this purpose only, if required.

These modifications were approved by the TMG and the TSC. A non-substantial amendment was submitted detailing these modifications. It also included minor changes to the statistical analysis so that BP readings collected in the ways mentioned above could be included in future analysis.

Table 3: Dates of 12 month follow up visits to 14th November 2020 showing delays

Date of randomisation	pt ID	Site	Date of planned follow up visit	Date of actual follow up visit	Min Delay (months)
11/04/2019	1001	UCLH	11/04/2020	early 2021	7
11/04/2019	1002	UCLH	11/04/2020	08/10/2020	6
23/04/2019	12001	St George's	23/04/2020	24/09/2020	5
13/05/2019	6001	Imperial	13/05/2020		6
10/06/2019	2001	Oxford	10/06/2020		5
13/06/2019	1003	UCLH	13/06/2020	17/09/2020	3
19/06/2019	5001	Glasgow	19/06/2020	07/08/2020	2
09/07/2019	6002	Imperial	09/07/2020		4
18/09/2019	4001	Edinburgh	18/09/2020	17/09/2020	0
25/07/2019	8001	Salford	25/07/2020	Withdrawn	N.A.
29/07/2019	11001	Sheffield	29/07/2020		3
05/08/2019	1004	UCLH	05/08/2020	15/10/2020	2
05/09/2019	7001	Kings	05/09/2020		2
18/09/2019	9001	Nottingham	18/09/2020	likely Dec 2020	2
25/09/2019	7002	King's	25/09/2020		1
03/10/2019	12002	St George's	03/10/2020	22/10/2020	1
23/10/2019	7003	King's	23/10/2020		1
24/10/2019	12003	St George's	24/10/2020		0
29/10/2019	1005	UCLH	29/10/2020	likely Dec 2020	0
05/11/2019	3002	Cambridge	05/11/2020		0
08/11/2019	7004	King's	08/11/2020		0
14/11/2019	11002	Sheffield	14/11/2020		

As at November 8th 2020 7 participants have had their 12 month follow up visits from 20 that are due (35%).

4. Study timelines and projected recruitment

Original planned timeline

- The original timeline was to start in 2016 after the funding was granted in July 2015. However, several revisions to the original timeline have been necessary.

First revision to timelines

- The revised timeline (due to various delays in post approvals, CRF finalisation, etc.) was recruitment over 1 year (starting March 2019, ending March 2020) – 112 patients at 12 sites = **0.8 patients per month per site.**

- The rate for recruitment per month has varied across sites from **0 to 0.8 patients per month per site**. Recruitment to date for the whole study has been at a mean rate of approximately **0.3 patients per month per site.**

Second revision to timelines

- It was planned that recruitment would finish by September 2020. To achieve this we would have needed to recruit **0.7 patients per month per site**.
- Extending recruitment to November 2020 would give a required recruitment rate of **0.6 patients per month per site.**
- Prior to COVID-19 recruitment had improved and this target seemed reasonable because the substantial amendment would increase the recruitment rate.
- The revised planned end date of PROHIBIT-ICH was 31st December 2021, allowing follow-up to be completed by September 2021 and 3 months for study close-out. We applied for a no cost extension until December 2021, and this was approved by the sponsor.

Third revision to timelines (including Impact of COVID-19):

- We paused recruitment on 20th March 2020 until 8th July 2020 when Sponsor confirmation of restart was issued.
- Current recruitment is 43 as at 8th November (38% of final target), leaving 69 patients to recruit. ***We have recruited 7 patients since restarting on July 8th.***
- Unfortunately, recruitment is currently slow but we anticipate we might finish recruitment by 31st December 2021 based on recruiting **0.4 patients per month per site**. We will continue to monitor recruitment post-COVID-19 pandemic peak to clarify likely recruitment for the remainder of the trial.
- Although recruitment post-COVID-19 is hard to predict, we anticipate that to complete 1 year follow-up the end date of PROHIBIT-ICH will need to be extended until at least 31st December 2022. We would like to seek approval for this extension.

Table 4: Site initiation start-up and restart after COVID-19 lockdown

Site	PI	Status	Site Initiation Visit	Site R&D approval	Green light	Restart following COVID-19
University College Hospital, London	Professor David Werring	Active	24/07/2018	15/10/2018	11/03/2019	20/08/2020
John Radcliffe Hospital, Oxford	Professor Peter Rothwell	Active	24/07/2018	09/11/2018	11/03/2019	31/07/2020
Charing Cross Hospital, London	Dr Soma Banerjee	Active	24/07/2018	18/03/2019	18/03/2019	Pending[5]
Royal Infirmary of Edinburgh	Professor Rustam Al-Shahi Salman	Active	18/09/2018	28/11/2018	11/03/2019	09/07/2020
Salford Royal Hospital, Manchester	Dr Adrian Parry-Jones	Active	10/09/2018	15/10/2018	11/03/2019	Pending[6]
Royal Preston Hospital	Prof Hedley Emsley	Active	24/09/2018	20/03/2019	20/03/2019	Pending
Kings College Hospital, London	Dr Laszlo Sztriha	Active	25/07/2018	13/06/2019	13/06/2019	25/09/2020
Addenbrookes Hospital, Cambridge	Dr Michele Pellizzaro Venti	Active	07/08/2018	19/10/2018	11/03/2019	09/07/2020
Nottingham University Hospitals NHS Trust	Dr Kailash Krishnan	Active	24/07/2018	12/04/2019	12/04/2019	20/10/2020
Queen Elizabeth University Hospital, Glasgow	Dr Keith Muir	Active	25/09/2018	15/03/2019	18/03/2019	21/07/2020
St George's Hospital, London	Dr Liqun Zhang	Active	25/09/2018	09/11/2018	11/03/2019	Pending
Sheffield Teaching Hospitals NHS Foundation Trust	Dr Kirsty Harkness	Active	14/09/2018	17/10/2018	11/03/2019	Pending

[5] Charing Cross Hospital is open for recruitment but only for those currently with clinical appointments in hospital. We are still seeking a full reopening.

[6] MRI scanner not in operation until March 2021 as it is being replaced

5. Strategies to increase recruitment and Amendments

The initial recruitment rate had proved optimistic and we have therefore revised the forecast recruitment rate and commenced measures to improve recruitment after the 2019 Trial Steering Committee.

The main factors identified limiting recruitment were:

i. Patient's blood pressure (BP) is too low
ii. Patients are on more than 3 BP drugs
iii. They are discharged to rehab unit or nursing care – addressed in the substantial amendment
iv. They are too unwell to recruit
v. Patients discharged/referred out of area and cannot be followed up – addressed in the substantial amendment
vi. Elderly patients who have trouble using technology

To increase recruitment, we hold regular teleconferences with all the sites. This is an opportunity to discuss strategies to increase recruitment. These teleconferences occur every few months with discussions with research staff. The last teleconference for all the sites was on 13th October 2020[7]. Individual calls were also made to sites that had not yet reopened the trial to identity the reasons behind their delay in reopening. Sites were asked to contact their R&D departments to request restarting the trial if they were in a position to do so. A major reason for recruitment not restarting at some sites appears to be the unavailability of a MRI research scanner (was previously the case for Imperial and is still the case for Salford).

We have improved our marketing and communication strategy by providing participating sites with PROHIBIT-ICH posters which gives information on the study. We have also increased the frequency of sending out newsletters to sites from monthly to fortnightly.

Furthermore, a number of substantial amendments including a change in the specified discharge destination of patients was submitted (**see Appendix 1**) as a way to increase recruitment. This substantial amendment was submitted on 22 October 2019[8].

We worked hard to implement the parts of the approved substantial amendment (see appendix) concerning the creation of Patient Identification Centres (PIC) sites and new sites. However, this is proving difficult as R&D departments are prioritising COVID-19 studies. We are communicating with the relevant R&D departments to ask them for regular updates on progress with the set up of these sites.

We invited 4 new research sites to participate in the study with the aim that they would undertake all research activities. We worked hard on this aim, based on high recruiting sites that undertook satisfactory MRI in other trials including RESTART. Two of these sites are still in the running to become new sites: Leeds and Birmingham. The other potential sites checked our protocol and were unable to follow the MRI scanning procedures according to the Imaging Manual.

[7] The other teleconferences since the last TSC progress report occurred were on 19th November 2019 and 13th March 2020.
[8] Date of HRA and Ethical approval for England and Wales: 25 November 2019
Date of Ethical approval for Scotland: 2 December2019

The UCL and Oxford teams communicate weekly and the UCL-Oxford Trial Management Group meet monthly to discuss the recruitment progress of the trial and minutes of these are available. The meetings continued during the COVID-19 lockdown period.

The Eligibility Screening Report **(see Paper 2)** gives details of reasons for non-recruitment at each site.

6. Budget and Staffing

Budget
So far with some reallocation of budget categories, we have sufficient funding to cover the UCL study co-ordinator salary until December 2021. All other costs for the Oxford site are covered until December 2021.

To complete the study as planned a budget uplift would be required for salaries and other adjustments for the study to be extended.
The additional costs for extending the study to 31st December 2022 were as follows:

• Trial Co-ordinator post, part time (until Dec 31st 2022):	£29,242
• BP coordinator post, part time (until Apr 30th 2022):	£20,016
• Clinical Research Fellow post, part time (Nov '20 – Oct '21): (previously funded by Oxford University)	£27,665
• Renewed use of eCRF database Sealed Envelope:	£5,000
Total funding requested:	**£81,923**

We also proposed a minimal option to continue the study without the funding of the Clinical Research Fellow post which would be an additional cost of £54,258.

We approached our sponsor the Stroke Association to request this extra funding. We received a response on 12th November. The Stroke Association strongly support the continuation PROHIBIT-ICH project. However, they felt that there were two potential benefits to stopping the MRI aspects of the study. First, they felt that a trial without the complexity of organising two MRI scans (especially with the backlog that hospitals are currently facing) would increase the recruitment rate by widening the eligibility criteria. Second, they felt that the cost savings from not undertaking the MRI scans could be used to help fund the extension to the trial.

Staffing
Shahena Butt is currently on Maternity leave (16th Dec 2019 – Nov 2020). Abi Chandrakumar was employed briefly as study co-ordinator from May 7th - December 20th 2019.

Maja Dabagh starting in the role of study co-ordinator on 3rd February 2020. The lack of staffing continuity has led to challenges in maintaining administrative knowledge of the trial, which itself has caused disruption and delays.

Shahena is returning to UCL for 3 months after her maternity leave, and we propose an overlap handover period so that Maja can then continue with the UCL trial co-ordinator role in 2021.

Appendix 1: Summary list of amendments

1. Removal of inclusion criteria number 4 from protocol:
    a. 'For patients recruited in hospital there should be a plan for home discharge (not to a nursing or care home) after their inpatient stay, or living at home at the time of recruitment'
2. Reducing the age limit to 30 and above
3. Patients can also be identified from site databases that contain patients who have had a previous ICH at any time, including databases of participants included in previous clinical trials (subject to agreement with the Chief Investigator of the other trial). Potentially eligible patients will be contacted by email or post. Patient invitation letters and patient information sheets (PIS) will be sent by post.
4. We will provide posters which gives information on the study, to be displayed at participating sites and NHS PIC sites; suitable locations include doctors or nurses offices, noticeboards, or in outpatient clinics.
5. Patient Identification Centre (PIC) sites will be included in the study. These sites will be NHS sites; the staff at these sites will identify potential patients and inform the study team at local PROHIBIT-ICH recruiting sites.

    Recruiting/research site: UCLH = proposed NHS PIC site: 1. Barnet, Royal Free and 2. North Middlesex

    Recruiting/research site: John Radcliffe Hospital, Oxford = proposed NHS PIC site: 1.Swindon's Great Weston Hospital 2.Stoke Mandeville Hospital in Aylesbury. 3.Reading Royal Berkshire Hospital

    Recruiting/research site: Addenbrooke's Hospital, Cambridge = proposed NHS PIC site: 1.West Suffolk 2.Peterborough -Temple 3. Hinchingbrooke

    Recruiting/research site: Salford Royal Hospital = proposed NHS PIC site: 1.Stepping Hill Hospital in Stockport 2.Fairfield Hospital at Pennine Acute

    Recruiting/research site: Sheffield Teaching Hospitals NHS Trust = proposed NHS PIC site: 1.Doncaster Royal Infirmary

    Recruiting/research site: St George's Hospital = proposed NHS PIC site: 1.Croydon University hospital 2.Epsom and St.Helier Hospital 3.Kingston Hospital.
6. We will invite 4 new research sites to participate in the study; they will conduct all research activities. These potential 4 sites are: 1. Royal Devon and Exeter Hospital 2. Sandwell and West Birmingham 3. Leeds teaching hospital NHS trust 4. Royal United Hospital, Bath
7. The addition of 3 month and 12 month GP letters is for sites to inform GPs of the clinic BP measurement at 3 months and 12 months for all participants. The reason to incorporate this is because after deliberation with the Trial Steering Committee, we have decided it is ethically appropriate to inform GPs of the patient's BP.

Appendix 2: Timeline of events since last year's TSC meeting on 5th September 2019

Date	Event
22 Oct 2019	Submission of substantial amendment
25 Nov	Date of HRA and Ethical approval for England and Wales for the amendment
2 Dec	Ethical approval for Scotland for the amendment
5 Dec	Investigator's meeting at the UKSF
16 Dec	Shahena Butt goes on maternity leave
20 Dec	Abi Chandrakumar leaves the role of study co-ordinator
3 Feb 2020	Maja Dabagh is employed as study co-ordinator
3 Mar	Oxford – UCL teleconference
13 Mar	All sites teleconference
17 Mar	Email sent to sites explaining we will contact them with a plan
20 Mar	Email sent to sites stating that PROHIBIT-ICH recruitment and 12 month follow up visits are paused
23 Mar	COVID-19 UK lockdown restrictions are imposed
3 Apr	Oxford – UCL teleconference
11 Apr	Due date of the first 12 month follow up visits for the first 2 participants recruited on 11 Apr 2019 is missed
17 Apr	Contingency plan sent to sites
10 May	COVID-19 lockdown restrictions begin to be lifted in England
5 June	Submission of Stroke Association COVID-19 Impact Survey
8 July	UCL JRO Sponsor issues re-open to recruitment confirmation email PROHIBIT-ICH can restart at Edinburgh and Cambridge
15 July 17 July	HRA Approval is given for a non-substantial amendment. The amendment consists of minor changes to the primary and secondary BP outcomes and minor changes to data collection and procedures for remote visits due to COVID-19 restrictions. An email is sent to sites containing a new version of the protocol and requesting sites to notify their R&D departments.
7 Aug	The trial's first 12 month follow up visit happens in Glasgow
31 Aug	Edinburgh recruits the first new participant since lockdown
7 Oct	Submission of Stroke Association Annual Progress Report
13 Oct	All Sites teleconference
14 Oct	Imaging group meeting
16 Oct	Meeting with Richard Francis from the Stroke Association
As of 8 Nov:	43 participants have been recruited 7 out of 12 sites have reopened fully 7 participants have been recruited since 9 July 7 participants have had their 12 month follow up visits from 20 that are due (35%).

Appendix 3:

PROHIBIT-ICH COVID-19 Contingency Plan

Version: 1.0 Date: 08/04/2020

Approved by: Professor David Werring, Professor Peter Rothwell

Purpose: This document provides guidance to all PROHIBIT-ICH research sites about how to manage trial-specific research activities during the COVID-19 pandemic.

Recruitment of new participants: suspended until further notice

- Please keep a screening log of potentially eligible patients for later recruitment.
- Once UK Government restrictions are lifted and there are MRI scanning facilities available for the baseline visit, recruitment can recommence.

3-month follow-up (Visit 2): to be performed remotely by each site

- 24-hour ABPM should still be performed by each participant; fitting can be performed by the participant or carer by following the video instructions on the PROHIBIT-ICH website www.prohibit-ich.org.uk and with telephone or video call guidance (if the participant has facilities available) from the Oxford BP Monitoring Team.
- Participants should continue to use pre-paid envelopes to return the 24-hour ABPM equipment to the Oxford team. This may require individual solutions for individual participants; please contact the Oxford team by email for guidance in advance. If participants show signs of fever or cough/shortness of breath, please instruct them to place the equipment into two bags prior to sending in the pre-paid envelope.
- Cognitive assessment is to be performed using a 22-point Telephone-MoCA (i.e. the MoCA items not requiring the use of a pencil and paper and/or visual stimulus).

12-month follow-up (Visit 3): postponed

- The 12-month follow-up visit should be performed as close as possible to the scheduled date, once restrictions are lifted. The MRI scan and 24-hour ABPM should happen on the same date, with the e-CRF completed at that time.

Participant Safety

- Please continue to report SAE's as outlined in the protocol.
- Where capacity issues may prevent timely reporting of SAE's, they should be reported as soon as possible after the issue is resolved and the delay recorded as a protocol deviation.

Relevant Guidance

- Guidance about COVID-19 for sponsors, sites and researchers has been provided by the HRA. Section 3.2 is relevant to sites: https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/

Appendix 4: Site Teleconference minutes 13 October 2020

Date: Tuesday 13th October 2020

Time: 1.30pm – 2.30pm

Attendees: Professor David Werring (DW), Professor Peter Rothwell (PR), Maja Dabagh (MD), Bindu Gregary (BG), Michelle Wilson (MW), Josephine Edens (JE), Allan Macraild (AM), Con Tibajia (CT), Rita Ghatala (RG), Sarah Stratton (SS), Lauren Binnie (LB), Rebecca Williams (RB), Kate Kennedy (KKe), Kim Hatherley (KH), Gwen Wilkes (GW), Kailash Krishnan (KKr), Kirsty Harkness (KH), Emma Richards (ER), Nina Francia (NF), Vaishali Dave (VD), Peter Wilding (PW), Sarah Finlay (SF), Thelma George (TG)

Not in attendance: Salford team

1. Welcome and Introductions

These monthly teleconferences are taking place to briefly update sites of study progress, recruitment, any challenges sites are facing and as an opportunity for sites to share recruitment and tips.

2. Progress and Study Update

- DW: 39 participants have been recruited, this is 35% of the target number of 112 participants. 6 sites have reopened fully, well done to those that have reopened. Postponed follow up visits are happening though there are challenges with organising some of them at some sites.
- PR: It is great to see that recruitment has started up again.
- DW: Let us now ask each site in turn for an update on recruitment and follow up visits and to see if the substantial amendment that got approved last year has made a difference.

3. Impact of COVID-19 on sites – how have you coped, have staff been redeployed, plans for restart & the restart process at sites not open yet

4. Review of screening logs from each site

5. Update on patient recruitment - tips and challenges

6. Update on patient follow-up - tips and challenges

King's, CT:

- 7 participants recruited
- Reopened Sept 25th
- Screening log: From reopening 52 screened (all strokes), 6 ICH, 1 recruited, x2 currently being screened.
- Reasons not recruited: EOL, BP well controlled
- They have been understaffed, normally have x2 coordinators, now down to x1, with an assistant on Monday & Tuesdays
- Con is full time on Covid studies now
- MRI are strict with number of staff coming there, just the 1 allowed to accompany the patient.
- Follow ups: in the process of being organised
- MW: For the patient recruited recently only 1 BP reading was recorded on the Bluetooth monitor.
  A new monitor was despatched and the 24 h machine has been returned to Oxford.

- **Top tips** – involve the consultants, down to the SHOs also, regularly train the junior doctors
- Screen for all studies
- The amendment allowing the 3 month follow up visit to be remote has been helpful

Cambridge, SF:

- 5 participants recruited
- Reopened in July. They have been able to reopen all studies and PROHIBIT-ICH was one of the first to reopen
- Screening log: From reopening 17 ICH screened
- They screen daily, they are on ward rounds and screen from the ICH clinic on the phone.
- Reasons not recruited: x 1 ineligible due to pacemaker, out of area, BP too well controlled
- x1 might be suitable on the ward
- 12 month follow ups: 1st in Nov, participant is in her 90s, 2nd end of Nov, is more agreeable to come in
- No one was redeployed
- Good news that MRI scanner has its own entrance
- Their research meeting has R&D involvement
- Their concern about recruiting from inpatient wards is that kit may go missing

DW: Just to clarify, when recruiting from the ward there is no need for eligible participants to be on their way home.

UCLH, NF:

- 5 participants recruited
- Reopened in August
- Screening log: for the whole trial 278 screened, 44 eligible, 16 declined.
- Running into same challenges described: pts are too ill, lack capacity, too many BP agents or BP too well controlled
- Currently x 4 ICH on the ward, 2 potentials
- Follow ups: x2 have happened

St George's, RG:

- 4 participants recruited
- Not open to recruitment yet, open to follow up
- Screening log: for the whole trial >200 screened, 36 eligible, 4 declined, 11 enrolled to other trials – 6 to BLOC-ICH trial, some have been repatriated before they could be recruited.
- Opened other stroke trials in July
- OP is shut, when they got the news that the 3 month follow up visit could be done remotely in Sept they contacted R&D to ask for restart and they await R&D's approval.
- R&D will not allow them to bring patients in for recruitment but can recruit from HASU but only a very small number will be recruited.
- Follow ups: x1 done, they are arranging the other two. They plan to do everything other than the MRI scan remotely.

Sheffield, KH (placed in Tier 2):

- 3 participants recruited
- Not reopened yet and there are increasing numbers of COVID-19 cases
- Screening log: they are keeping one, 3 potentials last week
- Reasons not recruited: cognitively impaired, repatriated to quite a distance away
- Staff weren't redeployed, though there has been staffing issues
- The vaccine study is overwhelming the research facility and staff

Nottingham, GW: (placed in Tier 2)

- 3 participants recruited
- Not reopened yet
- July move of wards and research from City to Queen's Medical Centre, KK (PI): the move was in June
- No permanent office yet and they still need to find clinic room space and transport files from the old site
- They might need to be redeployed back to COVID studies.
- MRI scanners x 3 before, now down to x 1 and they need to check if it is 3T or not.
- Restart forms have been submitted and R&D review will happen today
- 12 month follow up: x1 booked in but MRI have backlog and likely will happen Dec 2020.

DW: It Is important that the follow up MRI scans are done on the same machine.

Imperial, PW+VD:

- 2 participants recruited
- Not reopened yet
- They have a multi stage process for reopening and they cannot open studies that require face to face follow ups
- Also, because it requires a 3T scan, imaging cannot support such studies right now - as they have only one scanner and they are still figuring out Covid and non-Covid pathways.
- They are hopeful that soon they can get an exemption and reopen all of their studies in the near future.

Oxford, PR+MW:

- 3 participants recruited
- Reopened in July
- Recruited, 1 very recently last Friday
- IM emailed through screening log: since the beginning of the trial 76 patients have been screened, 17 have been eligible
- Last 3 ineligible due to having a pacemaker

Glasgow

- 3 participants recruited
- Reopened in July, all stroke studies are open.
- Screening log: 35 since reopening in July, 2 potentials
- No clinics running so they recruit from the ward or retrospectively
- Staffing: KH is the only research nurse as Angela is still seconded to the wards. KH has some support from 4 clinical research fellows but day to day is running all studies on her own.
- They are using the CRF but this is very busy with vaccine studies

Edinburgh, AM:

- 3 participants recruited
- Reopened in July, have reopened all stroke studies
- From March – July they were just doing Covid research
- They have been fortunate with their R&D department.
- Screening log: since reopening they have screened 6, recruited x2
- Reasons not recruited: x 2 BP too well controlled, x 1 declined MRI scan.
- The second participant is coming in on Thursday to have their MRI scan

- So far all 3 participants recruited have been in the control arm. This participant may have difficulties with the monitoring equipment, it is looking as though they might need to seek support from Oxford with managing this.

- Preston, BG:
- No participants recruited yet
- The situation is unchanged since the update given last week by the PI, Prof Emsley. COVID numbers are increasing.
- Only 2 stroke studies have been recommenced and R&D is prioritising which studies to reopen.

Discussion about trials competing with PROHIBIT-ICH
Potential competing trial: PRESTIGE-AF
Other trials mentioned: BLOC-ICH, PRECIOUS, ENRICH-AF
SF: PRESTIGE-AF is open in Cambridge, CT: King's is also going to open PRESTIGE-AF soon
AM: We need a decision quite soon for a participant coming in on Thursday about whether they can be co-enrolled to ENRICH-AF and PROHIBIT-ICH. The CI in Canada has no problem with this.

Action Point
- ➢ DW and PR to look at PRESTIGE-AF trial in more detail +/- reach out to the CI of PRESTIGE-AF trial to check they would allow for co-enrolment or not.
- ➢ DW to reply to AM's email about whether a potential participant in Edinburgh can be co-enrolled to ENRICH-AF and PROHIBIT-ICH.

7. Imaging data

We have now received some 12 month follow up scans. No problems so far. MD to quality check and tell sites the results. It is very important that 12 month follow up scans are done the same way as the baseline scans and that the same scanner is used. Let us know of any scanner upgrades.

Reminders:
- Make sure you are using Chrome or Firefox, Internet Explorer will not work.
- Ensure your scans are compressed into a zip file before uploading.
- We do not accept CDs with the scans on them.
- Please remind your radiographers to refer to the imaging manual.

8. Any other business

MW: We wish to encourage sites to keep talking to us, we're here to help.
For 3 months follow up visits done remotely we have sent some BP monitors directly to participants' homes and have the ability to continue doing this. You can also advise the participants to view the videos on our website.

DW: In terms of improving recruitment it looks as though training the junior doctors about the trial would be good practice going forwards. If you haven't done so already, please display the posters from the amendments where they'll be seen easily.

PR: We will be meeting our funders, The Stroke Association, soon to share what you have told us today.
DW: Thank you everyone for your support and hard work during this difficult time.

Action Point
- ➢ MD to make a list of top tips for sites

Next teleconference to be scheduled in a few months time

Paper 2

PROHIBIT-ICH Eligibility Screening Report

Table 1: Screening numbers from PROHIBIT-ICH sites

Site	No. of patients screened	No. of eligible patients	Why not eligible following screening?	Final no. appro-ached	No. agreed	Reasons unable to recruit to study
UCLH (numbers up to 12 Oct 2020)	278 ICH	44	- Declined (16) - BP is well controlled. - More than 3 BP medications - Patient too unwell to be part of the trial/ palliative/poor prognosis/RIP - Not likely to comply with BP monitoring/Dementia - Lives in care/ nursing home - Language Barrier - Lacked capacity -Out of Area/ Overseas/ No permanent residence - Did not like to be followed up after discharge - Unable to contact after discharge - Unable to come back for FU - Unsure aetiology/Bleed not BP related - On RCT	30	6	Staffing issues (4 people leaving/on mat leave) Unable to contact 1 potential participant since consenting
UCLH (numbers up to 30 Aug 2019)	1153	29	- Not had ICH - Patients have died - mRS > 4 - Patient has dementia - Under age limit	11	4	- BP consistently <130mmHg - Patient taking ≥3 antihypertensive agents. - Not approached all eligible patients
Imperial (numbers up to 11 Nov 2020)	1779	47	Same reasons given as below	15	7	Same reasons given as below
Imperial (numbers up to 30 Aug 2019)	753	25	- Not had ICH - Bleed post thrombolysis - Patients have died - Patients have been repatriated - cavernous/ aneurysm - mRS > 4 - Patient has dementia - Under age limit - Low GCS	12	2	- Unable to speak English - BP consistently <130mmHg - Patient taking ≥3 antihypertensive agents. - Patient overseas, unable to follow-up
King's (numbers from Oct 2019 to 28 Oct 2020)	752	81	- Not had ICH - mRS of 5 before ICH - Unable to undergo MRI (due to metal plates etc) - Palliative/end of life care - Language barrier - Traumatic ICH	10	4	- Taking > 2 anti-hypertensive meds - Refused: prefers natural remedies as below - Refused MRI - Covid+ swab

King's (numbers up to 30 Aug 2019)	357	21	- Not had ICH - mRS of 5 before ICH - cannot have MRI due to aneurysm clips – mRS 4 before ICH - Palliative care: mRS6	4	1	- Taking > 2 anti-hypertensive meds - Refused: prefers natural remedies and would not comply with taking antihypertensive medication
Addenbrookes (Cambridge) (numbers up to 23 Oct 2020)	146 ICH	15	- Patient reluctance to come back during Covid - Moved out of area. - Declined to have a second and third MRI scan, having had a clinical scan as part of post stroke work up. - Not MRI compatible due to cochlear implants/ PPM	15	11 (7 recruited)	- Competition with Prestige-AF study - On x3 anti-hypertensives
Addenbrookes (Cambridge) (numbers up to 30 Aug 2019)	43 ICH	10	- Patients have died - Patients have been repatriated (discharged out of area) - Have co-morbid conditions	10	0	- Low BP - More than 3 BP drugs - Discharged to nursing care home or Rehab unit
Nottingham (numbers up to 9 Nov 2020)	142 ICH	27	- Too unwell, EOL/RIP - mRS too high - Lacking capacity to consent and lacking suitable consultee - BP too low - Discharged out of area or to care facility	8	3	- BP resolved - Not interested - Patient reported did not want to have to take own BP measurements, unsure of technology -Limited English, not first language -Competing trials
Nottingham (numbers up to 30 Aug 2019)	30 ICH	5	- Too Unwell - Below age requirement - discharged to rehab unit or nursing care	5	1	- Not interested - Low BP
Oxford (numbers up to 26 Oct 2020)	76 ICH	17	- Structural cause - Severely disabled - From out of area – repatriating - Severe Dementia - Haemorrhagic transformation - Too frail - Too young	17	3	- Declining to take part in research (MRI scan, too anxious, previous side effects of BP medications) - Pacemaker in situ (x4) - Died before baseline visit
Oxford (numbers up to 30 Aug 2019)	36 ICH	12	- Re-bleed of AVM - Palliative/Died - Seizures in the context of CAA - mRS too high	12	1	- Nursing Home Pathway - Low BP -Pacemaker in situ

St George's (numbers up to 30 Aug 2019)	1150	26	- Not had ICH - Patients have died - Patients have been repatriated - mRS > 4: palliative care - Patients have dementia - Under age limit	5	2	- Unable to speak English - BP consistently <130mmHg - Patient taking ≥3 BP drugs - Declined: not interested - some not yet approached
Sheffield (numbers up to 30 Aug 2019)	127	24	- Not had ICH - Too sick with poor survival	5	1	- Non English speakers - Older patients are put off by technology aspect of the study - Not approached eligible patients yet
Royal Preston (numbers up to 30 Aug 2019)	22 ICH	12	- Patients have dementia - Patients have died - Below age limit	12	0	- Controlled BP - More than 3 BP drugs - Discharged to nursing care home or Rehab unit
Edinburgh (numbers up to 30 Aug 2019)	20 ICH	8	- Died in hospital - Too unwell - Have a guarded prognosis	8	1	- Have systolic BP levels <130 mmHg - Taking 4 agents for BP control already - Has a history of alcohol excess and ongoing behavioural issues on the ward - Russian speaker (no English) who has bilateral carotid disease - Declined as they was not interested
Glasgow (numbers up to 30 Aug 2019)	15 ICH	12	- Essential thrombocytopenia - Complex medical history - Cognitive impairment	12	1	- Non-English speaking - Recruitment to competing trial (1-TRIDENT) - Patient declined - Systolic blood pressure <130mmhg
Salford, Manchester (numbers up to 30 Aug 2019)	93 ICH	25	- Patients have died - Patients have been repatriated -Too young - Not suitable for follow-ups	5	1	- BP consistently <130mmHg - Patient taking ≥3 BP drugs - Declined: not interested - Recruited into TRIDENT

Paper 4

PROHIBIT-ICH Steering Committee
Imaging Report

Table 1: Summary of Baseline MRI scans that have been quality checked

Site	Scan no	Scans Received	3D T1	3D FLAIR	DTI	3D SWI	AXIAL T2	ASL	Notes
UCLH	10XX	5	100% (5/5)	100% (5/5)	100% (5/5)	100% (5/5)	100% (5/5)	100% (5/5)	6001 - DTI unusual format, T1 some motion present, djw checked
Imperial	60XX	2	100% (2/2)	100% (2/2)	100% (2/2)	100% (2/2)	100% (2/2)	100% (2/2)	
St George's	120XX	4	100% (4/4)	100% (4/4)	100% (4/4)	100% (4/4)	100% (4/4)	100% (4/4)	12003 - minor problem with T1 missing edge of temporal lobes checked; 12004 - 3D FLAIR (a bit motion corrupted); DTI (top of brain is missing)
Oxford	20XX	2	100% (2/2)	100% (2/2)	50% (1/2)	100% (2/2)	100% (2/2)	100% (2/2)	2002 - Had claustrophobia; 2003 - DTI not available at the time of scanning
Glasgow	50XX	3	67% (2/3)	67% (2/3)	67% (2/3)	33% (1/3)	67% (2/3)	33% (1/3)	5002 - Not to protocol. Asked to rescan. Can still be manually analysed; 3D T1 - not isotropic; 3D FLAIR - not isotropic; DTI - missing; 3D SWI - not isotropic; AXIAL T2 - not to protocol; 5003 - Pt terminated scan, movement
Sheffield	110XX	3	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	11002 - distortion of SWI in frontal lobes, likely useable data, checked
Edinburgh	40XX	4	100% (4/4)	100% (4/4)	100% (4/4)	100% (4/4)	100% (4/4)	100% (4/4)	
Nottingham	90XX	3	100% (3/3)	0% (0/3)	100% (3/3)	100% (3/3)	100% (3/3)	0% (0/3)	9001-9003 - Midline artefact and missing lat temp lobes on the FLAIR, checked
King's	70XX	6	100% (6/6)	100% (6/6)	100% (6/6)	100% (6/6)	100% (6/6)	100% (6/6)	7002 - mild motion artefact swi, djw checked
Cambridge	30XX	5	100% (5/5)	100% (5/5)	100% (5/5)	100% (5/5)	100% (5/5)	100% (5/5)	
Total		37	97% (36/37)	89% (33/37)	95% (35/37)	95% (35/37)	97% (36/37)	86% (32/37)	

Table 2: Summary of Follow up MRI scans that have been quality checked

Site	Scan no	Scans Received	3D T1	3D FLAIR	DTI	3D SWI	AXIAL T2	ASL	Notes
UCLH	1003	Yes	P	P	P	P	P	missing	Ask research team to chase, checked
St George's	12001	Yes	P	P	P	P	P	P	checked
St George's	12002	Yes	P	P	P	P	P	P	checked
Glasgow	5001	Yes	P	P	P	P	P	P	checked
Edinburgh	4001	Yes	P	P	P	P	P	P	checked

2nd Report to the Trial Steering Committee from the Oxford Blood Pressure Monitoring Centre

Iain McGurgan, Clinical Research Fellow, 08.11.2020

Baseline characteristics of participants randomised to date, unstratified by treatment allocation, are displayed in **Table 1**. Twenty-one (48.8%) participants were randomised to the intensive monitoring and treatment group. Two (4.7%) participants have voluntarily withdrawn from the study, one at baseline after all procedures except phlebotomy were performed, and the other just prior to the three-month follow-up assessment. The reasons for withdrawal were not provided by the participant in either case. One further participant refused 3-month follow-up but has not formally withdrawn at this point.

Table 2 outlines the extent of data clinical and blood pressure data completeness at baseline, 3-month and 12-month follow-up. The reasons for incomplete ambulatory blood pressure monitoring (ABPM) data are shown in **Table 3**, and **Table 4** displays other feasibility issues encountered with remote ABPM administration. The malfunctioning of ambulatory blood pressure monitors was attributed to a loss of their pre-programmed settings during postage without batteries, as is recommended by Royal Mail, or due to prolonged storage at trial sites. These problems have not been encountered in Oxford where the monitors are used soon after programming.

Table 5 summarises contingency measure taken due to COVID-19 restrictions.

Table 6 outlines a list of feasibility issues encountered in the intensive blood pressure monitoring group.

Blood pressure data at baseline and follow-up are presented in **Table 7**.

Table 1: Baseline characteristics of randomised participants

		Mean (SD) or frequency (%)
N		43
Age, years		66.8 (12.9)
Gender	**Male**	31 (72.1%)
Ethnicity	**White**	32 (74.4%)
	Black	6 (14.0%)
	Asian	4 (9.3%)
Smoking	**Never smoked**	24 (55.8%)
	Ex-smoker	16 (37.2%)
	Current smoker	3 (7.0%)
Alcohol, units/week		7.9 (14.1)
ICH	**Lobar location**	22 (51.2%)
	Time from ICH to randomisation, days	119.5 (195.1)
Past medical history	**Hypertension**	26 (60.5%)
	Hypercholesterolaemia	10 (23.3%)
	Ischaemic heart disease	0 (0.0%)
	Diabetes	3 (7.0%)
	Atrial fibrillation	4 (9.3%)
Antihypertensive therapy at baseline	**Receiving treatment**	35 (81.4%)
	Number of agents **Dose-adjusted number**	1.3 (0.8) 1.0 (0.8)

SD, standard deviation; ICH, intracerebral haemorrhage

Table 2: Clinical and BP data completeness of participants assessed or overdue follow-up assessment

	Baseline	3-month follow-up	12-month follow-up
Patients with complete clinical data, n/total assessed (%)	43/43 (100%)	33/35 (94.3%)	7/20 (35.0%)
Patients with complete assessment BP data, n/total assessed (%)	43/43 (100%)	33/35 (94.3%)	7/20 (35.0%)
Patients with complete ABPM data, n/total assessed (%)	35/43 (81.0%)	29/35 (82.9%)	7/10 (70.0%)

BP, blood pressure; ABPM, ambulatory blood pressure monitoring

Table 3: Reasons for missing ABPM data

Assessment	Number of participants	Reason for missing data
Baseline	3	Participant did not tolerate monitoring on first attempt (removed monitor after insufficient readings taken)
	3	Monitor not set to "automatic" mode (only test reading registered), or switched off at internal battery. 2nd monitor sent to patient, but taken off prematurely or refused.
	1	Refused 1st attempt ABPM
	1	Withdrew prior to baseline ABPM
3-month follow-up	4	Refused follow-up ABPM (hourly readings on HBPM used in lieu in one participant, as per protocol amendment)
	2	Withdrew prior to 3-month ABPM
	1	Virtual 3-month follow-up due to COVID-19, and patient unable to fit monitor themselves
12-month follow-up	2	Withdrew prior to 12-month ABPM
	1	Refused follow-up ABPM

ABPM, ambulatory blood pressure monitoring

Table 4: Other issues encountered in performing ABPM

Assessment	Number of participants	Issue encountered
Baseline	6	Programming issue requiring a new monitor to be sent to the participant, causing a delay
	3	Batteries expired prior to all readings being taken
	1	Participant did not tolerate monitoring on first attempt (removed monitor before all readings taken)
3-month follow-up	1	Batteries expired prior to all readings being taken
	1	Participant did not tolerate monitoring on first attempt (pressed stop key before all readings taken)

ABPM, ambulatory blood pressure monitoring

Table 5: COVID-19 follow-up contingency measures

Assessment	Number of participants	Contingency measures taken
3-month follow-up	3	No 3-month assessment BP; two ABPM test readings used in lieu
12-month follow-up	13	Follow-up postponed

BP, blood pressure; ABPM, ambulatory blood pressure monitoring

Table 6: Feasibility issues encountered in one or more participant in the intensive monitoring and treatment group, and actions taken to address these

Issue encountered	Action taken
HBPM telemetric kit technical issues	(i) Advised relocation of kit in participant's home (ii) New hub device shipped to participant (iii) Wrong size / type of BP cuff given to participant in error by site, new equipment shipped
Poor adherence to monitoring / delayed commencement of monitoring / other individuals using the participant's monitor	(i) Frequent phone calls to encourage adherence / explain the procedure again
Delays in securing contact with the participant's GP by phone and/or delays in patient appointments to receive an updated prescription	(i) Participant sought an appointment with an alternative GP at the practice or locum GP (ii) Sought email addresses for GPs from practice administrators
Pharmacy stock issues of amlodipine causing delays in starting treatment	(i) Encourage participants to attend alternative pharmacies
Nationwide shortage of nifedipine requiring an alternative formulation to be prescribed and a temporary dose reduction	(i) Trial site hospital pharmacy contacted for emergency supply (ii) Avoid new prescriptions of nifedipine
Nationwide shortage of valsartan	(i) Sought supply from other pharmacies (ii) Switched prescription to losartan (iii) Avoid new prescriptions of valsartan
Medication side effects prompting self-discontinuation of treatment	(i) Highlighted the need for participants to contact the Oxford BP monitoring centre before discontinuing treatment
Medications reduced by GP or local site investigator	(i) Participant advised to contact the Oxford BP monitoring centre when changes are made by other prescribers during the trial period
Lapses in telemetric BP monitoring due to trips overseas	(i) Participants encouraged to use the BP monitor (without the telemetric hub) when abroad where possible

HBPM, home blood pressure monitoring; GP, general practitioner; BP, blood pressure

Table 7: Blood pressure of randomised participants

Assessment	n	Mean (SD) BP, mm Hg	Clinic*	Daytime ABPM**	Nighttime ABPM**
Baseline	43	Systolic	146.0 (16.6)	146.4 (18.9)	133.7 (24.1)
		Diastolic	85.4 (10.8)	83.1 (11.8)	79.0 (13.3)
3-month follow-up	33	Systolic	132.1 (16.0)	136.6 (14.4)	124.8 (20.3)
		Diastolic	81.0 (12.0)	80.5 (9.1)	72.3 (11.6)
12-month follow-up	7	Systolic	132.3 (15.9)	137.8 (8.7)	133.5 (20.3)
		Diastolic	79.9 (7.0)	82.5 (7.9)	78.9 (10.4)

SD, standard deviation; BP, blood pressure; ABPM, ambulatory blood pressure measurement. *Home BP assessment used in lieu of clinic BP in 3 participants. ** ABPM performed in 34 of 43 participants.

PROHIBIT-ICH Trial Management Group's proposal to continue the study taking into account The Stroke Association's recommendations from Thursday 12th November

Tuesday 17th November

Baseline Visits:

- The recruitment of a new PROHIBIT-ICH participant should not be delayed if a site is unable to obtain an MRI scan; in this case they should be recruited with a routine clinical acute CT scan. We will explore methods of measuring small vessel disease markers on CT scans instead of MRI.

- We will also request all routine clinical MRI scans (within 6 months of randomisation) as these can also be used to measure the key markers of cerebral small vessel disease

12 month follow up visits:

- We would like to include the option for new participants to have a CT or MRI scan at the 12 month follow up visit, depending on the imaging modality provided at baseline (CT or MRI).

Target of 60 participants for the MRI study:

Where possible we would like to give sites the opportunity to obtain research MRI scans (which follow the PROHIBIT-ICH Imaging Manual protocol) from new participants at baseline, until we reach a target of 60 participants with MRI. We aim to fund these additional 17 sets of MRI scans (total ~£8500) using Oxford and UCL internal funds. We anticipate that this sample size will still be useful to see if we can detect changes in small vessel disease markers over time.

Delayed 12 month follow up visits:

- We would like to continue postponing the 12 month follow up visit until sites can obtain MRI scans i.e. we would prefer that the 12 month follow up BP data is not collected before the MRI scan but rather that both BP monitoring and the MRI scan are collected on the same visit date.

- We are happy for the MRI scans from the 12 month follow up visits to be delayed by up to approximately 2 years i.e. these can happen up to approximately 24 months from the baseline visit. Longer follow-up will not compromise the aims of the study (and might help detect MRI changes)

Set-up of new sites:

- We would like to recruit new sites (aiming for up to 8 new sites to bring the total to 20 sites) that would recruit with CT only. However, we need to clarify what the capacity of the BP equipment is if many more participants are recruited than expected.

Appendix 2.20

Link to Youtube Instructional Videos (On PDF version of this thesis, please click "PLAY ALL" link below)



Blood pressure training: Bluetooth

6 videos • 492 views • Last updated on 12 Feb 2019

Nuffield Department of Clinical Neurosciences

SUBSCRIBE

1 

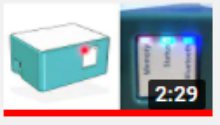
1 Digital Bluetooth Monitor

Nuffield Department of Clinical Neurosciences

2 

2 Digital Bluetooth Monitor

Nuffield Department of Clinical Neurosciences

3 

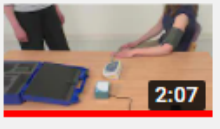
3 Digital Bluetooth Monitor

Nuffield Department of Clinical Neurosciences

4 

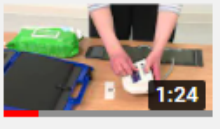
4 Digital Bluetooth Monitor

Nuffield Department of Clinical Neurosciences

5 

5 Digital Bluetooth Monitor

Nuffield Department of Clinical Neurosciences

6 

6 Digital Bluetooth Monitor

Nuffield Department of Clinical Neurosciences

Appendix 3.1

Triple therapy prevention of **R**ecurrent **I**ntracerebral **D**isease **E**ve**N**ts **T**rial (TRIDENT) UK Telemetric Home Blood Pressure Monitoring Sub-Study

Trial Sub-Study Clinical Investigation Plan

This Clinical Investigation Plan is to be used in conjunction with the full Protocol of TRIDENT
TRIDENT REC ID: 17/ES/0122
TRIDENT Protocol ID: GI-AU-NMH-2016-01

Full title of Investigation:	Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial (TRIDENT) UK Telemetric Home Blood Pressure Monitoring Sub-Study
Short title:	TRIDENT UK HBPM
Version and date of Clinical Investigation Plan (CIP):	Version 1.0, 30th August 2019
Sponsor:	The George Institute
Sub-study Host:	University of Oxford
UK Legal Representative:	The University of Edinburgh
Funder:	NIHR Biomedical Research Centre, Oxford (OxBRC)

1. Signatures

The Chief Investigators (CIs) have read this Clinical Investigation Plan (CIP) and agree to perform the investigations and to abide by this CIP.

The CIs agree to conduct the investigation in compliance with the approved CIP, EU Good Clinical Practice (GCP) and UK Regulations for Devices (SI 2002/618; as amended) for regulated studies, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Co-Chief Investigator
Professor Peter Rothwell
Centre for the Prevention of Stroke and Dementia
University of Oxford

Signature _____ **Date** _____

Co-Chief Investigator
Professor Craig Anderson
The George Institute for Global Health
University of New South Wales

Signature _____ **Date** _____

Co-Chief Investigator
Professor Rustam Al-Shahi Salman
Centre for Clinical Brain Sciences
University of Edinburgh

Signature _____ **Date** _____

2. Contents

1. Signatures **2**
2. Contents **3**
3. Glossary of Abbreviations and Terms **5**
4. Contact Information **8**
5. Overall Synopsis of the Clinical Investigation **9**
6. Background and Rationale **12**
6.1 Intracerebral haemorrhage burden *12*
6.2 Secondary prevention after ICH *12*
6.3 Blood pressure and ICH risk ..... ***Error! Bookmark not defined.***
6.4 Evidence for intensive and sustained blood pressure control after ICH *13*
6.5 Use and safety of a combination blood pressure-lowering pill *15*
6.6 Blood pressure variability; ICH risk and treatment effects *16*
7. Identification and Description of the Investigational Device **17**
8. Justification for the Design of the Clinical Investigation **20**
9. Risks and Benefits of the Clinical Investigation **21**
10. Methods **22**
10.1 Study design *22*
10.1.1 Summary of TRIDENT study design 22
10.1.2 TRIDENT UK BP HBPM Sub-study design 23
10.2 Eligibility criteria *23*
10.2.1 Inclusion criteria 24
10.2.2 Exclusion criteria 24
10.3 Schedule of Evaluations *25*
10.4 Procedures *25*
10.4.1 Subject identification and eligibility 25
10.4.2 Informed Consent Process 27
10.4.3 Baseline assessments 27
10.4.4 Intervention 27
10.4.4 Device accountability 29
11. Monitoring Plan **30**
11.1 Blood pressure safety monitoring *30*
11.2 Confidentiality *30*
11.3 Data management *31*
11.4 Record keeping and archiving *31*
12. Statistical Considerations **32**
12.1 Outcomes *32*
12.1.1 Primary Outcome 32
12.1.2 Secondary Outcomes 32

12.2 Sample size calculations *33*
12.3 Statistical analysis *34*
12.3.1 Primary and secondary outcome analysis 34
12.3.2 Sensitivity and other planned analyses 34

13. Amendments to the CIP **35**

14. Deviations from the Clinical Investigation Plan **36**
14.1 Procedures for recording, reporting and analysing CIP deviations *36*
14.2 Notification requirements and time frames *36*
14.3 Corrective and preventive actions and principal investigator disqualification criteria *36*
14.4 Procedure for reporting any protocol deviations *36*

15. Statements of Compliance **38**

16. Definition of End of Study **39**

17. Publication Policy **40**

18. References **41**

3. Glossary of Abbreviations and Terms

AE	Adverse Event
ABPM	Ambulatory Blood Pressure Monitoring
BP	Blood Pressure
CA	Competent Authority
CAA	Cerebral Amyloid Angiopathy
CABG	Coronary Artery Bypass Graft
CCB	Calcium Channel Blocker
CCC	Central Coordinating Centre
CI	Chief Investigator
CI	Confidence Interval
CIA	Clinical Investigation Agreement
CIP	Clinical Investigation Plan
COMMIT	Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment
CRF	Case Report Form
CRO	Contract Research Organisation
CVSD	Cerebral Small Vessel Disease
EC	European Commission
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
EUDAMED	European Medical Devices Regulatory Database
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice

HBPM	Home blood pressure monitoring
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	Intracerebral haemorrhage
IMD	Investigational Medical Device
INTERACT2	The second (main phase) of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial
ISF	Investigator Site File
ITT	Intention-to-treat
JRO	Joint Research Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Competent Authority
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute of Clinical Excellence
NIHR	National Institute for Health Research
NIST	National Institute of Standards and Technology
OxBRC	Oxford Biomedical Research Centre
OXVASC	Oxford Vascular Study
PI	Principal Investigator
PIS	Participant Information Sheet
PRoFESS	Prevention Regimen For Effectively Avoiding Second Strokes Study
PROGRESS	Perindopril Protection Against Recurrent Stroke Study

QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOP	Standard Operating Procedure
SPS3	Secondary Prevention of Small Subcortical Strokes (SPS3) Trial
SVD	Small Vessel Disease
TGI	The George Institute for Global Health
TIA	Transient Ischaemic Attack
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

4. Contact Information

Co-Chief Investigator	Professor Peter Rothwell Centre for Prevention of Stroke and Dementia, University of Oxford Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU peter.rothwell@ndcn.ox.ac.uk Tel: 01865 231603
Co-Chief Investigator	Professor Craig Anderson The George Institute for Global Health, University of New South Wales Level 10, King George V Building, 83-117 Missenden Rd Camperdown NSW 2050 Australia Tel +61 2 99934521 Email: craig.anderson@sydney.edu.au
Co-Chief Investigator	Professor Rustam Al-Shahi Salman Centre for Clinical Brain Sciences University of Edinburgh Tel: 0131 465 9618 rustam.al-shahi@ed.ac.uk
Clinical Research Fellow	Iain McGurgan Centre for Prevention of Stroke and Dementia, University of Oxford Level 6, West Wing John Radcliffe Hospital Headley Way Oxford OX3 9DU Tel: 01865 231601 ian.mcgurgan@ndcn.ox.ac.uk
Clinical Research Fellow	Tom Moullaali Centre for Clinical Brain Sciences University of Edinburgh Tel: 0131 465 9618 tom.moullaali@ed.ac.uk
Sub-Study Statistician	Dr Joanna Moschandreas Centre for Prevention of Stroke and Dementia, University of Oxford Level 6, West Wing John Radcliffe Hospital Oxford OX3 9DU Tel: 01865 234622 ziyah.mehta@ndcn.ox.ac.uk

5. Overall Synopsis of the Clinical Investigation

Title of Study: Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial, UK Telemetric Home Blood Pressure Monitoring Sub-Study
Short Title: TRIDENT UK HBPM
Device: A&D Digital Blood Pressure Monitor (UA-767PBT-Ci), CE Declaration UA-767PBT-Ci
Estimated Total Study Duration: 3 years
Study Duration per Participant: 6 weeks
Objectives: To determine the effects on mean blood pressure, blood pressure variability, diurnal blood pressure variation and any sustained hypotension of a single, fixed low-dose, combination blood pressure lowering pill ("Triple Pill" - telmisartan 20mg, amlodipine 2.5mg and indapamide 1.25mg) compared with matching placebo using telemetric home monitoring, in patients with recent spontaneous (non-traumatic) intracerebral haemorrhage (ICH).
Type of Investigation: A home telemetric blood pressure monitoring sub-study of a multicentre, double-blinded, placebo-controlled, parallel-group randomised controlled trial of a fixed low-dose combination blood pressure lowering pill ("Triple Pill") on top of standard of care, in patients with a history of spontaneous ICH and systolic blood pressure (SBP) levels defined as at least 'high normal to borderline high' (defined as ≥130 mm Hg) and on either minimal or no blood pressure lowering treatment according to standard guideline definitions.
Investigation Design and Methods: TRIDENT UK HBPM will involve the monitoring of home blood pressure using telemetric blood pressure monitors in randomised patients at TRIDENT UK centres that agree to participate in the sub-study. Participants randomised to the vanguard and main phases of TRIDENT UK that provide informed consent to participate in the sub-study will be provided with a home Bluetooth-enabled telemetric monitor to take blood pressure readings twice daily until their 6 week follow-up visit, at which point they will return the monitor and be fitted with a 24-hour ambulatory blood pressure monitor (ABPM). Multiple measures of blood pressure will enable the investigators to characterise the blood

pressure response to the intervention, any safety signal in relation to episodic, sustained or diurnal hypotension as well as the feasibility of home telemetric monitoring in this setting.
Planned Investigation Sites: Multicentre
Total number of Participants Planned: 40
Inclusion Criteria: The participant should meet all of the TRIDENT main trial inclusion criteria. *Single additional inclusion criterion for the TRIDENT UK HBPM sub-study* 1. Willingness and demonstration of ability to undertake home blood pressure measurements, either unassisted or with the help of a relative, friend or carer **Exclusion Criteria:** The participant should meet all of the TRIDENT main trial exclusion criteria. *Single additional exclusion criterion for the TRIDENT UK HBPM sub-study* 1. Known absence of mobile phone coverage from all network operators, in addition to an absence of any internet access in the patient's place of residence
Outcome Measures: TRIDENT UK HBPM is an observational trial sub-study aiming to characterise the effects on various measures of blood pressure of a combination blood pressure lowering pill in addition to usual care in ICH survivors. *Primary outcome:* (i) The magnitude of difference in mean SBP based on multiple home measurements after the first week of monitoring to the end of the monitoring period, in the intervention arm versus the control arm *Secondary outcomes:* (ii) The difference in blood pressure variability (expressed as SBP standard deviation and coefficient of variation) between the intervention and the control arms based on home telemetric readings (iii) The difference in mean daytime SBP, mean night-time SBP and nocturnal blood pressure fall ((awake mean SBP - asleep mean SBP)/awake mean SBP) between the intervention and the control arm based on 6 week 24-hour ABPM

(iv)	The above outcomes for diastolic blood pressure and mean arterial pressure
(v)	The safety of intervention as reflected in home telemetric blood pressure readings and ABPM: sustained hypotension (defined as mean SBP over seven consecutive days of home readings < 100 mm Hg) in the intervention versus the control arm, frequency of episodic hypotension (defined as daytime SBP < 80 mm Hg) in the intervention versus the control arm
(vi)	The feasibility of telemetric home BP monitoring: consent rate, dropout rate from telemetric monitoring process prior to 6 weeks

6. Background and Rationale

6.1 Intracerebral haemorrhage burden

Intracerebral haemorrhage (ICH) is the most severe form of stroke and is a major cause of severe disability and death worldwide. Spontaneous ICH results from rupture of blood vessels in the brain that is not caused by trauma, causing bleeding within the brain parenchyma. The rupturing of these vessels is a consequence of cerebral small vessel disease (SVD); blood vessels are damaged by hypertension-related degenerative changes (arteriosclerosis) or cerebral amyloid angiopathy (CAA) (1). The location of the bleed can help identify the underlying pathology; arteriosclerosis-associated ICH occurs most commonly in the deep structures, whereas β-amyloid deposition in cortical and leptomeningeal vessels in CAA causes cortical / sub-cortical "lobar" bleeds (2). ICH accounts for 10-15% of the 20 million new strokes in the world each year and has a high case fatality rate; the one month rate is about 40%, higher than that for ischaemic stroke or subarachnoid haemorrhage (3-5). Long term outcome after ICH is also poor; less than a half of patients survive one year and less than a third survive five years, while survivors have substantial cognitive and physical impairments (6). Despite the absolute number of incident ICH being around half that of ischaemic stroke globally, the burden of ICH in terms of "loss of productive life years" is substantially greater as ICH tends to affect people at earlier (working) ages (7). Additionally, a meta-analysis demonstrated that both ICH incidence and one month case fatality rates remained relatively constant between 1980 and 2008 (3), making ICH a persistent challenge for stroke research.

6.2 Secondary prevention after ICH

Survivors are at high risk of recurrent ICH and other serious cerebrovascular and cardiovascular events, with annual rates of up to 10% (6), and recurrent strokes result in higher mortality and disability than the first occurrence (8). There is also a high risk of dementia after spontaneous ICH, with an incidence of almost 30% at four years, likely higher than that for ischaemic stroke (9). Well-established risk factors for ICH recurrence include increasing age (10), hypertension (11), excessive alcohol use (12) and the presence of cerebral microbleeds on magnetic resonance imaging (13). Hypertension is the strongest modifiable risk factor for ICH and antihypertensive treatment appears to improve outcome after ICH regardless of bleed location (2). Observational research suggests a strong association between hypertension and ICH recurrence for both non-lobar and lobar bleeds, with associations seen even at "pre-hypertensive levels" (SBP 120-139 mm Hg and diastolic BP 80-89 mm hg) and stronger

associations with higher levels of blood pressure, suggesting that prolonged aggressive blood pressure control may substantially lower risk (11).

6.3 Blood pressure and ICH risk

Elevated blood pressure is the strongest modifiable risk factor for stroke in general, but particularly for ICH. People with hypertension have almost six times the risk of ICH compared to those without, after adjustment for other risk factors (14). This association might be explained by the effect of poorly controlled hypertension on small blood vessel walls, leading to hypertensive arteriopathy.

Following ICH, patients often have early hematoma expansion, and this is an independent determinant of death and poor functional outcome (15, 16). Early intensive blood pressure control after acute ICH has been shown in multiple large trials to reduce this expansion, with variable effects on functional outcome (17). Observational data suggest that blood pressure after ICH is substantially raised compared with premorbid levels, due to a rise in the days and weeks before the event and acutely after the event, significantly greater than that seen for ischaemic stroke (18). Sustained post-acute blood pressure management arguably holds the most potential to improve long-term prognosis and recurrence following an ICH, but there have been no dedicated trials targeting long-term blood pressure reduction after ICH.

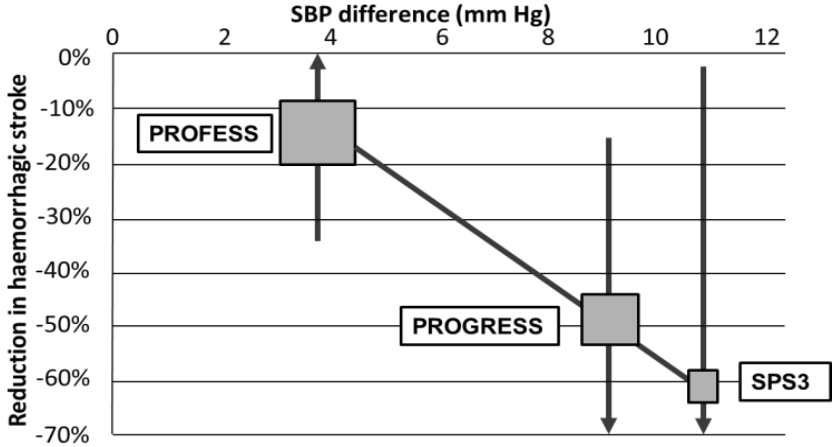
Current UK guidelines suggest a SBP target after stroke of 130 mm Hg (19). Nevertheless, in practice control of blood pressure remains poor. In the UK, less than 40% of TIA patients achieved the guideline blood pressure standard in a retrospective cohort study (20), and US cohort studies demonstrate similarly poor sustained blood pressure control (11, 21). Approximately 40% of stroke patients in the PROFESS study had blood pressure deemed “high” or “very high” (SBP >140 mm Hg) at follow-up, with a significantly increased risk of recurrent stroke in these groups (22). The proportion of stroke patients taking antihypertensive drugs declines rapidly (by about 25%) in the first 2 years after stroke (23), suggesting that patient adherence is an important barrier to effective blood pressure treatment. Poor adherence to blood pressure medications is also clearly associated with an increased risk of stroke (24). A systematic review of interventions to improve adherence found few high-quality studies, with a need to improve objective monitoring of adherence and blood pressure (25). A comprehensive review of research gaps in blood pressure treatment after stroke concluded that clinical trials evaluating implementation of evidence-based strategies for blood pressure control to prevent recurrent stroke are needed (26).

6.4 Evidence for intensive and sustained blood pressure control after ICH

The main prospective randomised data on the effects of long-term blood pressure lowering after ICH come from PROGRESS, a randomised, double-blind, placebo-controlled trial

involving 6105 patients with prior ischaemic stroke, ICH, or transient ischaemic attack (TIA), who were randomly assigned to either active treatment (perindopril with or without indapamide) or matching placebo(s), with a mean follow-up of 4 years (27). Among 660 participants with a history of ICH at baseline, there was a mean difference of 11 mm Hg systolic and 4 mm Hg diastolic blood pressure between perindopril- and indapamide-treated and placebo arm participants, with a reduction in the absolute rate of ICH from 2% to 1% over 3.9 years of follow-up. This 50% relative risk reduction for ICH was higher than the 24% reduction in ischaemic stroke (28). The stronger treatment effect in patients with ICH as compared to ischaemic stroke is consistent with the larger reductions of ICH as compared to ischaemic stroke outcomes in randomised trials of blood pressure-lowering in patients with hypertension (29). Consistent with this substantial risk reduction in ICH, the SPS3 trial in 3020 patients with recent subcortical infarction (presumed due to SVD, the main cause of ICH) showed that the risk of future ICH was significantly reduced (by 63%) by intensive blood pressure lowering (target systolic blood pressure <130 mm Hg compared with 130-139 mm Hg) (30). However, the largest trial of blood pressure-lowering after stroke, the PRoFESS study, showed no significant benefits of early initiation of treatment with an angiotensin receptor antagonist (telmisartan) on top of usual care for total stroke or ICH in 20,332 patients with recent ischaemic stroke (31). Yet, a meta-regression analysis (Figure. 1) of these three randomized trials performed by the TRIDENT investigators, which included an assessment of ICH as an endpoint, suggests that the PRoFESS findings may have been due to the small SBP difference between randomised groups; with evidence of a dose-response relation for SBP and reduction in the risk of ICH.

Figure 1: Reduction in haemorrhagic stroke in clinical trials (from the TRIDENT protocol, courtesy of the TRIDENT investigators)



There are also, nevertheless, concerns that intensive blood pressure lowering may have an adverse impact in older populations by reducing cerebral perfusion, causing cerebral ischaemia, progression of cognitive impairment and falls (32). There was a trend towards an increase in adverse events related to hypotension in the SPS3 study (23 versus 15, RR 1.53, P=0.2) (30), and overall in a meta-analysis of more versus less intensive blood pressure-lowering there were four trials that reported hypotension outcomes (5,118 participants, with 76 versus 16 events) with more intensive blood pressure control greatly increasing the risk of hypotension (RR 4.16, 95% CI 2.25–7.70, P<0.001) (33). Thus, although intensive blood pressure lowering is a very promising secondary prevention intervention in ICH, the optimum long term target blood pressure remains uncertain.

6.5 Use and safety of a combination blood pressure-lowering pill

(Adapted from the TRIDENT protocol, courtesy of the TRIDENT investigators)

Most hypertensive patients require two or more blood pressure-lowering agents to achieve adequate blood pressure control (34). However, the need to titrate medications and the addition of multiple classes of drugs requires multiple assessments that can adversely impact on adherence and/or attendance at scheduled visits (35). The requirement to take multiple medications, often in complex regimes, can also result in poor adherence (36). For physicians, the need for repeated up-titrating and/or adding extra medications can lead to therapeutic inertia and acceptance of inadequate blood pressure control (37, 38). The need to titrate blood pressure-lowering medications adds complexities to trials of ‘more’ versus ‘less’ blood pressure lowering (39). Dual combination blood pressure-lowering medication has been shown to improve achieved blood pressure reductions and CV event rates (39). Initiating dual combination therapy not only reduces the time taken to achieve blood pressure control but it also results in a lower final blood pressure target being attained (40, 41). For the patient, improved adherence has also been demonstrated without adversely affecting the side-effect profile (42). Further benefits in blood pressure control are also available via a simplified up-titration regime. There is a good pharmacological rationale to expect improved tolerability from a fixed-dose triple combination blood pressure-lowering agent (42, 43). The benefits of each component are additive, and low doses typically avoid most side-effects, whilst also achieving a large part of the potential blood pressure reduction associated from any given drug. Thus, three half-dose medications would typically lower blood pressure by about as much as two full-dose medications, but with fewer side-effects (42). A systematic review undertaken by TRIDENT investigators identified six trials comparing triple blood pressure-lowering vs. monotherapy, and it indicates that on average, there is a difference of 11 mm Hg systolic blood pressure compared to monotherapy. In addition, there is a steady increase in blood pressure reduction with each ½ dose and triple ½ dose, conferring an approximate 18 mm Hg SBP reduction compared to placebo with no increase in adverse events. Changing to the triple combination blood pressure-lowering agent approach has been shown to be safe and effective over 4 months in several thousand middle-aged hypertensive patients uncontrolled on

previous antihypertensive mono- or dual therapy (44, 45). Moreover, a meta-analyses of randomised trials investigating effects of blood pressure-lowering treatment in hypertension found that all major classes of blood pressure-lowering drugs (diuretics, beta-blockers, calcium channel blockers, ACE inhibitors and central agents) significantly and markedly (two- to three-fold) increase treatment discontinuations, with the relevant exception of angiotensin II receptor antagonists which were found not to increase discontinuations over those occurring with placebo (46). An angiotensin II receptor antagonists-based combination blood pressure-lowering strategy seems appropriate for both efficacy and tolerability in this population.

6.6 Blood pressure variability; ICH risk and treatment effects

In clinical trials of antihypertensive drugs, vascular risk reduction is usually associated with reductions in mean blood pressure, and the effects of reduction on within-individual blood pressure variability are rarely reported (47). Within-individual visit-to-visit variability in blood pressure, however, accounts for about a half of the variance in group SBP at any given follow-up (48). Therefore, comparing group SBP standard deviation in clinical trials can be used as a surrogate of the likely effect of antihypertensive treatment on within-individual visit-to-visit SBP variability (49). There exist significant medication class effects on such group SBP variance in randomised controlled trials of antihypertensive drugs, with calcium channel blockers and non-loop diuretic drugs providing the biggest reductions, and such reductions in inter-individual variation in SBP are associated with reductions in stroke risk independent of mean BP (49). As above, such reductions inter-individual SBP variance can be seen as a surrogate marker of reductions in within-individual SBP variability. In fact, in large trials of atenolol- and amlodipine-based treatments, opposite effects on within-individual variability (increases and decreases, respectively) were seen, and reduced event rates that were not fully accounted for by mean SBP reduction could be explained by such effects on variability (50).

In addition to raised mean blood pressure, within-individual blood pressure variation may predict early haematoma growth and functional outcome after ICH (51). In a *post hoc* analysis of the INTERACT2 randomised controlled trial, blood pressure variability in the hyperacute (first 24 hours) and acute (days 2-7) phases was shown to be strongly and independently associated with mortality and morbidity at 90 days post-ICH (52). Treatments that are effective at reducing blood pressure variability as well as mean blood pressure, therefore, might have important implications for secondary prevention after ICH. The “Triple Pill” in TRIDENT contains two medications with the greatest class effects on blood pressure variability reduction; therefore, this sub-study represents an ideal opportunity to accurately assess within-individual blood pressure variability in both study groups.

7. Identification and Description of the Investigational Device

Home telemetric home monitoring device for the TRIDENT UK HBPM sub-study

Telemetric home monitoring is a promising strategy to facilitate home blood pressure monitoring after stroke, which should improve adherence and optimise medication to better control blood pressure. Telemetry allows patients with hypertension to monitor their own blood pressure and automatically send the information to a secure website, available to their clinicians to monitor and adjust their treatment.

A recent UK randomised controlled trial of blood pressure home self-monitoring (with or without telemetric monitoring) versus usual clinic readings to guide medication titration in individuals with poorly controlled hypertension in primary care demonstrated significantly lower SBP in the telemetric monitoring group (-4.7 mm Hg [95% CI -7 to -2.4]) than in the usual care group after 12 months (53). These findings support those of an earlier, smaller UK trial of telemonitoring, using 6 month ABPM as the primary outcome (54).

Home telemetric Bluetooth blood pressure monitoring has been evaluated in patients with TIA and predominantly non-disabling stroke in the setting of the Oxford Vascular (OXVASC) Study by the Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT) study (unpublished data). In this population, the intervention was safe and effective, with few adverse events and high patient satisfaction. However, more research is required on the feasibility of use of this strategy in more disabling stroke and in patients with ICH, as well as on transferability to multiple centres beyond the previous research setting in Oxfordshire.

In the COMMIT study, we studied consecutive eligible consenting patients in the OXVASC study. After prescription of initial blood pressure-lowering therapy, if required, patients measured their blood pressure 3 times over 10 minutes on 3 occasions per day at home with a Bluetooth-equipped monitor for 1-3 months, depending on control. Measurements transmitted automatically in real time were checked daily on a secure web page. If blood pressure was consistently above 130/80 mm Hg or below 100/60 mm Hg antihypertensive therapy was adjusted.

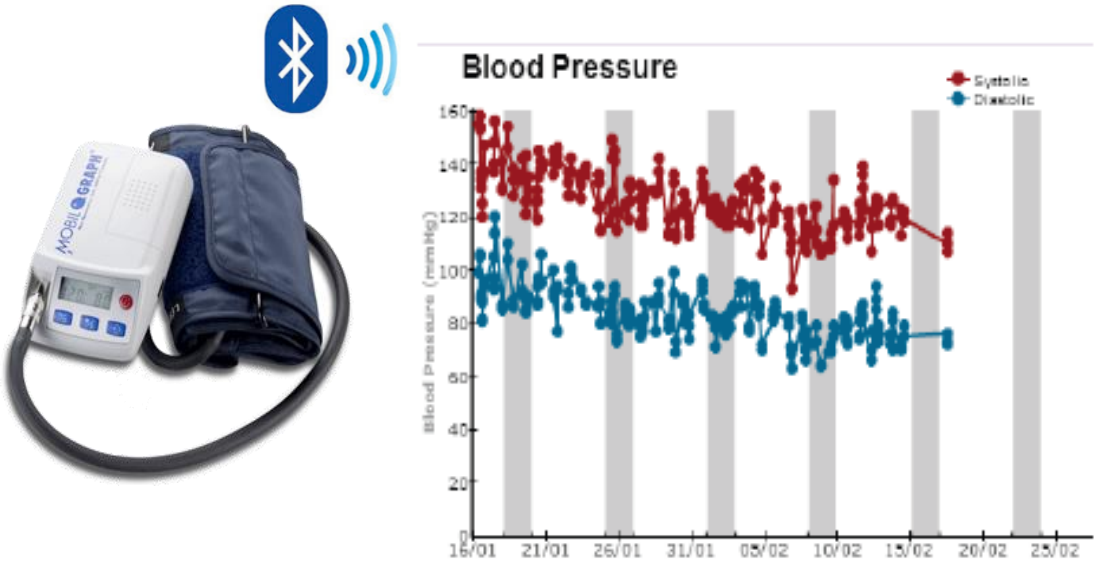
The results outlined below are from the first 1000 recruits (mean/SD age=69/13; range=21-98yr; 23% ≥ 80 years): (1) Rates and risk factors for masked hypertension. The prevalence of hypertension after TIA and stroke is often underestimated, with rates of “masked” hypertension (normal clinic blood pressure but elevated home readings) ranging from 10-30%. In COMMIT, masked hypertension (blood pressure ≤ 140/90 mm Hg at initial assessment and mean blood pressure > 135/85 mm Hg across the first 3 days of monitoring; AHA definition)

was found in 344 (34.4%). The much more detailed record of blood pressure obtained on home telemetric blood pressure-monitoring thus provided clinically important data that were not available from occasional clinic measurements. Masked hypertension has not been investigated in ICH; (2) Feasibility, medication changes and control of blood pressure. Blood pressure-lowering medication was initiated or increased at the pre-monitoring baseline visit in 555 (55.5%) patients. Medication was further initiated or adjusted at least once within the first month of home-monitoring in 558 (55.8%) patients and from 1-3 months in 393 (39%) patients. Mean blood pressure measured on clinic follow-up fell from 141/83 mm Hg at entry to 130/74 mm Hg at 1-month ($p<0.001$) and to 127/72 mm Hg at 3-months ($p<0.001$) (see Figure 2 for an example blood pressure trace). Telemetric home blood pressure monitoring was feasible irrespective of age, and informed titration of medication in the majority of patients and was associated with good blood pressure control; (3) Acceptability of telemetric home-monitoring to patients. Of 1000 patients recruited, 576 (57.6%) returned an anonymised questionnaire after 1 month of monitoring. 533 (90.8%) approved of the intensive monitoring, 522 (89%) felt reassured by the central surveillance and 500 (85.2%) thought it helpful to be able to discuss their blood pressure readings over the phone. However, 72 (12.3%) patients reported that monitoring their blood pressure made them anxious and 83 (14.1%) felt it was time consuming. Mean (SD) overall satisfaction (0%-extremely dissatisfied to 100%–extremely satisfied) was 89 (14) %; (4) Comparison with 24-hour ambulatory monitoring (ABPM). We validated telemetric HBPM and ABPM by association with hypertensive arteriopathy and risk of recurrent vascular events. Mean SBP at 1-month on nocturnal ABPM, awake ABPM and HBPM (3 measurements, 3 times daily for 7 days) was related to five markers of hypertensive arteriopathy (creatinine > 120 mmol/L; aortic pulse wave velocity > 12m/s; advanced leukoaraiosis on brain imaging; Montreal Cognitive Assessment < 25; stroke vs. TIA) and to risk of recurrent stroke, coronary events and death. Among 1000 patients, hypertensive arteriopathy was more strongly associated (p-diff=0.007) with HBPM-SBP (odds ratio per 10 mm Hg: 1.42, 1.28-1.56, $p<0.0001$) than with awake or nocturnal ABPM (awake 1.11, 1.00-1.24; nocturnal 1.28, 1.17-1.40). During 2775 patient-years of follow-up, residual hypertension at 1-month on HBPM (n=218/23%) predicted the risk of recurrent events (HR=2.00, 1.28-3.12, p=0.002) better than on awake ABPM (n=207/20%, HR=1.24, 0.78-1.98, p=0.37) or nocturnal ABPM (n=307/39%, HR=1.47, 0.95-2.26, p=0.08). In models combining all 3 measures, only HBPM independently predicted recurrent events (HR=1.34, 1.11–1.63, p=0.003). Thus, residual hypertension is more strongly associated with hypertensive arteriopathy and risk of recurrent vascular events on HBPM than on ABPM. HBPM is therefore likely to be the better measure of blood pressure-control after TIA/stroke, but has not yet been tested in major stroke or ICH.

From a safety perspective, despite rapid and effective BP control in COMMIT, only 4.2% of patients experienced falls during the first month, occurring at approximately the expected frequency for the population (55). Nine falls were associated with hypotension, of which two required a reduction in medication, and there were a further none medication changes due to hypotensive related symptoms but not associated with falling. No falls were associated with significant trauma. Between the first and second follow up there were a further 48 falls, six

associated with hypotension of which three resulted in medication changes, with eight further reductions due to hypotension without a fall.

Figure 2: Home monitoring blood pressure cuff and monitor (left), and a blood pressure trace from the COMMIT study showing improved blood pressure control over time (right)



8. Justification for the Design of the Clinical Investigation

Summary of the rationale for the sub-study

ICH remains a devastating disease for which prevention of recurrent stroke is a research priority. Blood pressure lowering is the most promising preventive strategy, but adherence and blood pressure control in clinical practice remain poor. There is thus an urgent need to improve ICH secondary prevention through improved long term blood pressure control.

TRIDENT has been designed to resolve persisting clinical uncertainty and provide definitive evidence on the effectiveness of more intensive blood pressure-lowering to prevent recurrent serious cardiovascular events after ICH using a simplified combination regimen of blood pressure-lowering agents. This observational sub-study will use telemetric home blood pressure monitoring and ABPM to characterise the effects of such a regimen on mean blood pressure over multiple home measurements, blood pressure variability and diurnal blood pressure variation, and address blood pressure-lowering safety concerns in the first six weeks of treatment. Such additional blood pressure characterisation will facilitate our understanding of the treatment effects of combination blood-pressure lowering therapy after ICH, and may highlight other safety measures that could be investigated in a larger sub-study such as the associations of sustained or episodic hypotension with clinical outcomes (e.g. falls, cognitive decline, hospital admissions, creatinine rise / renal dysfunction).

9. Risks and Benefits of the Clinical Investigation

The table below summaries the risks and mitigations of all investigational procedures and interventions being performed specific to this sub-study, above those being performed in TRIDENT.

Investigational Procedure / Intervention	**Potential risk**	**Risk management**
Invitation to the sub-study and patient information sheet provided	No potential risk	Research practitioner or member of research/ clinical teams, in hospital ward or clinic
Informed consent obtained	No potential risk	Research practitioner or member of research/ clinical teams, in hospital ward or clinic
Blood pressure measurement (telemetric home monitoring and ABPM)	The squeezing sensation may be uncomfortable but only lasts a few seconds	Performed by the informed participant or a family member / carer

The classification of medical devices in the European Union is outlined in Annex IX of the Council Directive 93/42/EEC (as amended). There are four classes, ranging from low risk to high risk.

Class I

Class IIa

Class IIb

Class III

The Medical Device used in this investigation is classified as Class I.

10. Methods

10.1 Study design

10.1.1 Summary of TRIDENT study design

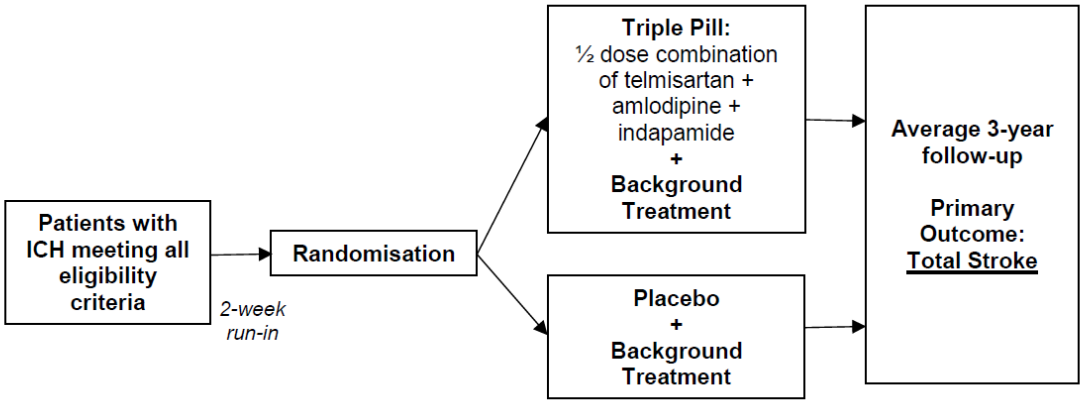
TRIDENT is an international, multicentre, investigator-initiated and conducted, double-blind, placebo-controlled, parallel-group, randomised controlled trial that will involve 4200 patients with prior ICH recruited from approximately 150 clinical centres located in the regions of Australia/New Zealand, Asia, UK/Europe, and the Americas.

The double-blind period will be preceded by a 2-week, single-blind (participants will remain blind), active run-in phase in which all potential participants will receive the Triple Pill (Fig. 3). The aim of this run-in phase is to ensure the randomisation of patients who tolerate the treatment regimen (both of more intensive blood pressure lowering and of specific agents) and to increase the likelihood of high treatment adherence during long term follow-up. Blinding of participants serves to reduce reporting bias of adverse events.

All patients with a history of imaging-confirmed primary ICH from one day (acute phase) and up to six months after symptom onset are considered eligible and will be screened for inclusion into the run-in phase. Those who successfully complete the run-in phase will be randomised. Reasonable attempts will be made to include diverse populations and to maintain a high level of retention of participation in the trial. Greater diversity of subjects allows for broader generalisation of the results.

Randomised participants will receive study medication for an average of three years.

Figure 3: TRIDENT study schema



10.1.2 TRIDENT UK BP HBPM Sub-study design

Patients at participating UK study sites randomised to the vanguard and main phases of TRIDENT (i.e. after the 2-week active run-in period) will be considered for inclusion into this observational sub-study. The vanguard phase seeks to assess the efficacy, tolerability, safety and adherence to the low-dose Triple Pill in the first six months of treatment.

All eligible participants (those who meet the inclusion and exclusion criteria for TRIDENT, plus one additional criterion for this sub-study) will be issued with a telemetric Bluetooth-enabled home blood pressure monitor at the time of the randomisation assessment. They will assess their home blood pressure for six weeks, i.e. until the six week TRIDENT assessment, at which point they will return the telemetric monitor and be fitted with a 24-hour ABPM.

10.2 Eligibility criteria

All participants who fulfil the eligibility criteria for TRIDENT are also eligible for the TRIDENT UK HBPM sub-study, with the addition of one sub-study specific inclusion and exclusion criterion.

10.2.1 Inclusion criteria

The participant should meet all of the TRIDENT main trial inclusion criteria.
Single additional inclusion criterion for the TRIDENT UK HBPM sub-study

1. Willingness and demonstration of ability to undertake home blood pressure measurements, either unassisted or with the help of a relative, friend or carer

10.2.2 Exclusion criteria

The participant should meet all of the TRIDENT main trial exclusion criteria.

Single additional exclusion criterion for the TRIDENT UK HBPM sub-study

1. Known absence of mobile phone coverage from all network operators, in addition to an absence of any internet access in the patient's place of residence

10.3 Schedule of Evaluations

Visit number (TRIDENT)	1	2	3
Case report form (TRIDENT)	A – Screening / Run-in start	B – Run-in completion C - Randomisation	D
Time relative to TRIDENT randomisation	-4 to -2 w	0 w	6 w
Case report form (HBPM sub-study)		Baseline	6 week visit
Written informed consent for blood pressure sub-study	X		
Blood pressure measured		X	X
Bluetooth-enabled blood pressure monitor issued		X	
Bluetooth-enabled blood pressure monitor collected			X
ABPM fitted for 24-hour period			X

10.4 Procedures

10.4.1 Subject identification and eligibility

Summary of TRIDENT procedure

All potentially eligible participants referred to or who contact the study team directly will undergo screening to determine eligibility to the study using the TRIDENT criteria. The screening process begins when a member of the study team makes contact with or is contacted directly by a potential study participant. This initial contact may be via telephone or face-to-face. Initial screening activities will include a brief verbal assessment of the potential participant's medical history, including history of hypertension and ICH, and current medications. If the member of the study team determines that the potential participant may be suitable for the study a copy of the patient information sheet (PIS) will be provided to the

potential participant. All potential participants screened and who have signed a consent form will be recorded on the screening log by the study team. If initial contact was via telephone, a face-to-face visit will be arranged, and the PIS may be sent or emailed to the participant in preparation for the screening visit, if time permits.

The run-in phase is for two weeks. However, participants may undergo a second two-week run-in phase if the first phase is interrupted, problematic or for another reason beyond the patient's control, but according to the decision of the physician. Thus, participants could have a maximum of four weeks for the run-in phase. Only participants who are eligible for and who agree to enter the run-in phase will be entered into the electronic CRF (eCRF).

TRIDENT UK BP HBPM Sub-study subject identification

All TRIDENT participants in UK centres that agree to take part in the sub-study who are found eligible to continue into randomisation after the run-in phase will also be considered eligible for the sub-study, unless they do not meet the additional criteria described in section 10.2. A PIS and written informed consent documents specific to the sub-study will be provided during eligibility screening for TRIDENT.

The local investigator will notify the Oxford device coordination centre by email when a potential participant is interested in taking part in the sub-study. No participant details are provided at this point. This will facilitate delivery of the necessary equipment to the site, as well as training for the local research team on how to administer the ABPM and telemetric BP monitoring kit and explain the monitoring process to the patient, for the first recruit at that site. Where a subject fails to fulfil any element of the inclusion and exclusion criteria for the sub-study, this will be documented and retained by the local investigator. The subject will not be advanced any further into the trial sub-study.

When a subject that is considered eligible for entry into this clinical investigation provides written informed consent to participate, the subject will be allocated the next available investigation number (subject ID number) and will be entered into the sub-study CRF by the local investigator. For subjects enrolled, this number will consist of HBPM 001 for the first subject, HBPM 002 for the second subject and so on. This number will be prefixed by the subject's unique eight digit TRIDENT participant ID to facilitate the linkage of those participating in one or more sub-studies to the main study. The resulting unique identifier of the subject will be noted on all documentation relating to that subject in the sub-study.

Each subject that is enrolled into the study will have their study participation recorded in their hospital notes, a copy of their signed consent form and patient information sheet should also be placed on his/her hospitals notes to identify the subject as participating in a clinical investigation. A letter template for the local investigator to send to the participant's GP to inform them of their patient's involvement in the sub-study will be completed and posted.

10.4.2 Informed Consent Process

It is the responsibility of the investigator, or a person delegated by the investigator to obtain written informed consent from each subject prior to participation in the sub-study, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The person taking consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI/PI on the delegation log. “Adequate time” will be given for consideration by the patient before taking part. The investigator or designee will explain the patients are under no obligation to enter the investigation and that they can withdraw at any time during the Investigation, without having to give a reason. No clinical investigation procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into the investigation. A copy of the signed informed consent document will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate. If a participant withdraws their consent from TRIDENT at any time, then consent is automatically withdrawn from the blood pressure monitoring sub-study.

10.4.3 Baseline assessments

At the sub-study baseline assessment, the following sub-study-specific procedure will be carried out by the local investigator:

Two blood pressure measurements will be taken with the participant rested in a seated position for five minutes, after an appropriate cuff size has been selected, using the monitor provided in the home kit. These readings will be documented in the baseline CRF. The initial seated measurements should be taken in each arm; if there is a significant difference (>20 mm Hg systolic) between them then the arm with the higher value should be used for subsequent home monitoring. The hub device should be plugged in for this assessment if possible, both to demonstrate the procedure to the participant or their carer and to serve as a test reading.

10.4.4 Intervention

Summary of TRIDENT study treatment

Participants who successfully complete the run-in phase and who meet the eligibility criteria for study continuation will be randomised to receive:

1) Triple Pill (active treatment) – telmisartan 20mg, amlodipine 2.5mg, and indapamide 1.25mg;

Or

2) Placebo triple pill – received via blinded study capsules.

Study treatment is double-blinded.

Strategies exist as outlined in the TRIDENT protocol for patients with side-effects deemed due to study medication and sufficiently severe to warrant a change of treatment, without the need for unblinding. If there is concern over ongoing hypertension, open label treatment can be added without the need to unblind. The recommended protocol in all countries involves adding in telmisartan 20 or 40 mg, amlodipine 2.5 or 5 mg, indapamide 1.25 or 2.5 mg, an equivalent dose of an ARB, CCB or thiazide-like diuretic, or a beta-blocker.

TRIDENT UK BP HBPM Sub-study intervention

Participants randomised to both the Triple Pill (active treatment) and placebo triple pill (control) arms will receive a telemetric Bluetooth home blood pressure-monitoring device at the randomisation face-to-face visit. Contact details (name, next of kin name, phone number and/or email address) will be sought for each included participant at the time of the randomisation/baseline assessment, and submitted along with the blood pressure monitor kit issuing form (completed by the local investigator) to the Oxford device coordination site.

The participant will be advised to take blood pressure readings (three readings over 10-minutes in the seated position in the non-dominant arm, unless there is severe hemiparesis) twice daily (early morning and afternoon/evening). The will be instructed how to fit and use the equipment by the local investigator, with further assistance in the form of an instructional leaflet and links to a series of blood pressure monitoring training videos. All blood pressure data will be automatically transmitted centrally in real time to a secure server, accessed by the device coordination site in Oxford. A dedicated blood pressure-monitoring team, blinded to treatment allocation, will be responsible for checking all blood pressure data daily from a safety perspective. This team will make contact with participants if blood pressure readings are not being transmitted or other technical difficulties are encountered, but participants will be asked to redirect clinical questions / adverse effects / missed doses / treatment discontinuation to the responsible researcher at their local study site.

Bluetooth-enabled blood pressure monitors will be collected at the six week TRIDENT follow-up visit, and an ABPM will be fitted by the investigator for a 24 hour period of recording. This will be provided with package instructions and a pre-paid envelope to be posted on completion by the participant to the Oxford coordination site.

10.4.4 Device accountability

The blood pressure equipment will be purchased by the monitoring team in Oxford. The telemetric blood pressure readings will be checked every working day by this team. In the absence of any readings, the monitoring team will troubleshoot the most common equipment problems over the telephone where possible, or arrange a replacement where necessary. There will be a service contract in place to replace or mend any monitors that are not working.

11. Monitoring Plan

11.1 Blood pressure safety monitoring

A dedicated blood pressure-monitoring team, blinded to treatment allocation, will be responsible for checking all blood pressure data daily. A summary of home blood pressure (expressed as a mean blood pressure, standard deviation, maximum/minimum and a percentage of blood pressure readings above 140/90 mm Hg during the monitoring period) would be available to the local site by the time of the 6 week follow-up visit upon request, but not automatically transferred.

Participants will have contact details for the Oxford device coordination centre provided with their telemetric blood pressure monitoring kit to report blood pressure recording issues, but will be asked to redirect clinical questions / adverse effects / missed doses / treatment discontinuation to the responsible researcher at their local study site.

If mean systolic and diastolic blood pressure are > 160 and > 90 mm Hg respectively, or mean systolic blood pressure is < 100 mm Hg over seven consecutive days, the Oxford centre will notify the local study site. Any intervention will be managed in accordance with the TRIDENT protocol.

11.2 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The Bluetooth-enabled blood pressure monitor kit issuing form returned to the Oxford centre will bear the participant's name and contact details. This is to facilitate contact with the participant if any difficulties are encountered in the measurement and transmission of blood pressure readings, and will be clearly explained to the participant in the PIS. Written consent for this will be sought.

Access to these data will be granted to authorised research staff and representatives from the sponsor, host institution and regulatory authorities, by arrangement with the CI, to permit study-related activities and monitoring. All records will be kept securely and confidentially and the data will be pseudo-anonymised for analysis.

All records are the responsibility of the investigators and will be kept in secure conditions. They will ensure that patients' identities are protected from any unauthorised parties. Study participants' data will be kept confidential and managed in accordance with the Data Protection

Act and Research Ethics Committee approval. All participant identifiable information will be anonymised in any study reports. The same standard will be followed if any patient information needs to be sent to a third party.

11.3 Data management

Blood pressure data are acquired via Bluetooth-enabled, regularly-calibrated, telemetric blood pressure monitors (A&D UA-767 BT), and anonymised measures are transmitted securely to a server hosting a password-protected website for daily review (t+ Medical, Abingdon, UK). Data are then exported in .mat (Matlab) format for offline analysis, stored for offline analysis within the Centre for Prevention of Stroke and Dementia along with the data securely downloaded from all 24-hour ABPM. All data are stored at this stage in pseudo-anonymised format, identified by two linked identifiers – the sub-study study ID and a specific blood pressure cohort ID. The master database of analysis results and patient clinical and demographic data is kept on the University of Oxford encrypted, centralised server. All blood pressure data will be stored only at the University of Oxford site in accordance to the data governance policy of the University of Oxford, and will be the responsibility of Professor Rothwell.

11.4 Record keeping and archiving

At the end of the trial, all essential data and documentation will be archived securely by the CI for a minimum of 20 years from the declaration of the end of the trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements. All archived documents will continue to be available for inspection by appropriate authorities upon request.

12. Statistical Considerations

12.1 Outcomes

12.1.1 Primary Outcome

The magnitude of difference in mean SBP based on multiple home measurements after the first week of monitoring to the end of the monitoring period, in the intervention arm versus the control arm

12.1.2 Secondary Outcomes

(i) The difference in blood pressure variability (expressed as SBP standard deviation and coefficient of variation) between the intervention and the control arm based on home telemetric readings

(ii) The difference in mean daytime SBP, mean night-time SBP and nocturnal blood pressure fall ((awake mean SBP - asleep mean SBP)/awake mean SBP) between the intervention and the control arm based on six week ABPM

(iii) The above outcomes for diastolic blood pressure and mean arterial pressure

(iv) The safety of intervention as reflected in home telemetric blood pressure readings and ABPM: sustained hypotension (defined as mean SBP over seven consecutive days of home readings < 100 mm Hg) in the intervention versus the control arm, frequency of episodic hypotension (defined as daytime SBP < 80 mm Hg) in the intervention versus the control arm

(v) The feasibility of telemetric home blood pressure monitoring: consent rate, dropout rate from telemetric monitoring process prior to six weeks. Feasibility criteria are: (a) ≥50% of eligible participants agree to participate; (b) <30% dropout from home blood pressure monitoring (against the advice of the blood pressure monitoring centre) prior to the six week follow-up visit

Standard deviation of systolic blood pressure will be used as the main parameter for blood pressure variability, because it is frequently used and relates directly to mean systolic blood pressure (52). Other chosen parameters to compare blood pressure variability between the groups will include the coefficient of variation (SD divided by the mean) and variation

independent of the mean (a transformation of SD uncorrelated with mean blood pressure, derived as SD/mean^x, with x estimated from curve fitting) (50).

12.2 Sample size calculations

The TRIDENT investigators provide a conservative estimate of a long-term SBP difference in the trial of ≥ 7 mm Hg (e.g. from an average baseline SBP of 145 to 137 mm Hg [placebo group] versus 130 mm Hg [Triple Pill group]), based on their systematic review of six trials comparing triple blood pressure-lowering vs. monotherapy, which indicates an average blood pressure difference of 11/6 mm Hg over short-term follow-up. We estimate, based on this, a SBP difference of 10 mm Hg in the first six weeks.

About 50% of the variation in group SBP variation at a single follow-up assessment is the result of within-individual visit-to-visit variability rather than differences between individuals in underlying mean blood pressure (49). TRIDENT doesn't have recruitment stipulations based on blood pressure readings remaining consistently within a certain range at different time points (only two SBP levels measured five minutes apart within the range 130 – 160 mm Hg are required), therefore patients with variable blood pressure aren't necessarily excluded. On this basis, using multiple measures of home blood pressure for each participant will result in decreased error than using a single clinic follow-up blood pressure measure in each participant. Reducing this error will allow us to use a smaller sample size to assess treatment effects on blood pressure. Using provisional data from the COMMIT study, we can compare the group standard deviation of SBP based on blood pressure measures on one follow-up visit versus that derived from multiple home readings. Mean SBP at the one month clinic visit for 1433 included participants was 131.5 mm Hg, with a standard deviation of 18.3 mm Hg. The mean SBP based on seven days of home readings in these participants was comparable, at 129.0 mm Hg, but the average standard deviation (calculated by taking the square root of the mean of the variance) is much lower at 8.4 mm Hg ($p < 0.0001$).

Using mean home seven day SBP with a standard deviation of 8.4 mm Hg, a sample size of 26 (13 in each group) would be required to detect a difference in mean SBP of 10 mm Hg between the treatment and placebo groups at 90% power with an α of 0.05 (one-tailed; expecting blood pressure lowering in the Triple Pill group). Conversely, by means of comparison, a sample size of 116 (58 in each group) would be required to detect the same effect when using a single six week clinic measurement (assuming a standard deviation of 18.3 mm Hg).

We plan to recruit 40 eligible patients randomised to TRIDENT in participating UK sites between 2018 and 2020 (projected randomisation period), accounting for drop-outs from monitoring and incomplete blood pressure measurement.

12.3 Statistical analysis

In general, the most suitable statistical analysis consistent with the form of data will be used and the underlying assumptions of the statistical method will be verified. Descriptive statistics, as appropriate (e.g. means and standard deviations for continuous variables; proportions for categorical variables), will be reported for variables measured at baseline. Age (mean, SD), sex, vascular risk factors, past medical history, prior antihypertensive medication use and baseline blood pressure (recorded at the screening visit) will be used for baseline comparability of the randomised groups.

12.3.1 Primary and secondary outcome analysis

Analysis will be performed according to the intention to treat principle.

The difference in mean SBP of multiple home measurements between randomised groups at 6 weeks will be compared using t-tests. T-tests will also be used to assess the differences in means between the groups for the 6-week ABPM secondary outcomes of daytime SBP, night-time SBP and nocturnal blood pressure fall. Proportions of participants fulfilling the criteria for sustained hypotension between randomised groups will be compared using Fisher's exact test. Proportions for the consent rate and drop-out rate will be calculated to determine if the required feasibility criteria were met.

The study sample size has been based on the primary efficacy outcome of a reduction in blood pressure and may lack power for the secondary outcomes; therefore, results will be interpreted in the light of these limitations.

12.3.2 Sensitivity and other planned analyses

Based on the small anticipated sample size, it may be necessary to address potential imbalances between randomised groups for influencing risk factors.

13. Amendments to the CIP

Amendments to this CIP may be necessary to protect the safety of the patients and integrity of the data. In collaboration with the investigator(s), the CIP amendments will be documented and submitted for ethical and regulatory approval (as required) prior to implementation. All changes will be evaluated for impact per sponsor SOPs. Amendments will be considered implemented after all ethical and regulatory approvals (as required) are received and all key sponsor and site staff has been trained. This process does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

14. Deviations from the Clinical Investigation Plan

A deviation is considered a departure from the conditions and principles of GCP in connection with that investigation, or the CIP relating to that investigation, as amended from time to time.

The investigator shall not deviate from this CIP except in situations that affect the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

14.1 Procedures for recording, reporting and analysing CIP deviations

If possible and appropriate, prior approval from the sponsor and REC shall be obtained by the investigator. All spontaneous CIP deviations shall be recorded and reported to the Oxford monitoring site. A deviation log shall be maintained by the study site. Deviations shall be reported to the REC and the regulatory authorities if required by national regulations. All deviations will be included, as required in the final study report.

14.2 Notification requirements and time frames

Requests for deviations by the investigator will be responded to within 48 hours of receipt.

14.3 Corrective and preventive actions and principal investigator disqualification criteria

Refer to the monitoring plan (as applicable) for corrective and preventative actions and principal investigator disqualification criteria.

14.4 Procedure for reporting any protocol deviations

Any deviation from the protocol that has not been previously approved by the sponsor (University of Oxford / TGI) must be reported to the sponsor within two working days of the deviation occurrence. Any deviations from the clinical investigation plan that are identified

during routine monitoring visits will be reported to the sponsor within 24 hours of being identified.

15. Statements of Compliance

The clinical investigation shall be conducted in accordance with the ethical principles of the Declaration of Helsinki, ISO standard 14155 and all other applicable device and UK regulations.

The clinical investigation shall not commence recruitment until all REC and regulatory (if applicable) permission is received. All additional requirements imposed by the REC or regulatory authority will be followed.

16. Definition of End of Study

The duration of the sub-study is contingent on the duration of TRIDENT (recruitment scheduled until 2020). The end of the sub-study is the date of the last follow-up of the last participant.

17. Publication Policy

We plan to present the results of the study at scientific meetings and publish the results in scientific journals. All participant data will be anonymised for this purpose. Authorship of publications will be determined by the ICMJE criteria.

18. References

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. The Lancet. 2009;373(9675):1632-44.
2. Samarasekera N, Smith C, Al-Shahi Salman R. The association between cerebral amyloid angiopathy and intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2012;83(3):275-81.
3. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet neurol. 2010;9(2):167-76.
4. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet neurol. 2009;8(4):355-69.
5. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet (London, England). 2010;376(9735):112-23.
6. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2014;85(6):660-7.
7. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. The Lancet Global health. 2013;1(5):e259-81.
8. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. Neurology. 1997;48(4):891-5.
9. Moulin S, Labreuche J, Bombois S, Rossi C, Boulouis G, Henon H, et al. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. Lancet neurol. 2016;15(8):820-9.
10. Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Annals of internal medicine. 2004;141(10):745-52.
11. Biffi A, Anderson CD, Battey TW, Ayres AM, Greenberg SM, Viswanathan A, et al. Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage. Jama. 2015;314(9):904-12.
12. Casolla B, Dequatre-Ponchelle N, Rossi C, Henon H, Leys D, Cordonnier C. Heavy alcohol intake and intracerebral hemorrhage: characteristics and effect on outcome. Neurology. 2012;79(11):1109-15.
13. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke. 2004;35(6):1415-20.
14. Feldmann E, Broderick JP, Kernan WN, Viscoli CM, Brass LM, Brott T, et al. Major risk factors for intracerebral hemorrhage in the young are modifiable. Stroke. 2005;36(9):1881-5.
15. Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. The Lancet Neurology. 2018;17(10):885-94.

16. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006;66(8):1175-81.
17. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M. How Should We Lower Blood Pressure after Cerebral Hemorrhage? A Systematic Review and Meta-Analysis. Cerebrovasc Dis. 2017;43(5-6):207-13.
18. Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, et al. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. Lancet neurol. 2014;13(4):374-84.
19. Rudd AG, Bowen A, Young G, James MA. National clinical guideline for stroke: 5th edition 2016. Clinical Medicine. 2017(1470-2118).
20. Lager KE, Wilson A, Khunti K, Mistri AK. Quality of secondary prevention measures in TIA patients: a retrospective cohort study. Postgraduate Medical Journal. 2012;88(1040):305.
21. Zahuranec DB, Wing JJ, Edwards DF, Menon RS, Fernandez SJ, Burgess RE, et al. Poor long-term blood pressure control after intracerebral hemorrhage. Stroke. 2012;43(10):2580-5.
22. Ovbiagele B, Diener HC, Yusuf S, Martin RH, Cotton D, Vinisko R, et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. Jama. 2011;306(19):2137-44.
23. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke. 2010;41(2):397-401.
24. Herttua K, Tabak AG, Martikainen P, Vahtera J, Kivimaki M. Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study. European heart journal. 2013;34(38):2933-9.
25. De Simoni A, Hardeman W, Mant J, Farmer AJ, Kinmonth AL. Trials to improve blood pressure through adherence to antihypertensives in stroke/TIA: systematic review and meta-analysis. Journal of the American Heart Association. 2013;2(4):e000251-e.
26. Boan AD, Lackland DT, Ovbiagele B. Lowering of blood pressure for recurrent stroke prevention. Stroke. 2014;45(8):2506-13.
27. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet (London, England). 2001;358(9287):1033-41.
28. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. Stroke. 2004;35(1):116-21.
29. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke. 2004;35(4):1024.
30. The SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. The Lancet. 2013;382(9891):507-15.
31. Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. The New England journal of medicine. 2008;359(12):1225-37.
32. Birns J, Markus H, Kalra L. Blood pressure reduction for vascular risk: is there a price to be paid? Stroke. 2005;36(6):1308-13.
33. Lv J, Neal B, Ehteshami P, Ninomiya T, Woodward M, Rodgers A, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: a systematic review and meta-analysis. PLoS Med. 2012;9(8):e1001293.

34. Cushman WC, Ford CE, Einhorn PT, Wright JT, Jr., Preston RA, Davis BR, et al. Blood pressure control by drug group in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich). 2008;10(10):751-60.
35. Johnston A, Stafylas P, Stergiou GS. Effectiveness, safety and cost of drug substitution in hypertension. British journal of clinical pharmacology. 2010;70(3):320-34.
36. Shaw E, Anderson JG, Maloney M, Jay SJ, Fagan D. Factors associated with noncompliance of patients taking antihypertensive medications. Hospital pharmacy. 1995;30(3):201-3, 6-7.
37. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension. 2006;47(3):345-51.
38. Faria C, Wenzel M, Lee KW, Coderre K, Nichols J, Belletti DA. A narrative review of clinical inertia: focus on hypertension. Journal of the American Society of Hypertension : JASH. 2009;3(4):267-76.
39. Thijs L, Richart T, de Leeuw PW, Kuznetsova T, Grodzicki T, Kawecka-Jaszcz K, et al. Morbidity and mortality on combination versus monotherapy: a posthoc analysis of the Systolic Hypertension in Europe trial. J Hypertens. 2010;28(4):865-74.
40. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension. 2009;53(4):646-53.
41. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet (London, England). 2011;377(9762):312-20.
42. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55(2):399-407.
43. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326(7404):1427.
44. Pall D, Szanto I, Szabo Z. Triple combination therapy in hypertension: the antihypertensive efficacy of treatment with perindopril, amlodipine, and indapamide SR. Clinical drug investigation. 2014;34(10):701-8.
45. Toth K. Antihypertensive efficacy of triple combination perindopril/indapamide plus amlodipine in high-risk hypertensives: results of the PIANIST study (Perindopril-Indapamide plus AmlodipiNe in high rISk hyperTensive patients). American journal of cardiovascular drugs : drugs, devices, and other interventions. 2014;14(2):137-45.
46. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. J Hypertens. 2016;34(10):1921-32.
47. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. The Lancet. 2010;375(9718):938-48.
48. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet (London, England). 2010;375(9718):895-905.
49. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet (London, England). 2010;375(9718):906-15.
50. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet neurol. 2010;9(5):469-80.

51. Rodriguez-Luna D, Pineiro S, Rubiera M, Ribo M, Coscojuela P, Pagola J, et al. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. Eur J Neurol. 2013;20(9):1277-83.
52. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. The Lancet Neurology. 2014;13(4):364-73.
53. McManus RJ, Mant J, Franssen M, Nickless A, Schwartz C, Hodgkinson J, et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. The Lancet. 2018;391(10124):949-59.
54. McKinstry B, Hanley J, Wild S, Pagliari C, Paterson M, Lewis S, et al. Telemonitoring based service redesign for the management of uncontrolled hypertension: multicentre randomised controlled trial. BMJ : British Medical Journal. 2013;346.
55. Gale CR, Cooper C, Aihie Sayer A. Prevalence and risk factors for falls in older men and women: The English Longitudinal Study of Ageing. Age and ageing. 2016;45(6):789-94.

Appendix 3.2



RESEARCH COLLABORATION AGREEMENT

BETWEEN

THE GEORGE INSTITUTE FOR GLOBAL HEALTH

ABN 90 085 953 331

AND

THE UNIVERSITY COURT OF THE UNIVERSITY OF EDINBURGH

AND

THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD

IN RESPECT OF THE ACADEMIC STUDY KNOWN AS:

TRIDENT UK Telemetric Home Blood Pressure Monitoring Sub-Study

RESEARCH COLLABORATION AGREEMENT

THIS AGREEMENT is made on 2020

BETWEEN:

1. **THE GEORGE INSTITUTE FOR GLOBAL HEALTH** (ABN 90 085 953 331) of Level 10, King George V Building, 83-117 Missenden Road, Camperdown NSW 2050, AUSTRALIA (**TGI**);
2. **THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD** whose administrative offices are at University Offices, Wellington Square, Oxford OX1 2JD, UK (**Oxford**); and
3. **THE UNIVERSITY COURT OF THE UNIVERSITY OF EDINBURGH** a charitable body registered in Scotland under registration number SC005336, incorporated under the Universities (Scotland) Acts and having its main administrative offices at Old College, South Bridge Edinburgh, EH8 9YL, Scotland, UK (**Edinburgh**)

Each a **Party** and together the **Parties**

RECITALS:

A. TGI is the global sponsor of a study known as the *Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial* (**TRIDENT Study**).

B. The Parties wish to collaborate on an investigator-led clinical trial as part of a sub-study to the TRIDENT Study known as "TRIDENT UK Telemetric Home Blood Pressure Monitoring Sub-Study" (**UK Sub-Study**). Under the UK Sub-Study, selected UK TRIDENT Study participants will be invited to participate in monitoring of home blood pressure, as described in the UK Sub-Study Protocol.

C. Oxford will be the local host of the UK Sub-Study, TGI will be the sponsor of the UK Sub-Study (**Sponsor**) and Edinburgh will be the legal representative of the Sponsor in the UK (**Legal Representative**). TGI and Edinburgh will provide the academic and regulatory support activities that accompany their roles as Sponsor and UK Legal Representative respectively.

D. The Parties enter into this Agreement to record the rights and obligations of each other in relation to the UK Sub-Study on the terms of this Agreement.

IT IS AGREED AS FOLLOWS:

1. DEFINITIONS & INTERPRETATION

1.1. **Definitions**

In this Agreement unless the context requires otherwise:

Applicable Laws means all laws and related regulations, rules and guidelines applying to the conduct of the UK Sub-Study, including Privacy Laws, ICH Harmonised Tripartite Guideline

for Good Clinical Practice (CPMP/ICH/135/95, as amended September 1997) and such other standards applicable to research of the same or similar nature to the UK Sub-Study.

Background Intellectual Property means any Intellectual Property which pre-exists the UK Sub-Study or is independently developed outside of the UK Sub-Study, that is owned or controlled by a Party and which that Party chooses at its sole discretion to make available for the purpose of carrying out the UK Sub-Study, and includes any improvements made solely by a Party to Intellectual Property Rights so owned or controlled by a Party.

Business Day means a day that is not a Saturday, Sunday or public holiday in the relevant jurisdiction.

Chief Investigator means Professor Rustam Al-Shahi Salman at Edinburgh.

Commencement Date means the date the last Party signs this Agreement.

Confidential Information means, in respect of a Party, information that is provided by one Party to the other in connection with the UK Sub-Study and at the time of provision is marked or otherwise designated to show expressly that it is imparted in confidence or the other Party knows or reasonably ought to know is confidential, and includes TRIDENT Study Data, UK Sub-Study Data, TRIDENT Protocol, UK Sub-Study Protocol, TRIDENT Study reports, UK Sub-Study Reports, and drafts thereof, medical related and technical information, product information, process and operations, and other Intellectual Property.

Data Controller has the same meaning as “Controller” under GDPR.

Data Protection Legislation means any law, statute, declaration, decree, directive, legislative enactment, order, ordinance, regulation, rule or other binding restriction (as amended, consolidated or re-enacted from time to time) which relates to the protection of individuals with regards to the Processing of Personal Data to which Oxford is subject, including the Data Protection Act 1998 and EC Directive 95/46/EC (up to and including 24 May 2018) and on and from 25 May 2018, the General Data Protection Regulation ((EU) 2016/679) (“GDPR”).

Dispute means a dispute between the Parties in relation to this Agreement.

Ethics Committee means any ethics or institutional review board, independent ethics committee or other body appointed in accordance with applicable law to review, to approve the initiation of, and to conduct periodic review of research involving human subjects; the primary purpose of such review is to assure the protection of the rights and welfare of Participants.

Ethics Committee Opinion means, in relation to the conduct of the UK Sub-Study, a current and valid favourable opinion expressed by an applicable Ethics Committee, setting out, among other things, the terms and conditions of its approval.

Intellectual Property means intellectual property of any description including but not limited to all patents, copyright, moral rights, designs, trademarks, trade secrets, know-how, inventions and discoveries, and includes any Intellectual Property Rights in respect of any of the foregoing and subsisting anywhere in the world.

Intellectual Property Rights means all current and future registered and unregistered rights in respect of Intellectual Property.

Legal Representative means the company, institution or organisation that is the legal representative of the UK Sponsor in the EEA for the purposes of the UK Sub-Study.

Participant means any person who has consented to be a participant in the UK Sub-Study.

Participating Sites means those sites participating in the TRIDENT Study and selected to participate in the UK Sub-Study.

Personal Data means any information relating to an identified or identifiable natural person.

Personnel means all employees, agents, authorised representatives and contractors of the relevant Party.

Principal Investigator means Professor Peter Rothwell at Oxford.

Privacy Laws means all privacy laws, regulations, codes and guidelines that apply to the conduct of the UK Sub-Study in the relevant jurisdiction.

Process and **Processing** means obtaining, recording and holding Personal Data, or carrying out any operation or set of operations on the Personal Data.

Regulatory Approval means, in relation to the conduct of the UK Sub-Study, any current and valid grant, renewal, validation, authorisation, certificate and/or registration of a Regulatory Authority required under applicable law.

Regulatory Authority means, in relation to the conduct of the UK Sub-Study, any competent authority in any applicable country or region that regulates medicines and healthcare and life sciences products, including the Medicines and Healthcare Products Regulatory Agency and the European Medicines Agency.

Term means the period defined in **clause 14.1**.

UK Sub-Study Personnel means the Chief Investigator, the Principal Investigator and any other individuals involved in the conduct of the UK Sub-Study by Oxford, whether or not employed by Oxford.

UK Sub-Study Protocol means the protocol for the UK Sub-Study, provided in **Schedule B,** as updated from time to time with approval by the UK Sub-Study management committee.

Work means the work, tasks and activities that are to be performed in connection with the UK Sub-Study as listed (and allocated to a Party) in **Schedule A**, as may be updated during the Term.

UK Sub-Study Completion Date is when the UK Sub-Study database is locked, all UK Sub-Study follow-up requirements have been met, and Oxford has issued a copy of its final report of the UK Sub-Study results to TGI and Edinburgh.

UK Sub-Study Data means all information, data, records and reports (other than actual Participant medical records located at Participating Sites) collected or created pursuant to or prepared in connection with the UK Sub-Study by a Party.

UK Sub-Study Intellectual Property means Intellectual Property created or arising as a direct result of the performance of the Work or conduct of the UK Sub-Study, as more fully set-out under clause 9.2, and includes UK Sub-Study Data.

1.2. **Interpretation**

In this Agreement, unless the context indicates a contrary intention:

(a) a reference to: one gender includes the others; the singular includes the plural and the plural includes the singular; a person includes a body corporate; a Party includes that Party's executors, administrators, successors, substitutes (including persons taking by novation) and permitted assigns; a clause, paragraph, schedule or annexure is a reference to a clause or paragraph of or schedule or annexure to this Agreement; this Agreement includes all schedules and annexures; any legislation or statutory instrument or regulation includes an amendment or re-enactment to that legislation and includes subordinate legislation in force under it; writing includes any means of reproducing words in a tangible and permanently visible form; and day will be construed as a calendar day unless qualified as a Business Day;

(b) mentioning anything after 'include', 'includes' or 'including' does not limit what else might be included;

(c) where a word or expression is given a particular meaning, other grammatical forms of that word or expression have a corresponding meaning;

(d) headings are for convenience only and do not form part of this Agreement or affect its interpretation;

(e) no provision of this Agreement will be construed adversely to a Party on the grounds that the Party is responsible for the preparation of it.

1.3. **Inconsistency**

In the event that any provision contained in this Agreement is inconsistent with the provisions contained in the UK Sub-Study Protocol, the Parties agree that the provisions regarding the actual conduct of the UK Sub-Study contained in the UK Sub-Study Protocol will prevail.

2. THE STUDY

2.1. Subject to the indemnity given to TGI and Edinburgh in clause 11,the Parties acknowledge and agree that TGI shall be named as the Sponsor and Edinburgh shall be named as the Legal Representative for the purpose of the UK Sub-Study for regulatory purposes. However, this does not limit Oxford's responsibilities and obligations under this Agreement.

2.2. The Parties agree to work collaboratively to carry out the UK Sub-Study in accordance with this Agreement, the UK Sub-Study Protocol, all Applicable Laws, policies and guidelines.

2.3. The Parties will jointly develop and finalise the UK Sub-Study Protocol.

3. NATURE OF WORK

3.1. The Parties will use their best endeavours to carry out their respective Work and obligations under this Agreement in a competent and efficient manner with all necessary skill, care and diligence expected in relation to similar services and must comply with all Applicable Laws, relevant Ethics Committee's and Regulatory Authority's approvals, standards, codes and guidelines relating to their respective Work.

3.2. Edinburgh, as Legal Representative, will be responsible for obtaining and maintaining all necessary Ethics Committee Opinions and Regulatory Approval (including, but not limited to, licences, authorisations, consents, approvals and permits required by Applicable Laws) for the UK Sub-Study. Edinburgh shall provide to Oxford a copy of all correspondence with the Ethics Committee and the Regulatory Authority in relation to the Ethics Committee Opinion and the Regulatory Approval for the UK Sub-Study.

3.3. The Parties acknowledge and agree that Oxford cannot (a) start the UK Sub-Study or cause the UK Sub-Study to be started or (b) conduct the UK Sub-Study unless the conditions set out in Clause 3.4 have been satisfied, The Parties also acknowledge and agree that Oxford cannot (a) recruit an individual to be a Participant or (b) issue an advertisement for the purpose of recruiting individuals to be Participants unless the condition set out in Clauses 3.4.2 and 3.4.3 have been satisfied.

3.4. The conditions referred to in Clause 3.3 are satisfied when:

3.4.1. the receipt of the Ethics Committee Opinion by Oxford; and Oxford, TGI and Edinburgh have unanimously confirmed in writing that the terms and conditions of the Ethics Committee Opinion (if any) are acceptable to all three Parties; and

3.4.2. the receipt of the Regulatory Approval by Oxford; and Oxford, TGI and Edinburgh have unanimously confirmed in writing that the terms and conditions of the Regulatory Approval (if any) are acceptable to all three Parties; and

3.4.3. Oxford's patient consent forms for the UK Sub-Study have been approved by the relevant Ethics Committees.

3.5. If requested by TGI, Oxford and Edinburgh will provide TGI with updated on the progress of the UK Sub-Study.

3.6. If a Party becomes aware of any deviations from the Clinical Investigation Plan (**CIP**) or the UK Sub-Study Protocol, that Party must promptly notify the other Parties. This clause does not limit the obligations or procedures set out in the UK Sub-Study Protocol in relation to CIP deviations.

3.7. Oxford will at its cost prepare a schedule detailing how the UK Sub-Study is to be carried out as between TGI, the Participating Sites and potential Study Participants (**UK Sub-Study Clauses**) and how/when payments will be made to Participating Sites and Study Participants. When the UK Sub-Study Clauses are in a form and on terms acceptable to TGI (acting reasonably), these will be attached as a schedule to the TRIDENT study clinical trial agreements to be entered into by TGI and Participating Sites.

3.8. **Audit & Inspections**

(a) Regulatory Authorities and applicable Ethics Committees will have the right to conduct, upon reasonable notice in writing and during normal working hours, audits and/or inspections of Oxford's and Edinburgh's equipment, policies, documentation, systems, data and any and all other records relating to the UK Sub-Study. In these circumstances, Oxford and Edinburgh will promptly notify TGI of the upcoming audit and/or inspection with as much notice as possible, and will expressly permit TGI or its

representative to be present at such audits and/or inspections (at TGI's discretion).

(b) The Parties agree to promptly take any reasonable steps that are required as a result of a Regulatory Authority audit, inspection or any subsequent changes required by Applicable Laws.

(c) TGI will have the right to conduct, upon reasonable notice in writing and during normal working hours but no more than once per year, audits and/or inspections of that portion of Oxford's and Edinburgh's equipment, policies, documentation, systems, data and all other records that relate to the UK Sub-Study solely for the purpose of auditing Oxford's compliance with the UK Sub-Study Protocol, this Agreement and all applicable principals, guidelines and guidance of competent authorities for current good clinical practice.

3.8 The Parties will cooperate and provide reasonable assistance to each other upon request (including providing to each other copies of any relevant documents or records) to enable each Party to comply with Applicable Laws in respect of the UK Sub-Study.

3.9. Each Party will keep complete and accurate relevant records regarding their respective Work in relation to the UK Sub-Study for a period of ten (10) years (or such longer period as required by Applicable Law) following completion or termination of the UK Sub-Study.

4. PAYMENTS

4.1. The Parties acknowledge that Oxford has sourced funding for the UK Sub-Study from NIHR Biomedical Research Centre, Oxford. Furthermore, the Parties acknowledge that this funding, and the payments and costs listed hereto in clauses 4.2 and 4.3, is to support a total participant recruitment of up to and including forty (40) participants. Notwithstanding the foregoing but subject to clause 6, Oxford may review the total number of participants it has funding to support for the UK Sub-Study without TGI or Edinburgh's consent.

4.2. Oxford will be responsible for all payments, where necessary, to Participating Sites, including costs associated with the training of UK Sub-Study staff at Participating Sites.

4.3. Oxford will be responsible for the supply and operation of any equipment required in relation to the UK Sub-Study including training costs, all transport costs in connection with the equipment, and any maintenance or replacement costs. TGI and Edinburgh will not be liable for any wear, tear, damage, loss, faulty and/or stolen equipment relating to the UK Sub-Study.

4.4. Oxford will bear all costs in relation to the UK Sub-Study unless expressly stated otherwise in this Agreement.

5. PRIVACY & DATA PROTECTION

5.1. The Parties agree to adhere to the principles of medical confidentiality.

5.2. Oxford will:

(a) only process Personal Data of Participants for the purpose for which the Participants have provided their consent; and

(b) ensure that all UK Sub-Study Data supplied to TGI and Edinburgh is anonymised to the greatest extent possible (**Anonymised UK Sub-Study Data**). Personal Data will not be disclosed to TGI except where this is required directly or indirectly to satisfy the requirements of the UK Sub-Study Protocol, the TRIDENT Protocol or for the purpose of adverse event reporting and subject always to compliance with the Privacy Laws.

5.3. The Parties acknowledge that, in accordance with Data Protection Legislation, Oxford, TGI and Edinburgh are Data Co-Controllers for the purposes of the UK Sub-Study. As such, the Parties agree to comply with all applicable requirements of the Data Protection Legislation as detailed in Schedule C.

5.4. .

5.5. To the extent that the Parties collect, store, use or otherwise process any Personal Data of Participants, UK Sub-Study Personnel or the other Parties' Personnel (**UK Sub-Study Personal Data**), the Parties agree to:

(a) comply with relevant Privacy Laws;

(b) take appropriate technical and organisational measures against accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access and against all other unlawful forms of processing of UK Sub-Study Personal Data;

(c) promptly report to the other Parties any unauthorised access to, use or disclosure of UK Sub-Study Personal Data of which it becomes aware, and will work with the other Parties to take reasonable steps to remedy the incident.

6. STUDY DATA

6.1. TGI agrees to amend the Study database for UK Participating Sites to include the data points referred to in the **UK Sub-Study eCRF** in Schedule C, for and up to 40 participants. Any subsequent changes to the eCRF requires TGI's prior written consent. Oxford agrees to pay TGI and Edinburgh for any costs incurred and resources used as a result of any subsequent changes to the UK Sub Study eCRF and UK Sub Study Protocol.

6.2. Oxford must seek Edinburgh's and TGI's prior written consent if Oxford wishes to:

(a) amend the UK Sub-Study eCRF as currently shown in **Schedule C**;

(b) amend the UK Sub-Study Protocol; and/or

(c) increase the number of participants in the UK Sub-Study above 40.

6.3. Oxford agrees to pay any costs incurred or to be incurred by TGI and/or Edinburgh in relation to any of the changes referred to in clause 6.2, including any time or resources incurred or to

be incurred by TGI, Edinburgh and/or third party in connection with considering and/or implementing such changes.

6.4. All UK Sub-Study Data will be owned by Oxford subject to clauses 6.5 and 9.

6.5. Oxford hereby grants to TGI and Edinburgh a perpetual, non-exclusive, non-transferable, worldwide, royalty-free licence to use, copy, and reproduce UK Sub-Study Data for:

(a) the purposes of this Agreement and/or carrying out the UK Sub-Study; and

(b) non-commercial research, teaching and academic purposes, subject to clauses 5, 7, 8 and 9.

6.6. TGI and Edinburgh makes no representations or warranties, whether written or oral, statutory, express or implied with respect to any information or any technical assistance which may be provided under this Agreement.

6.7. None of the Parties give any warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the UK Sub-Study.

7. PUBLICITY

7.1. The Parties must not:

(a) make any public announcement, press release, or other public communication regarding the UK Sub-Study except as required for the purposes of recruitment of Participants and consenting patients in order to indicate their willingness to participate in the UK Sub-Study; and/or

(b) disclose, release, publish or present any of the UK Sub-Study Data,

prior to the earlier to occur of (i) completion of the TRIDENT Study at all global sites and first publication of the main report relating to the TRIDENT Study or, if the main report of the TRIDENT Study will not be published, TGI informing Oxford as such; (ii) eighteen (18) months from the completion of the TRIDENT Study at all global sites, provided that TGI's and Edinburgh's prior written consent is obtained, such consent not to be unreasonably withheld; or (iii) the other Parties providing prior written consent, consent not to be unreasonably withheld, to Oxford that Oxford may proceed with the proposed publication in relation to the UK Sub-Study results only. The Parties must ensure that its Personnel complies with this clause 7.1.

7.2. A Party must not, without the other Parties' prior written approval:

(a) contract on behalf of or bind the other Parties;

(b) use the other Parties' name, trade mark or logo;

(c) publish any advertisement, press release or other information relating to the other Parties.

However, the Parties agree that their names may be used in reports, publications and presentations of results from the UK Sub-Study and the TRIDENT Study in acknowledgement of its participation in the UK Sub-Study and/or TRIDENT Study.

7.3. Publication of the results from the UK Sub-Study will be prepared by Oxford, and will be

published in accordance with the terms of the Protocol.

7.4. Despite anything else in this Agreement, if TGI proposes to publish or present results from the main TRIDENT Study (**Publication**) and there is reference to the UK Sub-Study, TGI will send to Oxford and Edinburgh a draft copy of such excerpts from the Publication that refers to the UK Sub-Study (**Excerpts**) at least 30 days before publication.

7.5. Within that period of 30 days, Oxford and Edinburgh may provide comments on the Excerpts to TGI. TGI must consider such comments but is not bound to follow them.

7.6. If TGI has not received any comments from Oxford and/or Edinburgh within 30 days of giving the Excerpts to them, TGI may proceed to publish or present the Publication.

8. CONFIDENTIALITY

8.1. Subject to clause 8.3, during the Term and for a period of five (5) years after completion of the UK Sub-Study, each Party (**Receiving Party**) will retain in confidence and will not disclose any Confidential Information of the other Party (**Disclosing Party**) except as expressly permitted by this Agreement, or with the prior written consent of the Disclosing Party.

8.2. The non-disclosure obligation will not apply to Confidential Information that:

(a) is in the public domain otherwise than as a result of a breach of an obligation of confidentiality;

(b) is obtained by the Receiving Party from a third party in circumstances where the Receiving Party has no reason to believe that there has been a breach of an obligation of confidentiality;

(c) is required to be disclosed by law, or by order of a competent authority or Ethics Review Board (including any regulatory or governmental body), provided that the Receiving Party promptly notifies the Disclosing Party in writing prior to such disclosure, and only discloses the minimum Confidential Information required to be disclosed in order to comply with the order;

(d) is lawfully in the possession of the recipient of the information from a third party who did not acquire it in confidence from the disclosing party, or someone owing a duty of confidence to the disclosing party; or

(e) is published in accordance with the express terms of this Agreement or is published with the prior written consent of the Disclosing Party.

8.3. Any Confidential Information that might allow Participants to be identified will be retained in confidence indefinitely, unless and to the extent specifically required to be disclosed by law.

8.4. Receiving Party may use Disclosing Party's Confidential Information required to supply the Work under this Agreement or for the purpose of the UK Sub-Study.

8.5. Receiving Party will limit access to Disclosing Party's Confidential Information to those of Receiving Party's Personnel who have a need to know to perform the Work under this Agreement or for the purpose of the UK Sub-Study. Receiving Party will ensure that such Personnel are informed of the confidential nature of the Confidential Information and the obligations of this Agreement before disclosure under this **clause 8**. The Receiving Party shall at all times be responsible for Receiving Party's Personnel's compliance with the obligations

set out in this Agreement.

8.6. If this Agreement expires or is terminated:

(a) each Party must immediately return (or if requested destroy) all Confidential Information of the other Party that is in its possession, power or under its control, including all notes, memoranda, correspondence, reports, summaries and all other things which in any manner refers to any part of the Confidential Information of the Disclosing Party.

(b) A Party may retain a copy of Confidential Information relating to the UK Sub-Study if it must be retained under Applicable Laws.

8.7. Each Party acknowledges that monetary damages may be an inadequate remedy for breach of the obligation of confidence under this clause so a Party may seek equitable relief including an injunction to protect its Confidential Information from unauthorised use or disclosure.

9. INTELLECTUAL PROPERTY

9.1. **Background Intellectual Property**

(a) Background Intellectual Property is not affected by this Agreement and all Background Intellectual Property remains the property of the Party that makes it available for the purposes of performing the Work or carrying out the UK Sub-Study. Each Party grants to the other Party a royalty-free, non-exclusive, non-transferable licence to use its Background Intellectual Property to the extent necessary to perform the Work under this Agreement or carry out the UK Sub-Study.

(b) For the purposes of this Agreement, TGI's Background Intellectual Property includes any Intellectual Property and/or data created or arising as a result of the TRIDENT Study.

9.2. **UK Sub-Study Intellectual Property**

(a) Subject to clause 9.1 all UK Sub-Study Intellectual Property will vest immediately upon its creation in Oxford.

(b) Oxford agrees to provide to TGI and Edinburgh copies of its final report, outcomes, UK Sub-Study Data and results from the UK Sub-Study (**Results**) in such form as reasonably requested by TGI and Edinburgh respectively.

(c) Oxford hereby grants to TGI and Edinburgh a perpetual, non-exclusive, non-transferable, worldwide, royalty-free licence to use, copy, and reproduce UK Sub-Study Intellectual Property (including Results) for non-commercial research, teaching and academic purposes, subject to **clauses 5**, **7**, and **8**. For the avoidance of doubt but subject to clauses 7.4 to 7.6, TGI and Edinburgh shall not disclose the contents of the final report, outcomes, UK Sub-Study Data, UK Sub-Study Intellectual Property or Results: (i) publicly or (ii) to a third party outside of this Agreement, until after Oxford has published on the UK Sub-Study Intellectual Property and Results.

10. RELATIONSHIP OF PARTIES

This Agreement does not create a relationship of employment, principal and agent, joint venture, or partnership between the Parties.

11. INDEMNIFICATION

11.1. Subject to clauses 11.2 and 11.3, Oxford shall indemnify each of TGI, Edinburgh and their respective Personnel (including, but not limited to the Study Personnel) against: any and all reasonable claims, proceedings and related costs, expenses, losses, damages and demands incurred by any such indemnified person in connection with any claim made or brought (whether successfully or otherwise) by a third party ("**Claims**") to the extent that they arise or result from (i) the UK Sub-Study Protocol or the procedures or instructions given by Oxford in relation to the conduct of the UK Sub Study; and/or (ii) the negligent acts or omissions of, or the wilful misconduct of, and/or breach by Oxford in its performance of this Agreement or in connection with the UK Sub-Study; and/or (iii) infringement of third party rights in relation to the UK Sub Study and/or the Results by Oxford or its Personnel.

11.2. An indemnity under clauses 11.1 shall only apply if the indemnified Party:

11.2.1. informs the Party providing the indemnity in writing as soon as reasonably practicable following receipt of notice of the claim or proceedings;

11.2.2. upon the indemnifying Party's request and at the indemnifying Party's costs gives the indemnifying Party full control of the claim or proceedings and provides all reasonable assistance; and

11.2.3. makes no admission in respect of such claim or proceedings other than with the prior written consent of the indemnifying Party.

11.3. Any indemnity under clauses 11.1 shall not apply to the extent any claims, proceedings and related costs, expenses, losses, damages or demands arise or result from the negligent acts or omissions or wilful misconduct or breach of statutory duty of the indemnified Party.

12. LIMITATIONS OF LIABILITY

12.1. Each Party is liable for its own acts and omissions in relation to the performance of the Work and/or participation in the UK Sub-Study. Oxford accepts no responsibility for any use which may be made of any work carried out under or pursuant to this Agreement, or of the Results, nor for any reliance which may be placed on such work or Results, nor for any advice or information given in connection with them.

.

.

12.2. Despite any other clause of this Agreement, and to the extent permitted by law, no Party will be liable to the other Party or its Personnel for any consequential, special, or indirect loss or damage (including resulting from the loss of business, revenue or profit), arising out of, or in connection with, this Agreement (whether under contract, tort, or otherwise).

12.3. Nothing in this Agreement limits of excludes a Party's liability for:

(a) death or personal injury resulting from its negligence;

(b) any fraud or fraudulent misrepresentation; or

(c) any sort of other liability which, by law, cannot be limited or excluded.

12.4. Each Party undertakes to make no claim in connection with this Agreement or its subject matter against any Personnel of the other Party (except for claims in relation to fraud or wilful misconduct). This undertaking is intended to give protection to individual researchers; it does not prejudice any right which a Party might have to claim against the other. The benefit conferred by this **clause 12.6** is intended to be enforceable by the persons referred to in it.

13. INSURANCE

13.1. Each Party will procure and maintain at its own expense and for at least three (3) years after the conclusion of the UK Sub-Study such type and amounts of liability insurance covering its respective Work or performing its obligations under this Agreement or which may otherwise be required by applicable Law.

13.2. A Party will provide to the other Parties with copies of the latest certificates of insurance, required to be maintained under this **clause 13**, within fourteen (14) days of receiving a written request from the other Party/Parties.

14. TERM AND TERMINATION

14.1. **Term**

This Agreement commences on Commencement Date and remains in effect until UK Sub-Study Completion Date, unless terminated earlier in accordance with this **clause 14**.

14.2. **Termination**

(a) The Parties may at any time mutually agree to terminate this Agreement.

(b) A Party may immediately terminate this Agreement by written notice to the other Parties if:

(i) one of the other Parties breaches a material obligation of this Agreement and fails to rectify that breach within thirty (30) days of the date of receiving a written notice requesting it to remedy that breach within a stated period. The notice shall include a detailed statement describing the nature of the breach. If the breach is capable of being remedied and is remedied within the thirty (30) day notice period, then the termination shall not take effect at the end of the thirty (30) day notice period in any event;

(ii) one of the other Parties becomes bankrupt, becomes subject to an arrangement, composition or compromise with its creditors, becomes insolvent, becomes subject to an order or resolution for winding up or dissolution, or has a receiver or administrator appointed to it, as the case may be;

(iii) in the reasonable judgment of the notifying Party, serious or life-threatening events raise issues of Participant safety; or

(iv) if the UK Sub-Study or TRIDENT Study in the United Kingdom is terminated early or suspended for whatever reason.

14.3. **Accrued Rights**

Termination of this Agreement by either Party for any reason will be without prejudice to such other rights as it may have in law and not affect the rights and obligations of the Parties accrued prior to the date of termination.

14.4. **Conclusion of Study**

At the conclusion of the UK Sub-Study, expiry or early termination of this Agreement:

(a) Edinburgh and Oxford will take appropriate action to close out the UK Sub-Study in a timely manner; and

(b) A Party will, in accordance with another Party's reasonable instructions, return or destroy that Party's Confidential Information.

Any provision of this Agreement which either expressly or by implication is intended to come into, or continue in, effect on or after the termination or expiry of this Agreement shall continue in effect.

15. FORCE MAJEURE

15.1. **No Liability**

A Party will not be liable for any failure of or delay in the performance of its obligations under this Agreement for the period (and to the extent) that such failure or delay was due to causes or circumstances beyond its reasonable control and not attributable to its own acts or omissions, such as (but not limited to) acts of God, natural events, fire, flood, hurricane, earthquake, explosion, volcanic eruption, war, embargo, events of terrorism, riot, crime, act of government or regulatory agency (each a **Force Majeure Event**).

15.2. **Steps to be Taken**

A Party relying on clause 16.1 must:

(a) promptly provide notice to the other Parties of the circumstances and effect of the Force Majeure Event; and

(b) take all steps reasonably necessary to mitigate the effects of the Force Majeure Event on its performance of this Agreement.

16. SURVIVORSHIP

The provisions of **clause 1** (Definitions & Interpretation), **clause 3.7** (Audits & Inspections), **clause 3.8** (Records), **clause 5** (Privacy & Data Protection), **clause 6** (Study Data), **clause 7**

(Publicity), **clause 9** (Intellectual Property), **clause 12** (Limitations of Liability), **clause 13** (Insurance), **clause 14.4** (Conclusion of Study), **clause 16** (Survivorship), **clause 17** (Notices), **clause 18** (Dispute Resolution) and **clause 19** (General) will survive the termination of expiration of this Agreement.

17. NOTICES

17.1. Unless expressly stated otherwise in this Agreement, all notices, consents, approvals, waivers and other communications (each a **notice**) in connection with this Agreement must be in writing and delivered by hand or sent by prepaid registered post, email or facsimile to the recipient as follows (or as subsequently amended by notice):

(a) if to **TGI**:

The George Institute for Global Health
Level 10, KGV, RPAH
Missenden Road,
Camperdown NSW, Australia 2000
Fax: +61 2 8052 4502
Attention: Ruth Freed
Email: rfreed@georgeinstitute.org.au

(b) if to **Edinburgh**

Research Support Office, The University of Edinburgh
5 Roxburgh Street, Edinburgh EH8 9TA, Scotland UK
Attention: Head of Research Support Office, Ref ct-4285
Email: RSO.Contracts@ed.ac.uk

(c) if to **Oxford**

The Chancellor, Masters and Scholars of The University Of Oxford
University Offices, Wellington Square, Oxford OX1 2JD
Attention: Director of Research Services

Email: research.services@admin.ox.ac.uk

With a copy to: Peter Rothwell, Nuffield Department of Clinical Neurosciences. Level 6, West Wing, John Radcliffe Hospital, Oxford OX3 9DU.

Email: peter.rothwell@ndcn.ox.ac.uk

17.2. Notices take effect from the time that they are received and:

(a) if delivered by hand, notice is taken to be received when delivered to an authorised representative of the recipient;

(b) if sent by registered post, a notice is taken to be received ten (10) Business Days after the date of posting, unless it has been received earlier; or

(c) if transmitted electronically, upon actual receipt by the addressee.

17.3. If a notice is received after 5:00pm in the place of receipt or on a day that is not a Business Day, it is taken to be received at 9:00am on the next Business Day.

18. DISPUTE RESOLUTION

18.1. **Mediation**

(a) A Dispute must be resolved in accordance with this clause.

(b) The Parties must first attempt to negotiate in good faith to resolve the Dispute.

(c) If the Dispute is not resolved within fourteen (14) days after good faith negotiations are commenced, then the Parties shall refer the matter to designated senior representatives of each Party to the dispute, who are not otherwise involved with the UK Sub-Study, in an attempt to resolve the issue within fourteen (14) days after the referral. If the Parties are not able to resolve the dispute within that fourteen (14) day period, either Party may refer the Dispute to mediation by a mediator appointed by the International Chamber of Commerce (ICC). The exchange of any relevant information and the structure to be adopted for the negotiation to be held in London shall be in accordance with the ICC arbitration procedure. If the Parties cannot agree on a mediator, the President of the Law Society will appoint a mediator on the terms of the Law Society's standard mediation agreement. Any information or documents obtained by either Party during the mediation must only be used to resolve the Dispute.

(d) If the Dispute is not resolved within twenty-one (21) days of commencing mediation, either Party may commence proceedings in a court of competent jurisdiction.

(e) Each Party must bear its own costs of resolving a Dispute under this clause 18, and unless the Parties otherwise agree, the Parties must bear equally the costs of the mediator.

18.2. **Continuing Performance**

The Parties must continue to perform this Agreement despite the existence of a Dispute or any proceedings under this clause 18.

18.3. **Exclusion**

Nothing in this clause 18 prevents a Party from seeking urgent injunctive relief, including with respect to the protection and/or enforcing of its Intellectual Property Rights.

19. GENERAL

19.1. **Entire Agreement**

This Agreement and the confidentiality agreement between TGI and Oxford dated 30 August 2018 contains the entire agreement between the Parties, and supersedes all previous communications, understandings and agreements, whether oral or written, between the Parties in respect of the UK Sub-Study. Any other agreements between any of the Parties in relation to the TRIDENT Study are not affected by this Agreement.

19.2. **Amendment**

This Agreement may only be amended by a written document signed by all Parties.

19.3. **Governing Law and Jurisdiction**

This Agreement is governed by, and is to be construed in accordance with, the laws of England and Wales; and the Parties submit to the exclusive jurisdiction of the courts of England and Wales, and any courts competent to hear appeals from those courts.

19.4. **No assignment or subcontracting**

A Party must not assign, subcontract nor transfer any of its rights or obligations under this Agreement without the prior written consent of the other Parties. Any such purported assignment will be void. The terms of this Agreement will be binding upon and will inure to the benefit of the Parties and their respective successors and permitted assigns.

19.5. **No Waiver**

A Party does not waive a right or entitlement it may have under this Agreement unless that waiver is notified in writing by the waiving Party to the Party seeking the benefit of the alleged waiver. A waiver by a Party in respect of an act or thing required to be done under this Agreement does not act as a waiver of any other act or thing required to be done under this Agreement.

19.6. **Severability**

Any clause of this Agreement which is prohibited or unenforceable is ineffective to the extent of the prohibition or unenforceability, but the validity or enforceability of the remaining clauses of this Agreement will not be affected.

19.7. **Further Assurances**

Each Party will do anything (including executing any document), and will ensure that its Personnel do anything (including executing any document), that the other Parties may reasonably require to give full effect to this Agreement.

19.8. **Rights of Third Parties**

Subject to clause 12.7, this Agreement does not and is not intended to confer any rights or remedies upon any person other than the Parties.

19.9. **Cost and Expenses**

Each Party must pay for its own costs and expenses in respect of the negotiation, preparation, execution and delivery of this Agreement and any other document executed pursuant to this Agreement.

19.10. **Counterparts**

This Agreement may be executed in any number of counterparts, and all counterparts together will constitute one instrument. A Party may sign any counterpart. A signed copy of this Agreement transmitted by facsimile, email or other means of electronic transmission will be deemed to have the same legal effect as delivery of an original executed copy of this Agreement.

19.11. **Warranties**

Each Party represents and warrants to the other Party that:

(a) it has full corporate power to execute, deliver and perform its obligations under this Agreement; and

(b) it has, and will continue to have, all licences, authorisations, consents, approval and permits required by all Applicable Laws to perform its obligations under this Agreement, and will comply, and continue to comply, with all Applicable Laws relating to the performance of those obligations.

Signature by Parties is on the next page

EXECUTED as an **AGREEMENT** between the Parties:

Executed for and on behalf of **THE GEORGE INSTITUTE FOR GLOBAL HEALTH** (ABN 90 085 953 331) by its duly Authorised Representatives:

Signature:	Signature:
Authorised Representative	Authorised Representative
Name:	Name:
Please print	Please print
Title:	Title:
Please print	Please print
Date:	Date:

Executed for and on behalf of **THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD** by its duly authorised representatives:

Signature:

Authorised Representative

Name:

Please print

Date:

Signed on behalf of **THE UNIVERSITY COURT OF THE UNIVERSITY OF EDINBURGH**

Signed: _____

Name: _____

Position: _____

Date: _____

SCHEDULE A – THE WORK

Responsibilities:

	TGI	Oxford	Edinburgh	UK sites
Global and UK Sponsor	X			
Legal Representative			X	
Local host		X		
Protocol development		X		
Protocol review & approval	X	X	X	
PISCF development		X		
PISCF review and approval			X	
Develop other documents and patient materials		X		
Review and approval of other documents			X	
Ethics & regulatory submissions & approvals			X	
Patient consent				X
Database set up and management		X		
Site selection		X	X	
Set up site contracts & payments		X		
BP Monitor supply & accountability		X		
Site training		X		
BP data monitoring and feedback to RCC & Sites on BP (high or low) for patient follow-up		X		
Analyses		X		

Publication	X	X	X	

Proposed Timeline

- Ethics /Reg/ contracts Dec –Feb 19
- FPI Mar 19

SCHEDULE B – THE PROTOCOL

The Protocol is attached

- Insert Protocol details

The Protocol may be as updated from time to time with approval by the management committee, and each approved version is incorporated into the Agreement.

SCHEDULE C – CRF

A copy of the eCRF for the UK Sub Study as at the date of this Agreement is attached.

SCHEDULE D – DATA PROTECTION

1. Data Protection

1.1 Each Party shall in relation to the Processing of the Personal Data comply with its respective obligations under the Data Protection Legislation. This Schedule C (Data Protection) is in addition to, and does not relieve, remove or replace, a Party's obligations under the Data Protection Legislation.

1.2 The Parties acknowledge that for the purposes of the Data Protection Legislation, each party is a Data Controller where it is Processing Personal Data on its own behalf, acting individually and in common. Annex 1 to this Schedule C sets out the scope, nature and processing by Oxford, the duration of the Processing and the types of Personal Data and categories of Data Subject.

1.3 Notwithstanding Clause 1.2, if any Party is deemed to be a joint Data Controller with the other Party in relation to the Personal Data, the Parties shall cooperate to do all necessary things to enable performance of such compliance obligations, except that each Party shall be responsible, without limitation, for compliance with its data security obligations set out in Clause 1.4.1 where Personal Data has been transmitted by it, or while Personal Data is in its possession or control.

1.4 Each Party shall:

1.4.1 ensure that all fair processing notices have been given (and/or, as applicable, consents obtained) and are sufficient in scope to enable each Party to Process the Personal Data as required in order to obtain the benefit of its rights and to fulfil its obligations under this Agreement in accordance with the Data Protection Legislation;

1.4.2 ensure that it has in place appropriate technical and organisational measures to protect against unauthorised or unlawful processing of Personal Data and against accidental loss or destruction of, or damage to, Personal Data, appropriate to the harm that might result from the unauthorised or unlawful processing or accidental loss, destruction or damage and the nature of the data to be protected, having regard to the state of technological development and the cost of implementing any measures (those measures may include, where appropriate, pseudonymising and encrypting Personal Data, ensuring confidentiality, integrity, availability and resilience of its systems and services, ensuring that availability of and access to Personal Data can be restored in a timely manner after an incident, and regularly assessing and evaluating the effectiveness of the technical and organisational measures adopted by it);

1.4.3 hold the Personal Data under at least the conditions of confidence as such Party holds personal data Processed by it other than the Personal Data;

1.4.4 ensure the reliability of any of its Personnel who have access to the Personal Data;

1.4.5 where required to do so, make due notification to the relevant data protection supervisory authority or regulator;

1.4.6 provide assistance to the other Party as is necessary to enable it to comply with any subject access or deletion requests and queries or complaints made under Data Protection Legislation;

1.4.7 not transfer any Personal Data outside of the European Economic Area ("EEA") or to an international organisation except as permitted in accordance with the Data Protection Legislation.

1.5 Notwithstanding the generality of Clause 1.4.7, the Parties acknowledge and agree that to the extent Oxford transfers Personal Data to TGI, it shall be transferring Personal Data outside the European Economic Area. In respect of such transfer, the Parties shall enter into the Standard Contractual Clauses (approved by the European Commission for such Controller-to-Controller transfers, as updated and/or amended from time to time), as set out in their current form at Annex 2 to this Schedule C, on the date of this Agreement, such clauses being incorporated into and forming part of this Agreement. In the event of a conflict between the terms of Annex 2 and the rest of this Agreement, the terms of Annex shall take precedence.

Annex 1

Data Protection Particulars

The subject matter and duration of the Processing	
The nature and purpose of the Processing	
The type of Personal Data being Processed	
The categories of Data Subjects	

Annex 2

Commission Decision C(2010)593
Standard Contractual Clauses

For the purposes of Article 26(2) of Directive 95/46/EC for the transfer of personal data to processors established in third countries which do not ensure an adequate level of data protection

Name of the data exporting organisation: .....

Address: .....

Tel.:..... ; fax: .....; e-mail:.....

Other information needed to identify the organisation:

……
(the data **exporter**)

And

Name of the data importing organisation:.....

Address:.....

Tel.: .....; fax:..... ; e-mail: .....

Other information needed to identify the organisation:

……
(the data **importer**)

each a “party”; together “the parties”,

HAVE AGREED on the following Contractual Clauses (the Clauses) in order to adduce adequate safeguards with respect to the protection of privacy and fundamental rights and freedoms of individuals for the transfer by the data exporter to the data importer of the personal data specified in Appendix 1.

Clause 1

Definitions

For the purposes of the Clauses:

(a) *'personal data', 'special categories of data', 'process/processing', 'controller', 'processor', 'data subject'* and *'supervisory authority'* shall have the same meaning as in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the

protection of individuals with regard to the processing of personal data and on the free movement of such data[1];

(b) '*the data exporter'* means the controller who transfers the personal data;

(c) *'the data importer'* means the processor who agrees to receive from the data exporter personal data intended for processing on his behalf after the transfer in accordance with his instructions and the terms of the Clauses and who is not subject to a third country's system ensuring adequate protection within the meaning of Article 25(1) of Directive 95/46/EC;

(d) *'the subprocessor'* means any processor engaged by the data importer or by any other subprocessor of the data importer who agrees to receive from the data importer or from any other subprocessor of the data importer personal data exclusively intended for processing activities to be carried out on behalf of the data exporter after the transfer in accordance with his instructions, the terms of the Clauses and the terms of the written subcontract;

(e) '*the applicable data protection law'* means the legislation protecting the fundamental rights and freedoms of individuals and, in particular, their right to privacy with respect to the processing of personal data applicable to a data controller in the Member State in which the data exporter is established;

(f) *'technical and organisational security measures'* means those measures aimed at protecting personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing.

Clause 2

Details of the transfer

The details of the transfer and in particular the special categories of personal data where applicable are specified in Appendix 1 which forms an integral part of the Clauses.

Clause 3

Third-party beneficiary clause

1. The data subject can enforce against the data exporter this Clause, Clause 4(b) to (i), Clause 5(a) to (e), and (g) to (j), Clause 6(1) and (2), Clause 7, Clause 8(2), and Clauses 9 to 12 as third-party beneficiary.

2. The data subject can enforce against the data importer this Clause, Clause 5(a) to (e) and (g), Clause 6, Clause 7, Clause 8(2), and Clauses 9 to 12, in cases where the data exporter has factually disappeared or has ceased to exist in law unless any successor entity has assumed the entire legal obligations of the data exporter by contract or by operation of law, as a result of which it takes on the rights and obligations of the data exporter, in which case the data subject can enforce them against such entity.

3. The data subject can enforce against the subprocessor this Clause, Clause 5(a) to (e) and (g), Clause 6, Clause 7, Clause 8(2), and Clauses 9 to 12, in cases where both the data exporter and the data importer have factually disappeared or ceased to exist in law or have become insolvent, unless any successor entity has assumed the entire legal obligations of the data exporter by contract or by operation of law as a result of which it takes on the rights and obligations of the data exporter, in which case the data subject can enforce them against such entity. Such third-party liability of the subprocessor shall be limited to its own processing operations under the Clauses.

4. The parties do not object to a data subject being represented by an association or other body if the data subject so expressly wishes and if permitted by national law.

[1] Parties may reproduce definitions and meanings contained in Directive 95/46/EC within this Clause if they considered it better for the contract to stand alone.

Clause 4

Obligations of the data exporter

The data exporter agrees and warrants:

(a) that the processing, including the transfer itself, of the personal data has been and will continue to be carried out in accordance with the relevant provisions of the applicable data protection law (and, where applicable, has been notified to the relevant authorities of the Member State where the data exporter is established) and does not violate the relevant provisions of that State;

(b) that it has instructed and throughout the duration of the personal data processing services will instruct the data importer to process the personal data transferred only on the data exporter's behalf and in accordance with the applicable data protection law and the Clauses;

(c) that the data importer will provide sufficient guarantees in respect of the technical and organisational security measures specified in Appendix 2 to this contract;

(d) that after assessment of the requirements of the applicable data protection law, the security measures are appropriate to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing, and that these measures ensure a level of security appropriate to the risks presented by the processing and the nature of the data to be protected having regard to the state of the art and the cost of their implementation;

(e) that it will ensure compliance with the security measures;

(f) that, if the transfer involves special categories of data, the data subject has been informed or will be informed before, or as soon as possible after, the transfer that its data could be transmitted to a third country not providing adequate protection within the meaning of Directive 95/46/EC;

(g) to forward any notification received from the data importer or any subprocessor pursuant to Clause 5(b) and Clause 8(3) to the data protection supervisory authority if the data exporter decides to continue the transfer or to lift the suspension;

(h) to make available to the data subjects upon request a copy of the Clauses, with the exception of Appendix 2, and a summary description of the security measures, as well as a copy of any contract for subprocessing services which has to be made in accordance with the Clauses, unless the Clauses or the contract contain commercial information, in which case it may remove such commercial information;

(i) that, in the event of subprocessing, the processing activity is carried out in accordance with Clause 11 by a subprocessor providing at least the same level of protection for the personal data and the rights of data subject as the data importer under the Clauses; and

(j) that it will ensure compliance with Clause 4(a) to (i).

Clause 5

Obligations of the data importer[2]

The data importer agrees and warrants:

[2] Mandatory requirements of the national legislation applicable to the data importer which do not go beyond what is necessary in a democratic society on the basis of one of the interests listed in Article 13(1) of Directive 95/46/EC, that is, if they constitute a necessary measure to safeguard national security, defence, public security, the prevention, investigation, detection and prosecution of criminal offences or of breaches of ethics for the regulated professions, an important economic or financial interest of the State or the protection of the data subject or the rights and freedoms of others, are not in contradiction with the standard contractual clauses. Some examples of such mandatory requirements which do not go beyond what is necessary in a democratic society are, *inter alia,* internationally recognised sanctions, tax-reporting requirements or anti-money-laundering reporting requirements.

(a) to process the personal data only on behalf of the data exporter and in compliance with its instructions and the Clauses; if it cannot provide such compliance for whatever reasons, it agrees to inform promptly the data exporter of its inability to comply, in which case the data exporter is entitled to suspend the transfer of data and/or terminate the contract;

(b) that it has no reason to believe that the legislation applicable to it prevents it from fulfilling the instructions received from the data exporter and its obligations under the contract and that in the event of a change in this legislation which is likely to have a substantial adverse effect on the warranties and obligations provided by the Clauses, it will promptly notify the change to the data exporter as soon as it is aware, in which case the data exporter is entitled to suspend the transfer of data and/or terminate the contract;

(c) that it has implemented the technical and organisational security measures specified in Appendix 2 before processing the personal data transferred;

(d) that it will promptly notify the data exporter about:

(i) any legally binding request for disclosure of the personal data by a law enforcement authority unless otherwise prohibited, such as a prohibition under criminal law to preserve the confidentiality of a law enforcement investigation,

(ii) any accidental or unauthorised access, and

(iii) any request received directly from the data subjects without responding to that request, unless it has been otherwise authorised to do so;

(e) to deal promptly and properly with all inquiries from the data exporter relating to its processing of the personal data subject to the transfer and to abide by the advice of the supervisory authority with regard to the processing of the data transferred;

(f) at the request of the data exporter to submit its data processing facilities for audit of the processing activities covered by the Clauses which shall be carried out by the data exporter or an inspection body composed of independent members and in possession of the required professional qualifications bound by a duty of confidentiality, selected by the data exporter, where applicable, in agreement with the supervisory authority;

(g) to make available to the data subject upon request a copy of the Clauses, or any existing contract for subprocessing, unless the Clauses or contract contain commercial information, in which case it may remove such commercial information, with the exception of Appendix 2 which shall be replaced by a summary description of the security measures in those cases where the data subject is unable to obtain a copy from the data exporter;

(h) that, in the event of subprocessing, it has previously informed the data exporter and obtained its prior written consent;

(i) that the processing services by the subprocessor will be carried out in accordance with Clause 11;

(j) to send promptly a copy of any subprocessor agreement it concludes under the Clauses to the data exporter.

Clause 6

Liability

1. The parties agree that any data subject, who has suffered damage as a result of any breach of the obligations referred to in Clause 3 or in Clause 11 by any party or subprocessor is entitled to receive compensation from the data exporter for the damage suffered.

2. If a data subject is not able to bring a claim for compensation in accordance with paragraph 1 against the data exporter, arising out of a breach by the data importer or his subprocessor of any of their obligations referred to in Clause 3 or in Clause 11, because the data exporter has factually disappeared or ceased to exist in law or has become insolvent, the data importer agrees that the data subject may issue a claim against the data importer as if it were the data exporter, unless any successor entity has assumed the entire legal obligations of the data

exporter by contract of by operation of law, in which case the data subject can enforce its rights against such entity.

The data importer may not rely on a breach by a subprocessor of its obligations in order to avoid its own liabilities.

3. If a data subject is not able to bring a claim against the data exporter or the data importer referred to in paragraphs 1 and 2, arising out of a breach by the subprocessor of any of their obligations referred to in Clause 3 or in Clause 11 because both the data exporter and the data importer have factually disappeared or ceased to exist in law or have become insolvent, the subprocessor agrees that the data subject may issue a claim against the data subprocessor with regard to its own processing operations under the Clauses as if it were the data exporter or the data importer, unless any successor entity has assumed the entire legal obligations of the data exporter or data importer by contract or by operation of law, in which case the data subject can enforce its rights against such entity. The liability of the subprocessor shall be limited to its own processing operations under the Clauses.

Clause 7

Mediation and jurisdiction

1. The data importer agrees that if the data subject invokes against it third-party beneficiary rights and/or claims compensation for damages under the Clauses, the data importer will accept the decision of the data subject:

   (a) to refer the dispute to mediation, by an independent person or, where applicable, by the supervisory authority;

   (b) to refer the dispute to the courts in the Member State in which the data exporter is established.

2. The parties agree that the choice made by the data subject will not prejudice its substantive or procedural rights to seek remedies in accordance with other provisions of national or international law.

Clause 8

Cooperation with supervisory authorities

1. The data exporter agrees to deposit a copy of this contract with the supervisory authority if it so requests or if such deposit is required under the applicable data protection law.

2. The parties agree that the supervisory authority has the right to conduct an audit of the data importer, and of any subprocessor, which has the same scope and is subject to the same conditions as would apply to an audit of the data exporter under the applicable data protection law.

3. The data importer shall promptly inform the data exporter about the existence of legislation applicable to it or any subprocessor preventing the conduct of an audit of the data importer, or any subprocessor, pursuant to paragraph 2. In such a case the data exporter shall be entitled to take the measures foreseen in Clause 5 (b).

Clause 9

Governing Law

The Clauses shall be governed by the law of the Member State in which the data exporter is established, namely…….

Clause 10

Variation of the contract

The parties undertake not to vary or modify the Clauses. This does not preclude the parties from adding clauses on business related issues where required as long as they do not contradict the Clause.

Clause 11

Subprocessing

1. The data importer shall not subcontract any of its processing operations performed on behalf of the data exporter under the Clauses without the prior written consent of the data exporter. Where the data importer subcontracts its obligations under the Clauses, with the consent of the data exporter, it shall do so only by way of a written agreement with the subprocessor which imposes the same obligations on the subprocessor as are imposed on the data importer under the Clauses[3]. Where the subprocessor fails to fulfil its data protection obligations under such written agreement the data importer shall remain fully liable to the data exporter for the performance of the subprocessor's obligations under such agreement.

2. The prior written contract between the data importer and the subprocessor shall also provide for a third-party beneficiary clause as laid down in Clause 3 for cases where the data subject is not able to bring the claim for compensation referred to in paragraph 1 of Clause 6 against the data exporter or the data importer because they have factually disappeared or have ceased to exist in law or have become insolvent and no successor entity has assumed the entire legal obligations of the data exporter or data importer by contract or by operation of law. Such third-party liability of the subprocessor shall be limited to its own processing operations under the Clauses.

3. The provisions relating to data protection aspects for subprocessing of the contract referred to in paragraph 1 shall be governed by the law of the Member State in which the data exporter is established, namely ……
……
……

4. The data exporter shall keep a list of subprocessing agreements concluded under the Clauses and notified by the data importer pursuant to Clause 5 (j), which shall be updated at least once a year. The list shall be available to the data exporter's data protection supervisory authority.

Clause 12

Obligation after the termination of personal data processing services

1. The parties agree that on the termination of the provision of data processing services, the data importer and the subprocessor shall, at the choice of the data exporter, return all the personal data transferred and the copies thereof to the data exporter or shall destroy all the personal data and certify to the data exporter that it has done so, unless legislation imposed upon the data importer prevents it from returning or destroying all or part of the personal data transferred. In that case, the data importer warrants that it will guarantee the confidentiality of the personal data transferred and will not actively process the personal data transferred anymore.

2. The data importer and the subprocessor warrant that upon request of the data exporter and/or of the supervisory authority, it will submit its data processing facilities for an audit of the measures referred to in paragraph 1.

[3] This requirement may be satisfied by the subprocessor co-signing the contract entered into between the data exporter and the data importer under this Decision.

On behalf of the data exporter:

Name (written out in full): …….

Position:
……
…

Address:
…….

Other information necessary in order for the contract to be binding (if any):

Signature…….

(stamp of organisation)

On behalf of the data importer:

Name (written out in full): …….

Position:
……
…

Address:
…….

Other information necessary in order for the contract to be binding (if any):

Signature…….

(stamp of organisation)

APPENDIX 1 TO THE STANDARD CONTRACTUAL CLAUSES

This Appendix forms part of the Clauses and must be completed and signed by the parties.

The Member States may complete or specify, according to their national procedures, any additional necessary information to be contained in this Appendix.

Data exporter

The data exporter is (please specify briefly your activities relevant to the transfer):

……
……

Data importer

The data importer is (please specify briefly activities relevant to the transfer):

……
……

Data subjects

The personal data transferred concern the following categories of data subjects (please specify):

……
……

Categories of data

The personal data transferred concern the following categories of data (please specify):

……
……

Special categories of data (if appropriate)

The personal data transferred concern the following special categories of data (please specify):

……
……

Processing operations

The personal data transferred will be subject to the following basic processing activities (please specify):

……
……

DATA EXPORTER

Name:……

Authorised Signature ……

DATA IMPORTER

Name:……

Authorised Signature ……

APPENDIX 2 TO THE STANDARD CONTRACTUAL CLAUSES

This Appendix forms part of the Clauses and must be completed and signed by the parties.

Description of the technical and organisational security measures implemented by the data importer in accordance with Clauses 4(d) and 5(c) (or document/legislation attached):

……
……
……
……
……

Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial (TRIDENT)

UK Telemetric Home Blood Pressure Monitoring Sub-Study

PATIENT INFORMATION SHEET

We would like to invite you to take part in our research study, which runs alongside the main TRIDENT study in the UK. The purpose of this sub-study is to compare the effects on blood pressure of the "Triple Pill" (combination blood pressure lowering tablet) versus a placebo (dummy) pill in the first few weeks of TRIDENT, using a special blood pressure monitor that automatically sends measurements taken at home to our research team.

Before you decide to take part, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information sheet, and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please do not hesitate to get in touch with us using the contact information below.

1. What is the purpose of this study?

About 1 in 10 strokes are due to a bleed into the brain from a ruptured (burst) artery, called intracerebral haemorrhage. Intracerebral haemorrhage is frequently the result of high blood pressure. The TRIDENT study, which you have enrolled in, compares the blood pressure lowering effects and safety of a "Triple Pill" (combination blood pressure lowering tablet) versus a placebo (dummy) pill in patients with recent Intracerebral haemorrhage.

This sub-study runs alongside TRIDENT in the UK, and involves the collection of some extra blood pressure measurements taken by participants at home to compare the effects of the treatment in more detail in the first six weeks. This sub-study will enable us to understand the effects of the "Triple Pill" on blood pressure variability (short term changes), to ensure blood pressure doesn't drop too low, and to see if measuring blood pressure at home using this technology is feasible after intracerebral haemorrhage.

2. Why have I been invited to take part in this study?

You have been invited to take part because you have been enrolled in TRIDENT. All participants in TRIDENT in participating centres in the UK are invited to join this sub-study that runs alongside the main trial.

3. Do I have to take part?

No, participation is entirely voluntary. It is completely up to you to decide if you would like to participate or not. If you agree to take part, you will be asked to read and sign an extra consent form. You are free to withdraw from this study at any time, without giving a reason. This will have no impact on your clinical care, and won't affect your participation in TRIDENT.

4. What will happen to me if I decide to take part?

The member of the research team that you met when joining TRIDENT will explain this sub-study to you, and will be able to answer any questions you may have. You are considered eligible to take part by virtue of the fact that you have been enrolled in TRIDENT, if you are also willing and able to take blood pressure measurements at home (either yourself or with the help of someone else).

You will be given a unique study number at the point of joining and issued with a Bluetooth-enabled home blood pressure monitoring kit, as shown in Figure 1. A member of the research team will demonstrate how to use this, and you will be given some written information about the kit and contact details for the Oxford centre to get in touch if you encounter any technical problems. The team at the University of Oxford will not have information about whether you have been allocated to receive the "Triple Pill" or the placebo (dummy pill), and it is advised that all queries about your treatment, potential adverse effects, missed doses or treatment discontinuation be addressed to your TRIDENT contact point at your local hospital. However, your contact details will be sought (name, next of kin name, phone number(s) and/or email address) so that we can reach out to you if any issues are encountered with the kit.



Figure 1. Blood pressure home monitoring kit

You will be advised to take blood pressure measurements using the kit in a seated position three times in your non-dominant arm (the one that you don't usually use for things like writing, unless you have been told otherwise) twice daily (morning, and afternoon/evening). Your blood pressure readings will be transmitted automatically as soon as you take them to the team at the study centre in Oxford. At the time of your six week TRIDENT follow-up visit, you will be asked to stop using the monitor and to bring the kit in with you for collection. At this visit, you will be fitted with a different blood pressure monitor for 24 hours that records measurements every 30 minutes during the day and hourly at night. You will be given a pre-paid envelope and packing instructions to return this monitor to Oxford after the recording period.

5. What are the potential benefits of taking part?

Participation in the study will allow you to monitor and understand your own blood pressure for the six week period of recording. In addition, your blood pressure will be checked on a daily basis by the team in Oxford from a safety perspective. If your blood pressure is consistently too high or too low over seven consecutive days, the Oxford centre will notify your local TRIDENT study site. The study will increase understanding about the effects of combination therapy for blood pressure after intracerebral haemorrhage, benefiting the stroke research community and ultimately improving care for intracerebral haemorrhage survivors.

6. Are there any possible disadvantages or risks from taking part?

Taking blood pressure readings results in a squeezing sensation in the arm, but this will only last a few seconds. These readings will be performed by you or your carer at home after you have been discharged form hospital.

All staff on the study will be fully trained in good clinical practice, and will always consider your well-being as their primary concern. You can withdraw from the study at any time without affecting your clinical care.

7. Will my General Practitioner/family doctor (GP) be informed of my participation?

Yes, they will be aware of your participation in the study.

8. What will happen to the results of this study?

The information from all participants taking part in this study will be collected and stored at the Oxford study centre. After analysing the data, the results will be published in scientific journals. With your consent, the research team may use the data collected in this study for future research.

9. What happens if I encounter problems with the blood pressure monitoring kit?

In the absence of any blood pressure readings being transmitted, the Oxford study team will troubleshot the most common equipment problems with you by telephone, or arrange a replacement to be sent out where necessary.

10. What will happen if I don't want to carry on with the study?

Participation is entirely voluntary and you may withdraw at any time, without providing a reason. Withdrawing from TRIDENT will also result in automatic withdrawal from the sub-study.

11. How will my information be kept confidential?

All information relating to your blood pressure and your contact details will only be used for medical research. Identifiable information will be anonymised in any reports. The research team will ensure that all information is protected from any unauthorised parties. The clinical data records will be kept securely at the Centre for Prevention of Stroke and Dementia at the University of Oxford. Data from the study may be used for future research on stroke in Oxford and other research institutions in the UK or worldwide, but your confidentiality will be maintained.

12. Who is organising the study?

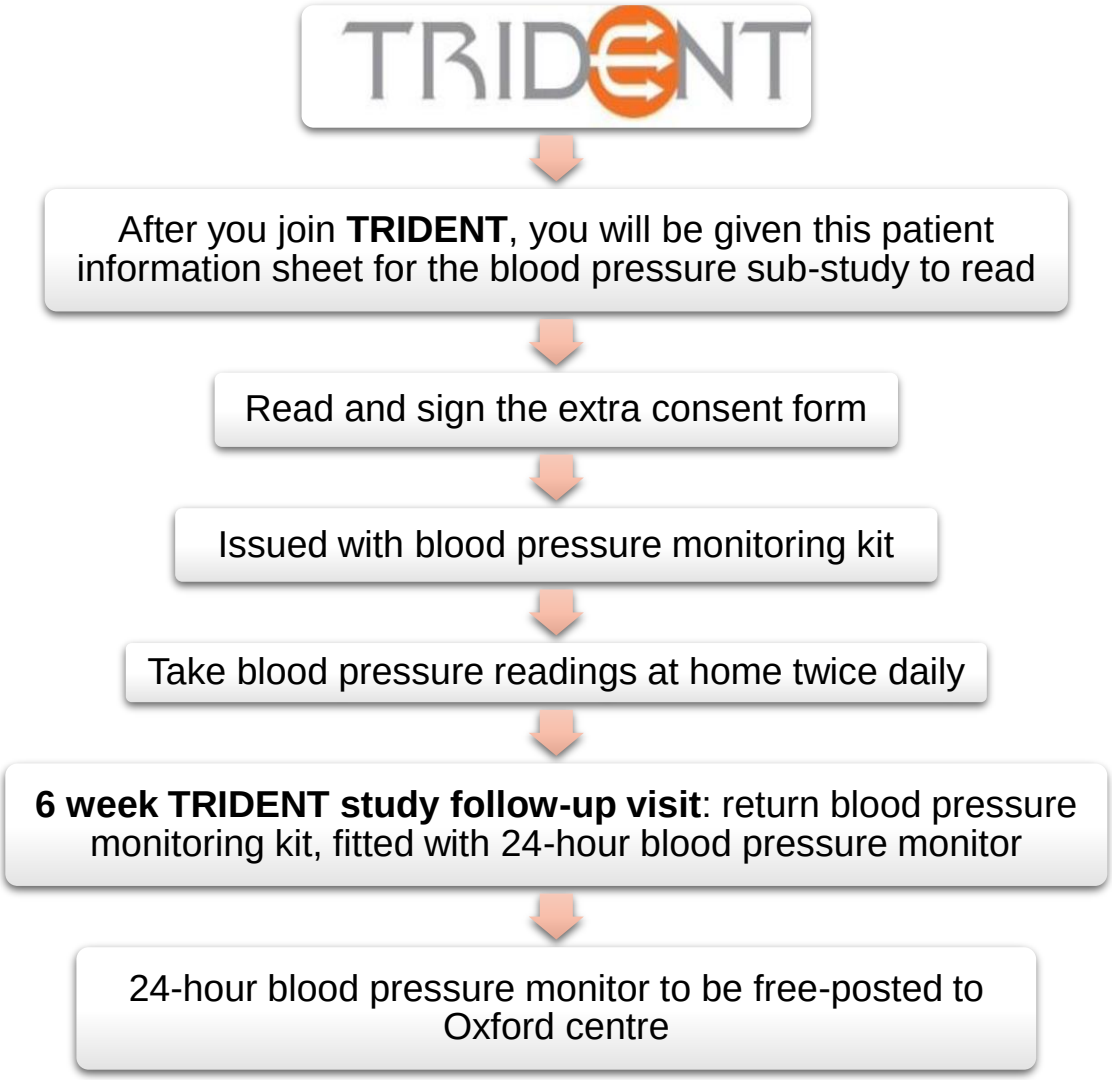
The research is being organised by Professor Peter Rothwell (Centre for Prevention of Stroke and Dementia, University of Oxford), Professor Rustam Al-Shahi Salman (Centre for Clinical Brain Sciences, University of Edinburgh), and Professor Craig Anderson (The George Institute for Global Health, University of New South Wales).

13. Who has approved the study?

All research in the NHS is looked at by an independent group called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and approved by East of Scotland Research Ethics Committee. Approval has also been granted by your local hospital.

Thank you for reading this information sheet and taking the time to consider participating in this study. If you agree to take part, you will be given a copy of this information sheet and a copy of the consent form for you to sign.

Summary flowchart of what is involved if you decide to take part:



Further information can be obtained from the study team at the Oxford centre, contact details:

Iain McGurgan
Clinical Research Fellow
Centre for Prevention of Stroke and Dementia
University of Oxford
Level 6, West Wing, John Radcliffe Hospital
Oxford OX3 9DU

Email: ian.mcgurgan@ndcn.ox.ac.uk
Tel: 01865 231601

Appendix 3.4

Participant Identification Number: _ _ _ _ _ _ _ _ HBPM _ _ _

CONSENT FORM

Title of Study: Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial (TRIDENT) UK Telemetric Home Blood Pressure Monitoring Sub-Study

	Please initial box
1. I confirm that I have read the information sheet dated 04/09/2019 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I give permission for the University of Oxford study team to have access to my contact details for this study in order to facilitate blood pressure monitoring.	☐
4. I give permission for the University of Oxford study team to store my blood pressure measurements for this study and for future research.	☐
5. I agree to my General Practitioner being informed of my participation in the study.	☐
6. I agree to take part in the above study.	☐

Name of participant	Date	Signature
Name of person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

BASELINE CASE REPORT FORM

Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial (TRIDENT)
UK Telemetric Home Blood Pressure Monitoring Sub-Study

This form should be completed by the local investigator and stored in the local site files, with a copy emailed to the Oxford device coordination centre (orh-tr.oxvasc@nhs.net) with the patient contact details form and the blood pressure monitor kit issuing form.

1. PATIENT ELIGIBILITY

Inclusion Criteria		
Has the patient met the inclusion criteria for TRIDENT?	**Yes** ☐	**No** ☐
Is the patient willing and can demonstrate an ability to undertake home blood pressure measurements, either unassisted or with the help of a relative, friend or carer?	**Yes** ☐	**No** ☐
Exclusion Criteria		
Has the patient met any of the exclusion criteria for TRIDENT?	**Yes** ☐	**No** ☐
Is there a known definite absence of any mobile phone coverage in addition to an absence of any internet access in the patient's place of residence?	**Yes** ☐	**No** ☐

2. BASELINE PARTICIPANT INFORMATION

Sub-study Participant Identification Number: [Format: TRIDENT ID followed by sub-study identifier]	_ _ _ _ _ _ _ _ HBPM _ _ _
Date of enrolment in TRIDENT:	☐☐ / ☐☐ / ☐☐☐☐
Date of randomisation in TRIDENT:	☐☐ / ☐☐ / ☐☐☐☐
Has written consent from the patient been obtained for the blood pressure monitoring sub-study?	**Yes** ☐ **No** ☐

3. BASELINE PROCEDURES

Date of baseline assessment:	☐☐ / ☐☐ / ☐☐☐☐
Blood pressure – 1st reading [using the BP monitor in the home BP monitoring kit if possible]	**SBP** ☐☐☐ **DBP** ☐☐☐ **Arm used** ☐
Blood pressure – 2nd reading [using the BP monitor in the home BP monitoring kit if possible]	**SBP** ☐☐☐ **DBP** ☐☐☐ **Arm used** ☐
Has the telemetric home blood pressure monitoring kit been issued to the participant?	**Yes** ☐ **No** ☐
If yes, date issued:	☐☐ / ☐☐ / ☐☐☐☐
If yes, blood pressure kit identification number:	☐☐☐☐☐☐☐☐☐☐

4. CRF SIGN OFF

Date form completed:	☐☐ / ☐☐ / ☐☐☐☐
Name of person completing form:	☐☐☐☐☐☐☐☐☐☐
Job title of person completing form:	☐☐☐☐☐☐☐☐☐☐

6 WEEK VISIT CASE REPORT FORM

Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial (TRIDENT)
UK Telemetric Home Blood Pressure Monitoring Sub-Study

This form should be completed (parts 1-3) by the local investigator and stored with the local site files, with a copy emailed to the Oxford device coordination centre (orh-tr.oxvasc@nhs.net).

1. PATIENT INFORMATION

Sub-study Participant Identification Number: [Format: TRIDENT ID followed by sub-study identifier]	_ _ _ _ _ _ _ _ HBPM _ _ _
Date of follow-up (6 week) visit:	☐☐ / ☐☐ / ☐☐☐☐

2. 6 WEEK VISIT PROCEDURES

Blood pressure	**SBP** ☐☐☐ **DBP** ☐☐☐
Has the telemetric home blood pressure monitoring kit been collected?	**Yes** ☐ **No** ☐
If yes, date returned:	☐☐ / ☐☐ / ☐☐☐☐
If not returned, please provide reason:	☐
Has the 24-hour ambulatory blood pressure monitor been fitted?	**Yes** ☐ **No** ☐
If yes, date fitted:	☐☐ / ☐☐ / ☐☐☐☐
If yes, time fitted:	☐☐ : ☐☐

If not fitted, please provide the reason:	

3. CRF SIGN OFF

Date form completed:	/ /
Name of person completing form:	
Job title of person completing form:	

4. 24-HOUR AMBULATORY BLOOD PRESSURE RECORDING (to be completed by the Oxford device co-ordination centre)

Has the 24-hour ambulatory blood pressure monitor been returned?	**Yes** ☐ **No** ☐
If yes, date received:	/ /
If not returned, please provide reason:	
Has the 24-hour ambulatory blood pressure been downloaded?	**Yes** ☐ **No** ☐
If yes, download date:	/ /
If not downloaded, please provide reason:	

PLEASE NOTE

For your safety, the blood pressure machine should not be switched on whilst driving.

During the 24 hours

- you should not do any vigorous sport or use machinery
- you are asked not to shower or bath

The recorder is programmed to take your blood pressure automatically half-hourly during the day and hourly at night (2300-0700). Once switched on, you do not need to do anything else to it.

You should be seated and remain QUIET and STILL while the recorder is taking your blood pressure and avoid any sudden movement.

When the recorder starts to take a measurement SIT DOWN if possible. Rest the arm with the cuff on it on the chair arm or table, with the hand relaxed and the palm facing upwards. If you cannot sit down, rest your arm on your midriff until you feel the cuff deflate.

The measurement process may take 20-30 seconds. Do not worry if the cuff inflates again – this is perfectly normal.

When the machine is switched off only the current time is displayed.

To switch the machine on press and hold the black button marked AUTO ON/OFF
A small A will appear in the top left hand corner
The machine will now automatically take your blood pressure.

To switch the machine off press and hold the black button marked AUTO ON/OFF. The small A will then disappear.

Please switch the machine off after you have completed the 24 hours and remove the cuff.

If a 'B' is displayed on the screen this indicates the batteries are low. In the unlikely event of this happening, or if there are any other problems, please contact us. In an emergency the machine can be switched off and the cuff removed.

Have a normal day. Do not spend the day relaxing!

Patient Details and Diary

Monitor number:

Date recording commenced:

Test reading (mmHg):

Full name:

Study site:

The following questions will be useful in the analysis of your recording:

Today were you at work? ☐ at home? ☐

What sort of day did you have?

Average ☐ Unusually quiet ☐ Unusually busy ☐ Unusually stressful ☐

How well did you sleep?

What time did you go to bed? What time did you get up?

Were you awake during the night?

Please see the instructions for returning the monitor by post once you have completed the 24-hour monitoring period. Many thanks.

Appendix 3.8

Returning 24-Hour Blood Pressure Monitors to the University of Oxford Study Team

PARTICIPANT GUIDE

You should have been provided with:

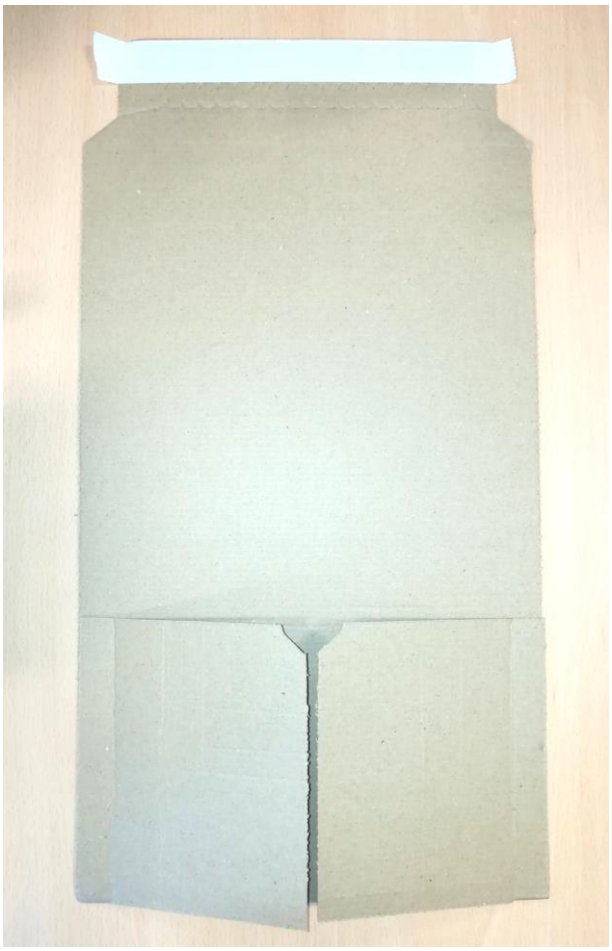
1. Patient detail and diary form
2. Blood pressure monitor (in blue cover)
3. Blood pressure cuff
4. A flat cardboard parcel (to be assembled)
5. A pre-labelled, pre-paid, padded envelope





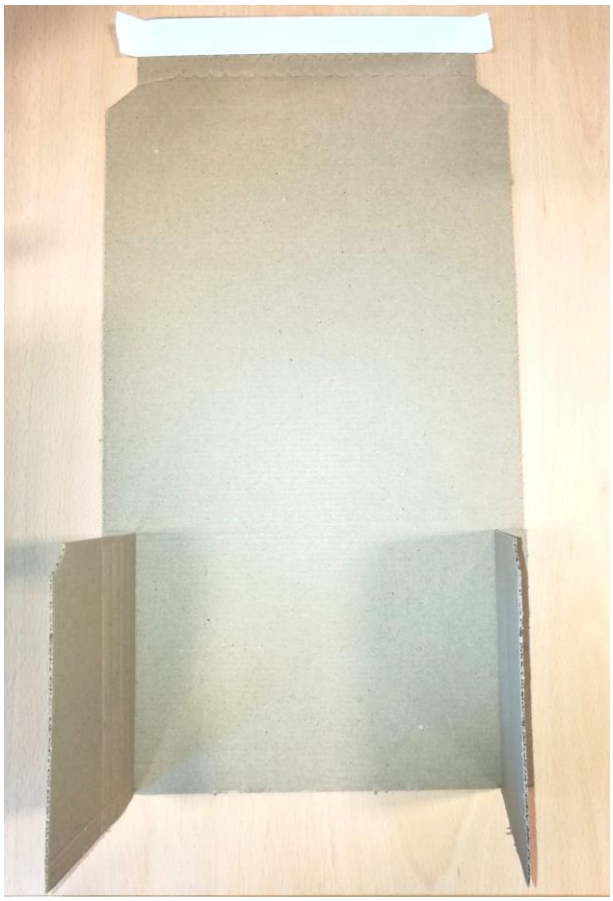
Step 1

Break along the perforated line in centre of the lower flap



Step 2

Bend the flaps back and crease.



Step 3

Place the completed patient details and diary form in between the flaps.



Step 4

Place the blood pressure cuff in next, to one side.



Step 5

Please remove the monitor from the blue cover and remove the batteries, as these cannot be posted, before placing it back into its blue cover.



Step 6

Place the blood pressure monitor in next with the strap lying across the blood pressure cuff.



Step 7

Fold the side flaps over the blood pressure monitor and cuff.



Step 8

Hold the flaps down, carefully roll the parcel up over itself, and fold the top flap down.



Step 9

Remove the tape, fold over the flap and stick it down.



Step 10

Place the parcel in the provided pre-paid labelled envelope and post.



Thank you!

24 Hour Ambulatory Blood Pressure Monitor Site Guidelines

To fit the recorder
Ask the patient to remove their shirt or blouse as appropriate.

Select the appropriate arm

- BP should be measured in clinic in each arm (as per the baseline CRF). Unless contraindicated, use the non-dominant side. In cases where there is a difference of >20mmHg systolic between sides, use the arm with the highest pressure.

Fit the appropriate size cuff (see guide on cuff)

- for the left arm, cuffs are available in small, adult or large adult
- for the right arm only an adult cuff is purpose made; for other sizes please use a left sided cuff taking care over positioning
- The bottom of the cuff should sit at least 3 cm above the crease of the elbow
- If using the left arm, the yellow tab should sit over the brachial artery
- Tighten the cuff so you can fit your first and second finger between the cuff and the patient's arm
- If the cuff is not positioned correctly, the recorder may not measure the BP correctly and an error may occur.

Connect the cuff to the recorder by screwing it in

Take a test reading

- Ensure the patient is seated (legs uncrossed), relaxed and remains quiet and still whilst taking the measurement
- Press and briefly hold the red start/stop button once. The cuff will inflate to an initial pressure of approximately 185mmHg. It may inflate further if the BP has not been detected, or during movement or arrhythmia. The average time taken is 20-30 seconds. The maximum measurement time is 90 seconds.
- Ideally, listen using a stethoscope / palpate over the brachial artery during the test reading.
- After the test measurement, the result will briefly display on the screen (this will only happen during the test measurement and not during subsequent readings).
- The time will reappear on the screen.
- If any adjustments are required with the cuff, this process can be repeated. If no changes are required, the cuff can be taped into position across the shoulder if there are no allergies reported. Advise the patient to remove the tape if redness or itching should occur. Of note, the cuff contains rubber.

Turn the recorder onto automatic mode by pressing and holding the black Auto on/off button for approx. 3 seconds. Once switched on, the patient should not need to do anything else to the recorder

- The letter 'A' will appear in the top left hand corner of the display.
- Instruct the patient to have a normal a day as possible. Ideally, when they feel the cuff inflate they should take a seat, with the arm supported. If this is not possible, they should try to stay still with the arm across the midriff until the feel the cuff fully deflate.

Instruct the patient to turn it off (by pressing and holding the black Auto on/off button for approx. 3 seconds)

- when driving (this may not apply to all patients)
- if there is excessive arm pain

And take it off at the end of 24 hours

Use the belt and carry case to keep the recorder around the patient's waist (this can be removed for sleeping and dressing as necessary).

Should the letter 'B' appear, the batteries need replacing. All data stored on the device will be retained by a backup battery.

Ensure the patient has the instruction sheet (which advises against vigorous sport, using machinery or heavy physical work), knows to complete the patient diary (especially sleep and awake times) and is prepared to free-post the equipment after the monitoring period. It will be supplied with the necessary packaging and a pre-paid envelope. The monitor cannot get wet, and bathing or showering should be avoided until the equipment is removed.

<u>Replace/charge the batteries:</u>

- Remove the battery cover
- There is a spare set of batteries in each blue case. These should be should be charged and therefore available for immediate use. Replace the battery cover.
- Charge the used batteries using the charger found in the box before returning them to the blue box

Appendix 3.10

Loan of Medical Equipment

Equipment Issued	Kit number	Cuff (please circle)	Arm (please circle)	Date	Signature
Bluetooth BP monitoring kit		Sm / Med / Lg	Left / Right		
24 hour BP monitor at 6 week assessment		Sm / Med / Lg	Left / Right		

Study Centre		***Participant Study ID***		***Participant Name***	

This form should be completed by the local investigator and emailed to the Oxford device coordination centre (orh-tr.oxvasc@nhs.net) with the patient contact details form and a copy of the relevant CRF.

DATE

GP NAME

Address

Dear Dr

PATIENT NAME
DOB
NHS NUMBER

The above-named patient has agreed to participate in Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial (TRIDENT)
UK Telemetric Home Blood Pressure Monitoring Sub-Study.

The purpose of this sub-study is to compare the effects on blood pressure of the "Triple Pill" (combination antihypertensive tablet) versus placebo in the first six weeks of TRIDENT. A telemetric home monitoring device is used to carefully record blood pressures that are sent automatically to a monitoring centre in the University of Oxford. The research team in Oxford are blinded to TRIDENT treatment allocation, and there is no deviation from the original TRIDENT trial proceedings.

All participants take blood pressure readings at home twice daily until their 6-week TRIDENT follow-up visit, at which point they are fitted with a 24-hour ambulatory blood pressure monitor.

How are you (GP) involved?
Please notify us in the event of hospitalisation (for any reason) or death.

Enclosed is a copy of the information sheet supplied to the patient and a signed consent form.

Yours sincerely,

_____
PI at site

Participant Contact Details Form

Centre name: _____

Participant Details
Surname……...……Forename(s)……..

Date of birth ___/ ___ / ___ (day/month/year) Male ☐ Female ☐

Address…….....
City.....
Postcode…….....
Home Telephone……..... Mobile number……....
Email address……

Contact details of relative/friend (at a **different** telephone number/address)
……..
……..
Telephone.....Email address……....

Please email to the Oxford device coordination centre: **orh-tr.oxvasc@nhs.net**

THINK POSITIVE

blood pressure



PARTICIPANT GUIDE

Doc Ref: 001-2027-LMAN3 Version: R1, Issue Date: 12 MAR 2018

Edited for the TRIDENT UK HBPM Sub-Study, 04 SEP 2019

Trademarks: t+ Medical® is a registered trade mark of OBS Medical Ltd.

Contents

Introduction 4
- Indications 4
- Welcome to t+ blood pressure 4
- How does t+ blood pressure work? 5
- Why should I use t+ blood pressure? 6
- When should I not use t+ blood pressure? 6
- Caution 6

Getting Started 7
- Set up instructions 7
- Bluetooth Hub 8
- Blood Pressure Meter 9
- Blood Pressure Cuffs 9
- Taking a blood pressure reading 9

Troubleshooting and Support 11
- Description of maintenance 11
- Storage instructions 11
- Troubleshooting – Blood Pressure Meter 12
- Troubleshooting – Bluetooth Hub 13
- t+ blood pressure support 14
- Oxford contact information 14
- T+ contact information 14

Introduction

Indications

The t+ blood pressure is intended for periodically recording blood pressure readings for the purpose of improving blood pressure management.

The t+ blood pressure provides real-time readings, graphs, and trends directly to healthcare professionals. It is intended to be used in the home to aid you to monitor your blood pressure in between hospital visits.

The t+ blood pressure is available only through healthcare professionals.

Welcome to t+ blood pressure

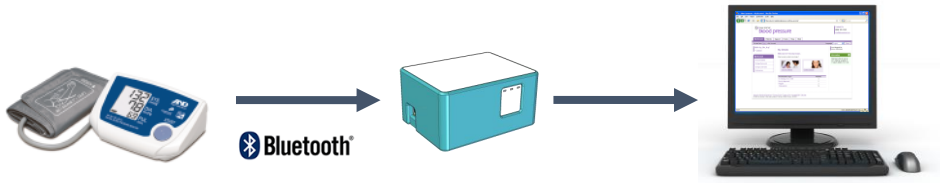
t+ blood pressure is a simple tool to help you and your health care professional keep track of your blood pressure in between hospital visits. This means they can spot any changes and track any trends as they happen.

How does t+ blood pressure work?

t+ blood pressure uses a Bluetooth Hub and a blood pressure meter (with Bluetooth) to safely and securely send information about your blood pressure directly to health care professionals.

The information about your blood pressure is automatically sent to health care professionals who can look at it on their computer.

It is really simple for you to use, all you have to do is put the blood pressure cuff on your arm and press the Start button.



You take your blood pressure at home using the Blood Pressure monitor (with Bluetooth)

The readings are automatically transmitted via Bluetooth to the Bluetooth Hub and onto the t+ System Servers

Healthcare professionals are then able to see your readings via a secure web site

Why should I use t+ blood pressure?

You will have been specifically chosen by your healthcare professional to use this equipment, and advised by them how to use it.

Through the use of t+ blood pressure, both you and your healthcare professional will have a much greater insight into your health. It will help you both monitor your condition more closely.

When should I not use t+ blood pressure?

You should not use t+ blood pressure if you feel unwell before, during or after taking your blood pressure. Please inform your healthcare professional.

Caution

Please read all the instructions provided in this user guide, and ensure you are confident using the equipment. If you need any additional help using the equipment please speak to your healthcare professional.

This equipment is intended only to be used by the person it was supplied to, and must only be used as instructed.

Getting Started

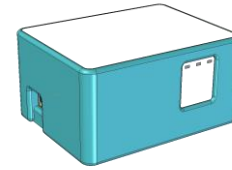
You will have been specifically chosen by your healthcare professional to use this equipment, and advised by them how to use it.

Set up instructions

You will have received:



Blood pressure meter and medium sized cuff *



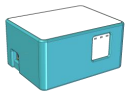
Bluetooth Hub



A t+ blood pressure

Patient user guide

*Other cuff sizes are available please discuss with you healthcare professional



Bluetooth Hub

You have been issued a Bluetooth Hub that will automatically send your blood pressure readings directly to healthcare professional to monitor your progress.

For the blood pressure monitor to transmit readings to the Bluetooth Hub, they need to be within a 10 meter range of each other, so where possible please try to use your blood pressure monitor in the same room as the Bluetooth Hub.

The Bluetooth Hub will come with a mains charger. Please plug the mains charger into a socket as soon as you get home. We would recommend leaving the Bluetooth Hub plugged in and switched on at all times.

Once plugged in, the three indication lights will illuminate for 10 seconds then go off.



Then one or more indication lights will illuminate as follows:

- Green Light (Status)
  - Intermittent flashing – the hub is trying to connect to the secure t+ servers
  - When permanently illuminated – the hub is now connected to secure t+ servers
- Blue Light *(Bluetooth)*
  - When illuminated – the BP Meter is transmitting readings to the Bluetooth Hub
- Red Light *(Memory)*

- When illuminated – the BP Readings have been stored awaiting transmission when connected



Blood Pressure Meter

You have been issued with a home digital blood pressure monitor as part of the TRIDENT UK HBPM sub-study.

It is important that only you use the blood pressure monitor.

Please do not allow anyone else to use the machine or interfere with the equipment.

Blood Pressure Cuffs

Your healthcare professional will advise you on which arm we would like you to measure and provide you with the appropriate size of cuff for your arm.

Taking a blood pressure reading

Your healthcare professional will instruct you on how to use the home blood pressure monitor.

Please refer to the below instructions for further information.

When to take your readings

Set 1 – as soon after wakening as possible

Set 2 – afternoon/evening

At each sitting we would like you to measure your blood pressure **3 times**.

You should allow a couple of minutes in between each of the 3 blood pressure measurements.

If you wish to take your blood pressure more frequently, please ensure that this is in addition to the above schedule, not instead of it.

How to take your readings

For the best results:

- Please rest for a few minutes prior to taking your readings.
- All measurements should be done sitting, at a table if possible.
- Please always take your blood pressure on the same arm.
- Try not to talk or move whilst the cuff is inflating.

Troubleshooting and Support

Description of maintenance

Product damage may occur if proper care is not taken whilst unpacking, installation and use.

Do not submerge any of the components in water or any other fluids. If the equipment does get wet, dry immediately.



If the batteries in the blood pressure meter run low, the battery power indicator will begin to blink.

Important: When the battery symbol on the BP Meter begins to blink; you should replace the batteries immediately.

The meter takes 2x AA batteries. More information on replacing the batteries this can be found in the BP meter user guide.

The Bluetooth Hub is mains powered and should be left on at all times to ensure the timely receipt and transmission of your daily BP readings for clinical review.

Storage instructions

Store the t+ blood pressure equipment in a dry area, and remove batteries from the BP meter if it is to be stored for extended periods of time.

Troubleshooting – Blood Pressure Meter



Problem	Possible Reason	Recommended Action
Nothing appears in the display even when the power is turned on	Batteries are drained	Replace all batteries with new ones
	Battery terminals are not in the correct position	Reinstall the batteries with negative and positive terminals matching those indicated on the battery compartment.
The Cuff does not inflate	Battery power is low Low Battery Mark – blinks If the batteries are drained completely, the mark does not appear	Replace all batteries with new ones
The unit does not measure.	The cuff is not applied properly	Apply the cuff correctly
	You moved your arm or body during the measurement	Make sure you remain very still and quite during the measurement
Readings are too high or too low	The cuff position is not correct	Sit comfortably and still. Raise your hand so that the cuff is at the same level as your heart using a pillow or support.
		If you have a very weak or irregular heartbeat, the device may have difficulty in determining your blood pressure
Other		Remove the batteries. Place them back properly and try the measurement again.

Troubleshooting – Bluetooth Hub



Problem	Possible Reason	Recommended Action
BT Hub Status (Green) indication light is not ON or flashing	Mains power not connected	Check the mains power is connected to the BT Hub and that mains power is switched on at the plug socket.
BT Hub Status (Green) indication light is flashing intermittently	Poor network signal at the current BT Hub location	Relocate the BT Hub to another part of the building and retry. The Status (Green) indication light needs to be permanently ON
BT Hub Bluetooth (Blue) indication light does not come on when taking a BP reading	The BT Hub and BP Meter are not within 10 meters of each other	Check both the BT Hub and BP Meter are within 10 meters of each other and retry reading
	The BP meter needs to be reconnected with the BT Hub	BP Meter - Press and hold the start button until the word **uPr** appears. Lift and re-press the start button and the words **END** appears. Now retake a BP reading. The Bluetooth (Blue) indication light should now come on.
BT Hub Memory (Red) indication light is on.	BT Hub is not connected to secure t+ system so it is storing readings	Check the Status (Green) indication light is permanently ON

t+ blood pressure support

For study specific questions, please contact the relevant research team as detailed via your Patient Information Letter issued along with the t+ blood pressure system.

Oxford contact information

If you have any concerns or questions regards your blood pressure investigations, please contact the Oxford blood pressure monitoring centre at the during office hours Monday – Friday 8:30am until 5pm

Call: 01865 234 893

T+ contact information

If you have any technical problems, please contact the customer service team who can be reached during office hours Monday - Friday 9am to 5pm excluding bank holidays.

Call: 01235 432050
Email: support@tplusmedical.com

This page has intentionally been left blank

UK Head Office
5G Park Square
Milton Park
Abingdon
OX14 4RR
UK