Improving secondary prevention after transient ischaemic attack and minor ischaemic stroke

Thesis submitted for degree of D.Phil

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ABSTRACT

IMPROVING SECONDARY PREVENTION AFTER TRANSIENT ISCHAEMIC ATTACK AND MINOR ISCHAEMIC STROKE

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Stroke is the second most common cause of death worldwide and the leading cause of long-term neurological disability. In the UK, stroke accounts for approximately 6% of total National Health Service and Social Services expenditure. The burden of stroke is predicted to increase because of the ageing population. Whilst effective primary prevention is important, about 30% of strokes occur in individuals with a previous transient ischaemic attack (TIA) or minor stroke. Recent prospective studies have shown a high early risk of recurrent stroke in the days after TIA or minor stroke. The prompt use of preventative strategies has been shown to be highly effective in reducing this early risk of recurrence and there is now a consensus in favour of rapid access services and urgent secondary prevention after TIA. However, there are several areas where clinical practice still needs to be improved, including delays in seeking medical attention, the reliability of clinical diagnosis of TIA in the acute phase, prediction of stroke recurrence risk and the control of risk factors, particularly blood pressure (BP), in longer-term secondary prevention. My thesis will focus on these clinically important areas.

I have used data from a population-based study; the Oxford Vascular Study (OXVASC). OXVASC is a prospective, population-based incidence study of vascular disease in all territories in Oxfordshire, UK, which started in 2002 and is ongoing. The study population comprises approximately 91 000 individuals registered with nine general practices and uses multiple overlapping methods of “hot” and “cold” pursuit to identify all patients with acute vascular events.

The research described in this thesis has several clinically useful findings which address areas for improvement during the patient journey after TIA and minor ischaemic stroke. First, I have highlighted that despite public education campaigns, about 70% of patients still fail to correctly recognise TIA or minor stroke symptoms and about 30% delay seeking medical attention for over 24 hours. Second, I have shown that recurrent TIA within 7-days is not associated with a greater stroke risk than after a single TIA, other than in the capsular warning syndrome. Third, in patients with definite posterior circulation TIA or stroke, preceding transient isolated “brainstem” symptoms occur in 26%, which has implications for the current diagnostic criteria for TIA. Fourth, I have shown that the Face Arm and Speech Test does not reliably identify patients at high early risk of recurrent stroke after TIA and minor stroke and has limited potential to improve access to care. Fifth, I have shown that outpatient management of clinic-referred minor stroke is feasible and may be as safe as inpatient care. Sixth, that stroke recurrence risk after minor stroke is delayed compared with TIA, and is high during the subacute phase despite current best medical treatment. Seventh, I have assessed Bluetooth-based home BP monitoring after TIA or minor stroke as a way of achieving better BP control and shown that this method is feasible, irrespective of age, and patient satisfaction is high. Finally, I have studied the late outcomes after TIA and stroke in OXVASC in comparison with a similar cohort from the 1980’s. I have shown that the age and sex specific later risk of recurrent stroke after TIA and stroke in Oxfordshire has fallen. However, the risk of fatal recurrent stroke remains high in contrast with the risk of fatal cardiac events which is low.

DECLARATION

I certify that this thesis entitled “Improving secondary prevention after transient ischaemic attack and minor ischaemic stroke” was performed whilst I was a full time postgraduate student at the University of Oxford.

I declare that this thesis is of my own composition, and the research contained herein is my own original work. No portion of this work has been submitted in support of an application for any other degree.

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PUBLICATIONS

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Paul NLM, Chandratheva A, Rothwell PM. Recurrent TIA, capsular warning syndrome, ABCD2 score and early risk of stroke: population-based study. J Neurol Neurosurg Psychiatry. 2010 Nov;81(11):e28

Paul NLM, Chandratheva A, Rothwell PM. Major unmet need for more effective secondary prevention in the subacute phase after minor ischaemic stroke: a population-based study. J Neurol Neurosurg Psychiatry. 2010 Nov;81(11):e27-8

Geraghty OC, **Paul NLM**, Chandratheva A, Rothwell PM. Low risk of rebound events after discontinuation of a short course of clopidogrel in acute TIA or minor stroke. Neurology. 2010 Jun 8;74(23):1891-6

Paul N, Chandratheva A, Lasserson D, Rothwell PM. Time trends in patient behaviour immediately after TIA or minor stroke: 2002-2009. Cerebrovasc Dis 2009;27 (suppl 6):1

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TABLE OF CONTENTS

ABSTRACT ii

DECLARATION iii

ACKNOWLEDGEMENTS iv

PUBLICATIONS v

ORAL PRESENTATIONS vii

TABLE OF TABLES xiv

TABLE OF FIGURES xix

TABLE OF APPENDICES xxiii

CHAPTER 1. Introduction 1

1.1 The burden of arterial vascular disease 2

1.2 The burden of stroke 2

1.2.1 Stroke incidence, prevalence, mortality and time trends 3

1.3. Transient ischaemic attack and minor stroke: definitions 5

1.3.1 Incidence and prevalence of TIA 6

1.3.2 Short term prognosis after TIA and minor stroke 7

1.3.3 Long term prognosis after TIA and minor stroke 8

1.4 Early recurrent stroke risk predictions after TIA and minor stroke 10

1.4.1 Risk prediction by clinical features: the ABCD and ABCD2 scores 10

1.4.2 Risk prediction by vascular territory 13

1.4.3 Risk prediction by aetiology 13

1.4.4 Risk prediction by imaging findings 16

1.5 Secondary prevention after TIA and minor stroke 18

1.5.1 Antiplatelet therapy 19

1.5.2 Anticoagulation 21

1.5.3 Blood pressure lowering 22

1.5.4 Cholesterol-lowering 23

1.5.5 Carotid endarterectomy 24

1.6 Optimal service provision after TIA and minor stroke 25

1.7 The Oxford Vascular Study 30

1.7.1 Case ascertainment and follow-up 31

1.7.2 Definitions and diagnosis 32

1.7.3 Patient consent and ethical approval 33

1.8 OXVASC contribution 33

1.9 Thesis Aims 34

1.10 References 36

CHAPTER 2. Time trends in patient behaviour after TIA and minor stroke 50

2.1 Introduction 51

2.2 Methods 52

2.2.1 Analysis 53

2.3 Results 54

2.4 Discussion 64

2.5 References 68

CHAPTER 3. Population based study of capsular warning syndrome and prognosis after early recurrent TIA 71

3.1 Introduction 72

3.2 Methods 72

3.2.1 Analysis 73

3.3 Results 74

3.4 Discussion 81

3.5 References 84

CHAPTER 4. Population-based study of NINDS-defined TIA: evidence of substantial under-diagnosis of posterior circulation events 88

4.1 Introduction 89

4.2 Methods 90

4.3 Results 91

4.4 Discussion 98

4.5 References 101

CHAPTER 5. Utility of the FAST test in prediction of early stroke risk after TIA and minor ischaemic stroke: implications for public education 104

5.1 Introduction 105

5.2 Methods 106

5.2.1 Analysis 107

5.3 Results 108

5.3.1 FAST and 7-day recurrent stroke risk 111

5.3.2 FAST and 90-day recurrent stroke risk 115

5.3.3 FAST in those who did not seek medical attention at the time of event 115

5.3.4 FAST in those who delayed seeking medical attention 115

5.4 Discussion 120

5.5 References 123

CHAPTER 6. Feasibility, safety and cost of outpatient management of TIA and acute minor ischaemic stroke: a population based study 125

6.1 Introduction 126

6.2 Methods 126

6.3 Results 129

6.4 Discussion 138

6.5 References 142

CHAPTER 7. Prognosis of TIA and minor stroke in the subacute phase 145

7.1 Introduction 146

7.2 Methods 146

Analysis 148

7.3 Results 148

7.4 Discussion 161

7.5 References 166

CHAPTER 8. Treating blood pressure to target levels in patients with TIA and non-disabling stroke: Feasibility, acceptability and blood pressure control with intensive Bluetooth home BP-monitoring 169

8.1 Introduction 170

8.2 Methods 171

8.2.1 Patients included in the study 171

8.2.2 Assessment and management of hypertension in the clinic 172

8.2.3 Patient training in home BP monitoring 172

8.3 Results 175

8.4 Discussion 184

8.5 References 189

CHAPTER 9. Long term outcomes after TIA and stroke 193

9.1 Introduction 194

9.2 Methods 195

9.2.1 Analysis 197

9.3 Results 197

9.4 Discussion 215

9.5 References 218

CHAPTER 10. Change in late recurrent stroke, fatal stroke and fatal cardiac event risk after TIA and stroke in Oxfordshire from 1981-2010 221

10.1 Introduction 222

10.2 Methods 223

10.2.1 Definition of recurrent stroke in OCSP and OXVASC 224

10.2.2 Definition of fatal recurrent stroke and cardiac deaths 225

10.2.3 Analysis 225

10.3 Results 226

10.4 Discussion 238

10.5 References 242

CHAPTER 11. Conclusions and further research 245

11.1 Introduction 246

11.2 Time trends in patient behaviour after TIA and minor stroke 246

11.3 Population based study of capsular warning syndrome and prognosis after early recurrent TIA 247

11.4 Population-based study of NINDS-defined TIA: evidence of substantial under-diagnosis of posterior circulation events 248

11.5 Utility of the FAST test in prediction of early stroke risk after TIA and minor ischaemic stroke: implications for public education 249

11.6 Feasibility, safety and cost of outpatient management of acute minor ischaemic stroke: a population based study 250

11.7 Prognosis of TIA and minor stroke in the subacute phase 250

11.8 Treating blood pressure to target levels in patients with TIA and non-disabling stroke: Feasibility, acceptability and blood pressure control with intensive Bluetooth home BP-monitoring 251

11.9 Long term outcomes after TIA and stroke 252

11.10 Change in late recurrent stroke, fatal stroke and fatal cardiac event risk after TIA and stroke in Oxfordshire from 1981-2010. 253

TABLE OF TABLES

Table	Table title	Page
1.1	Risk of stroke within 90 days by number of risk factors (age >60 years, symptom duration >10 minutes, diabetes mellitus, and symptoms of weakness or speech impairment) in Johnston cohort of 1707 emergency department attendees with TIA	11
1.2	The ABCD score	12
1.3	The TOAST classification of ischaemic stroke	15
1.4	Secondary prevention strategies of proven benefit	25
1.5	Elements of stroke detection tools	29
2.1	The first contact with healthcare services in patients with TIA or minor stroke	54
2.2	Delay to seeking medical attention stratified by demographic, clinical characteristics and vascular risk factors	59
2.3	Delay to seeking medical attention stratified by weekday on which event occurred	60
2.4	Demographics, clinical characteristics and vascular risk factors in stroke patients who did not seek medical attention for a preceding TIA or minor stroke	63
3.1	Baseline characteristics of all patients, n=1000	75
3.2	Stroke risk at 7 days after single and recurrent TIA stratified by ABCD2 score and TOAST classification, % risk (95% CI)	76
3.3	Characteristics of patients with stroke within 7 days of second TIA	80

Table	Table title	Page
4.1	Territory of all ischaemic events presenting to medical attention	91
4.2	Territory of all definite ischaemic events, n= 1117	92
4.3	Baseline characteristics, vascular risk factors and premorbid medication of definite ischaemic events by territory, n=1117	92
4.4	TNA/TIA in 90 days preceding definite event by territory	94
4.5	Presence of VB stenosis and TNA within preceding 90 days in those with definite VB events and VB imaging, n=180	97
4.6	Presence of ≥50% symptomatic internal carotid artery stenosis and TNA within preceding 90 days in those with definite carotid events and carotid imaging, n=776	97
5.1	Baseline characteristics of all patients with TIA, n =1000 and MIS, n=775	109
5.2	Vascular territory, ABCD2 score and TOAST subtype of all patients with TIA and MIS by FAST, n=1775	110
5.3	Characteristics of patients who did not seek medical attention at time of TIA or MIS but presented after a recurrent stroke within 90-days	117
5.4	Characteristics of patients who presented to medical attention after TIA by delay to presentation, n=933	118
5.5	Presenting symptoms of FAST negative patients who did not seek medical attention at time of event but presented after a recurrent stroke (39 TIA, 7 MIS) and of those with delay in seeking medical attention > 24 hours (179 TIA, 71 MIS)	119
6.1	Baseline characteristics of patients with minor stroke (NIHSS≤3) by treatment provision setting, n=411	133

Table	Table title	Page
6.2	Reasons for non elective admission in patients with TIA and minor ischaemic stroke up to 7 and 30 days after discharge from treatment provision setting, n=810	135
6.3	Secondary prevention measures at discharge and one year follow-up in patients with MIS seen in the clinic and hospital, n=387	137
7.1	Baseline characteristics, vascular risk factors and premorbid medication of patients presenting with TIA or ischaemic stroke.	149
7.2	Recurrent strokes (% risk, 95% CI) up to 2 years after TIA and ischaemic stroke	151
7.3	Recurrent strokes (% risk, 95% CI) up to 2 years from time of seeking medical attention after TIA and minor ischaemic stroke	155
7.4	Mortality (% risk) up to 2 years after TIA, minor stroke and major stroke	159
7.5	Secondary prevention measures assessed at 1 month follow-up in patients with TIA and minor ischaemic stroke who presented to medical attention at the time of their event	160
7.6	Secondary prevention measures assessed at 1 year follow-up in all patients	161
8.1	Baseline clinical characteristics of all 248 patients with a TIA or non-disabling stroke	176
8.2	Office BP readings and home blood measurements	177
8.3	BP in patients before and after TIA and minor stroke participating in HBPM	177
8.4	Adverse events in those participating in Bluetooth home BP monitoring, n=219	183

Table	Table title	Page
9.1	Baseline characteristics, vascular risk factors and premorbid medication of patients presenting with TIA or ischaemic stroke, n=1928	198
9.2	Recurrent strokes (% risk, 95% CI) up to 8 years after TIA and ischaemic stroke from event onset and time of seeking medical attention	199
9.3	Median time to recurrent event within the first year of event onset (n=1928) and time of seeking medical attention	204
9.4	Risk of cardiac events (% risk, 95% CI) with median time to event up to 8 years after TIA and ischaemic stroke	205
9.5	Mortality (% risk, 95% CI) up to 8 years after TIA and ischaemic stroke	208
9.6	Secondary prevention measures assessed at 1 month and 1 year follow-up in all patients	211
9.7	Risk of recurrent ischaemic stroke pre and post 90 days up to 8 years from time of seeking medical attention after TIA and ischaemic stroke	212
9.8	TOAST classification of all recurrent events by first event seeking medical attention	213
9.9	Difference in TOAST classification of recurrent stroke from TOAST classification of first event from time of seeking medical attention	214
10.1	Baseline characteristics, vascular risk factors and premorbid medication in patients with incident TIA	226
10.2	Baseline characteristics, vascular risk factors and premorbid medication in patients with incident stroke	227
10.3	Recurrent strokes (% risk, 95% CI) post 90 days up to 5 years after TIA and stroke in OCSP and OXVASC	228
10.4	Mortality up to 5 years after TIA and stroke in OCSP and OXVASC	232

Table	Table title	Page
10.5	Post 90 day mortality risks up to 5 years after TIA and stroke in OCSP and OXVASC	232
10.6	Risk of fatal MI or sudden cardiac death (% risk, 95% CI) up to 5 years after TIA and ischaemic stroke in OCSP and OXVASC	234
10.7	Risk of fatal recurrent stroke (% risk, 95% CI) up to 5 years after TIA and ischaemic stroke in OCSP and OXVASC	235

TABLE OF FIGURES

Figure	Figure title	Page
1.1	Annual incidence by age per 1000 population of all types of stroke combined in selected population based studies	4
1.2	Risk of recurrent stroke after first seeking medical attention in all patients with TIA or stroke who were referred to the EXPRESS study clinic	27
1.3	The nine OXVASC GP practices	30
2.1	First medical attention call in patients with TIA and minor stroke by year of study (2002-2009)	55
2.2	Patients with TIA and minor stroke who sought medical attention within 24 hours by year of study (2002-2009),	56
2.3	Patients with TIA and minor stroke presenting within 3 hours by year of study (2002-2009),	57
2.4	Patients with correct recognition of symptoms by year of study (2002-2009)	61
2.5	Patients with TIA and minor stroke by FAST result and year of study	62
3.1	7-day stroke risk after the first TIA in single and recurrent TIA of lacunar and non-lacunar type.	77
3.2	30-day stroke risk after the first TIA in those with recurrent TIA and capsular warning syndrome, ≥50% symptomatic carotid stenosis, AF or neither of these aetiologies	78
4.1a & 4.1b	Distribution of time from TIA/TNA to definite events in those with TIA/TNA in preceding 90 days	96
5.1	Act FAST stroke awareness poster	106

Figure	Figure title	Page
5.2a & 5.2b	7-day risk of stroke by FAST after a) TIA and b) MIS	112
5.3	7-day risk of stroke after TIA by FAST test and duration	113
5.4	7-day risk of stroke after FAST positive TIA by TOAST	114
6.1	Distribution of patients referred to secondary care by event type, event severity and treatment provision setting, n=1213	130
6.2	First medical assessment provider of patients with minor stroke seeking medical attention within 24 hours and referred to secondary care, n=327	131
7.1	Risk of recurrent stroke up to 2 years after TIA and MIS	150
7.2	Risk of recurrent stroke up to 90 days after TIA, minor ischaemic stroke and major ischaemic stroke	152
7.3	Risk of recurrent stroke between 8-90 days of onset of TIA and minor ischaemic stroke	153
7.4	Risk of recurrent stroke within 90 days of first seeking medical attention after TIA and minor ischaemic stroke	156
7.5	Risk of recurrent stroke between 8-90 days of fist seeking medical attention after TIA and minor ischaemic stroke	157
8.1	Schematic diagram of process of home blood-pressure monitoring	174
8.2	Flowchart of patients included in the study	175
8.3a& 8.3b	BP control before and after the event in patients participating in HBPM	178
8.4	Number of interventions in patients participating in HBPM	179

Figure	Figure title	Page
8.5	Percentage of patients on blood pressure lowering drugs	180
8.6a	Patients opinion on blood pressure self-measurement with Bluetooth system	181
8.6b	Patients opinion on blood pressure self-measurement with Bluetooth system	182
9.1a & 9.1b	Risk of recurrent stroke up to 8 years after TIA, minor ischaemic stroke and major ischaemic stroke: a) from event onset and b) from time of seeking medical attention	201
9.2	Post 90 day risk of recurrent stroke up to 8 years from time of first seeking medical attention after TIA or ischaemic stroke	202
9.3	Risk of recurrent stroke up to 8 years post 90 days from time of first seeking medical attention after TIA or MIS	203
9.4	Risk of cardiac events (including NSTEMI, STEMI and sudden cardiac death) up to 8 years after TIA or ischaemic stroke	206
9.5	Mortality (% risk) up to 8 years after TIA and ischaemic stroke,	207
9.6	Mortality (% risk) by cause of death up to 8 years after TIA and ischaemic stroke	209
10.1a, 10.1b &10.1c	Post 90-day risk of recurrent stroke up to 5 years in OCSP and OXVASC after a) all events, b) TIA, c) stroke	229
10.2a, 10.2b & 10.2c	Post 90-day risk of recurrent stroke up to 5 years after TIA in OCSP and OXVASC by age a)≥75 years, b)65-74, c)<65	230
10.3a, 10.3b & 10.3c	Post 90-day risk of recurrent stroke up to 5 years after stroke in OCSP and OXVASC by age a)≥75 years, b)65-74, c)<65	231

Figure	Figure title	Page
10.4a, 10.4b & 10.4c	Risk of mortality up to 5 years after stroke in OCSP and OXVASC by age a)≥75 years, b)65-74, c)<65	233
10.5a & 10.5b	Risk of a) fatal MI or sudden cardiac death (SCD) b) fatal recurrent stroke up to 5 years in OCSP and OXVASC	236
10.6a & 10.6b	Risk of a) fatal MI and b) SCD up to 5 years in OCSP and OXVASC	237

TABLE OF APPENDICES

Appendix I	**Royal College of Physicians TIA management algorithm**	254
Appendix II	**ICD-10 diagnostic codes**	255
Appendix III	**Ascertainment form for TIA and Stroke**	258
Appendix IV	**Ascertainment form for Acute Coronary Syndrome**	282
Appendix V	**Classification of Vascular Deaths in OXVASC**	308
Appendix VI	**Information sheet for OXVASC participants**	310
Appendix VII	**OXVASC Study Consent Form**	312
Appendix VIII	**OXVASC Study Assent Form**	313
Appendix IX	**NINDS criteria of symptoms not to be included as TIA**	314
Appendix X	**Classification system for TNAs**	315
Appendix XI		
Appendix XI.i	**Patients instructions for daily home BP monitoring (HBPM)**	317
Appendix XI.ii	**Flow chart of how problems with the Bluetooth mobile phone were managed**	320
Appendix XI.iii	**Patients instructions for weekly HBPM**	321
Appendix XI.iv	**HBPM Patient questionnaire**	323
Appendix XI.v	**Montreal Cognitive Assessment**	325
Appendix XI.vi	**Print screens of blood pressure results acquired by Bluetooth mobile phone**	326
Appendix XII	**Definitions of cause of death in OXVASC**	328

CHAPTER 1

Introduction

1.1 The burden of arterial vascular disease 2
1.2 The burden of stroke 2
1.2.1 Stroke incidence, prevalence, mortality and time trends 3
1.3 Transient ischaemic attack and minor stroke: definitions 5
1.3.1 Incidence and prevalence of TIA 6
1.3.2 Short-term prognosis after TIA and minor stroke 7
1.3.3 Long term prognosis after TIA and minor stroke 8
1.4 Early recurrent stroke risk prediction after TIA and minor stroke 10
1.4.1 Risk prediction by clinical features: the ABCD and ABCD2 scores 10
1.4.2 Risk prediction by vascular territory 13
1.4.3 Risk prediction by aetiology 13
1.4.4 Risk prediction by imaging findings 16
1.5 Secondary prevention after TIA and minor stroke 18
1.5.1 Antiplatelet therapy 19
1.5.2 Anticoagulation 21
1.5.3 Blood pressure lowering 22
1.5.4 Cholesterol-lowering 23
1.5.5 Carotid endarterectomy 24
1.6 Optimal service provision after TIA and minor stroke 25
1.7 The Oxford Vascular study 30
1.7.1 Case ascertainment and follow-up 31
1.7.2 Definitions and diagnosis 32
1.7.3 Patient consent and ethical approval 33
1.8 OXVASC contribution 33
1.9 Thesis aims 34
1.10 References 36

1.1 The burden of arterial vascular disease

Arterial disease, usually due to atherosclerosis is the most prevalent chronic disease in the developed world[1-3] and is rapidly increasing in the developing world.[4,5] Although arterial disease can cause stable or slowly progressive clinical syndromes, such as stable angina and intermittent claudication, the main clinical burden consists of acute, usually ischaemic, vascular events such as myocardial infarction and stroke. Acute arterial vascular events are the leading cause of death world wide, accounting for 17.7 million deaths each year.[1] The prevalence of vascular risk factors is increasing and combined with the ageing population, this number is predicted to increase to approximately 25 million deaths by 2020, if current trends continue.[6]

1.2 The burden of stroke

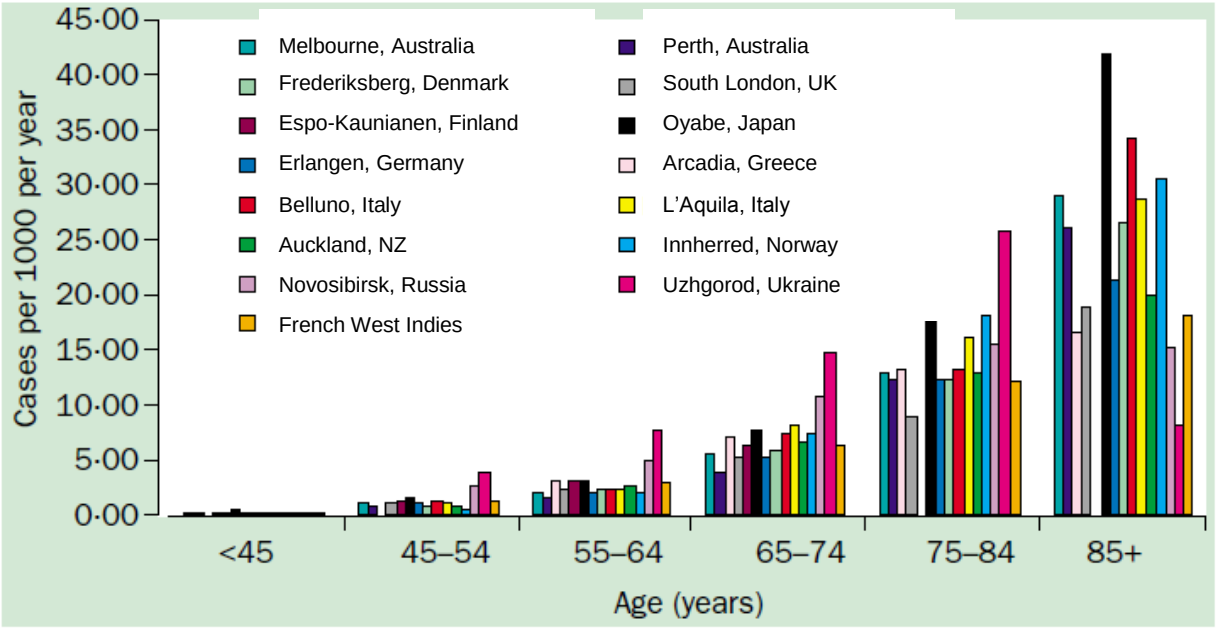
A stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at time global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of brain function, with symptoms lasting more that 24 hours or leading to death, with no apparent cause other than that of vascular origin.[7] Around 85% of strokes are ischaemic and 15% haemorrhagic.[7] Stroke causes 9% of all deaths worldwide and has been reported to be the second most common cause of death after ischaemic heart disease.[8] However, mortality data underestimate the true burden of stroke since, in contrast to coronary artery disease, the major burden of stroke is chronic disability rather than death.[9] It is estimated that there are 4.5 million deaths a year from stroke in the world and over 9 million stroke survivors.[10] Almost one in four men and nearly one in five women can expect to have a stroke if they live to be 85 years old.[11] In 2002, stroke-related disability was the sixth most common cause of reduced disability-adjusted life-years[8] (the sum of life years lost as a result of premature death and years lived with disability adjusted for severity) and stroke is predicted to rise to fourth in this list by 2030.[12] It is the main cause of long-term neurological disability in adults, with over half of survivors left

dependent on others for everyday activities.[13] Stroke is also a major cause of depression, dementia, epilepsy, falls and fractures and accounts for more hospital and care-home bed days than any other disorder.[13,14] Physical disability and cognitive deficits can substantially affect the quality of life of patients and their families.[9] In the UK, around 150 000 people have a stroke each year, resulting in about 53 000 deaths.[15] Patients with stroke occupy around 20% of all acute hospital beds and 25% of long term beds.[16] The costs of stroke in the UK are estimated to be nearly twice those of coronary heart disease,[17,18] accounting for about 6% of total National Health Service and Social Services expenditure.[18] In England, the annual cost of stroke to the economy has been estimated at £7 billion, this comprises direct costs to the NHS of £2.8 billion, costs of informal care of £2.4 billion and costs because of lost productivity and disability of £1.8 billion.[19]

1.2.1 Stroke incidence, prevalence, mortality and time trends

Although there have been many stroke incidence studies reported worldwide, differing methodology has made comparisons between studies unreliable.[20] The most reliable data comes from population based studies since hospital based studies are subject to referral bias.[20] Stroke incidence rises with age, more than half of all strokes occur in those over the age of 75 years. The annual stroke incidence by age from a review of 15 population based studies is shown in Figure 1.1.[21]

Figure 1.1 Annual incidence by age per 1000 population of all types of stroke combined in selected population based studies.[21]



There is substantial geographic variation in stroke incidence. A recent systematic review of 56 population-based studies from 1970-2008 from 28 countries[22] found the age-adjusted stroke incidence per 100 000 person-years in developed countries to range from 58 (Dijon, France)[23] to 375 (Oyabe, Japan).[24] Since the 1970s, there has been a 42% decrease in stroke incidence in high-income countries, however there has been more than a 100% increase in low to middle income countries.[22] Stroke mortality in developed countries has fallen over 60 years, falling by 1% per year until 1960s followed by a more steep fall of as much as 5% per year,[11] though this decline has since levelled off.[25-27] The proposed reasons for the decline in incidence include improved control of vascular risk factors, especially hypertension and cigarette smoking. The high and increasing incidence of stroke in developing countries has mirrored increasing exposure to vascular risk factors (particularly smoking, hypertension, diabetes, westernised diets and physical inactivity) and the ageing population. In the developed word, improvements in treatment of vascular risk factors, better living standards and improved post-stroke care have lead to reductions in stroke mortality.[28,29] Stroke prevalence in European studies is

approximately 5/1000 population[30] and in 65 to 74 year olds is approximately 50/1000 in men and 25/1000 in women.[31,32] Despite falling mortality, the burden of stroke is increasing due to the ageing population, which has prompted the development of national and international guidelines to improve acute stroke management and prevent recurrent stroke after transient ischaemic attack (TIA) and minor stroke.[33-38]

1.3 Transient ischaemic attack and minor stroke: definitions

The classical definition of TIA is an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease.[7] However, since the 24-hour time limit is arbitrary, rather than being based on clinical, imaging or pathological criteria, a new definition of TIA was proposed in 2002 and was incorporated into the American Heart Association guidelines in 2009.[39] The new definition comprises a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.[39] The advantages of the tissue-based definition are that it acknowledges the majority of TIAs last for less than 60 minutes[40,41] and 30-50% of classically defined TIAs show brain injury on diffusion-weighted magnetic resonance imaging (MRI).[42-45] It also encourages use of neurodiagnostic investigations and emphasises the prognostic importance of cerebral infarction which is associated with a 2-15% increased early risk of recurrent stroke after TIA.[43,45,46] The disadvantages of the new definition are that diagnosis is based on interpretation of imaging which is subject to variation between individuals and centres, diagnosis cannot be made in centres where imaging is not available, brain imaging can be normal in clinically definite stroke, silent infarction can occur and imaging sensitivity is highly dependent on both imaging method and the area of brain being examined.[47] Use of the time-based definition of TIA means that diagnosis can be made prior to imaging or at centres where imaging is

unavailable and that it enables comparison with previous studies which use this definition. The classical, time-based definition of TIA is used throughout this thesis.

The same pathology that causes a TIA may, if more severe or prolonged, cause a stroke[48] and the investigation of patients with these conditions is similar. However, in TIA and minor stroke, the priority is rapid identification and treatment of the underlying cause in order to prevent a recurrent and possibly more severe event, whereas in severe stroke the initial priority is targeting treatment to minimise subsequent deficit. There is no accepted definition for what constitutes 'minor stroke'.[49] The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Investigators developed five working definitions of "minor stroke" based on appearances on CT scan and features on clinical presentation, namely baseline National Institute of Health Stroke Scale (NIHSS) score, baseline NIHSS individual items, and baseline stroke subtype.[50] The definitions of minor stroke most widely used in studies are NIHSS≤3 or NIHSS≤5 at assessment or a modified Rankin scale (mRS) of ≤2 at 1 month.[49,50] Such distinctions are problematic as the NIHSS score will vary with time after the stroke and the mRS at 1 month may increase if a minor stroke is followed by a major stroke. In this thesis, I have taken the pragmatic view that minor stroke includes those strokes mild enough for patients to be seen in an emergency outpatient setting or to be sent home after initial assessment and treatment in hospital. This generally includes those with NIHSS≤3 at assessment, and also some of those with NIHSS≤5.

1.3.1 Incidence and prevalence of TIA

It is estimated that 54 000 TIAs occur in England each year.[51] The true incidence and prevalence of TIA are difficult to determine as many patients who experience TIA fail to present to medical attention.[52] The annual incidence of TIA from population-based studies has ranged from 0.16 per 1000 in Novosibirsk, Russia to 0.80 in Segovia Spain.[48,53-58] However, in

these studies, the stringent definition of 'first ever in a lifetime,' definite TIA, may underestimate the overall burden of TIA, which includes those with non-vascular diagnoses (TIA mimics) that present to medical attention. More recent data from a comparison with a previous population based study in Oxfordshire has shown the standardized incidence of any definite or probable TIA is approximately 1.08 (95% confidence interval (CI) 0.95–1.21) per 1000 population, almost double the rate calculated according to the definition of first ever in a lifetime, definite TIA, as used in previous incidence studies.[59]

1.3.2 Short-term prognosis after TIA and minor stroke

TIAs were previously thought to be benign, the early stroke risk was thought to be as low as 1-2% at one week and 2-4% at one month.[60-61] These risks are now considered to be underestimates as they were based on studies in which patients were recruited some time after their initial event and patients who experienced subsequent stroke before recruitment were excluded.[14] Prospective studies from the last decade of patients event onset have revealed a high early risk of recurrent stroke.[51,58,62-68] Up to 23% of strokes are preceded by TIA and a similar proportion of major strokes are probably preceded by minor strokes.[62] In a recent systematic review including 18 independent cohorts, which reported stroke risk in 10,126 TIA patients, the pooled 7-day stroke risk was 5.2% (95% CI 3.9-6.5).[69] There was considerable heterogeneity between studies ($p<0.0001$), with risks ranging from 0% to 12.8% at 7-days.[69] However, the risks from individual studies over different intervals of follow-up were highly consistent and the heterogeneity between studies was almost fully explained by differences in study method, setting and treatment.[69] Lowest risks were seen in specialist, rapid access stroke services offering urgent treatment and the highest risks were seen in population-based studies without urgent treatment.[69] Furthermore, the very early stroke risk after TIA has been shown to be particularly high, with 42% of all strokes during the 30 days after a first TIA occurring within the first 24 hours.[70] TIA is therefore an important predictor of

stroke and presents an opportunity to intervene before a major disabling stroke occurs. The risk of cardiac events is also elevated after TIA. In one large Californian study, 2.6% of patients with TIA were hospitalised for major cardiovascular events (myocardial infarction, unstable angina or ventricular arrhythmia) within 90-days.[71] The same study found that 2.6% of patients died and 12.7% had recurrent TIAs. [71] Whilst much is known about risks after TIA, less is known about the risk of recurrent stroke after minor stroke. In a population-based study of 87 patients seen in a specialist neurovascular clinic, the 7-day risk of recurrent stroke after minor stroke (defined as NIHSS≤ 3) was 11.5% (4.8-18.2) and the 90-day risk was 18.5% (10.3-26.7).[68] Internationally, there is considerable variation in the management of these patients, with some healthcare systems offering hospital admission and inpatient care and others offering non-urgent outpatient assessment with little consensus about which strategy is most cost-effective. Data on longer term prognosis, the effectiveness of secondary prevention and barriers to effective management are therefore required to optimise clinical services for TIA and minor stroke.

1.3.3 Long term prognosis after TIA and minor stroke

In the same way that data on the early risk of stroke following TIA or minor stroke are needed to inform acute management, data on the medium (one to five years) and long (five years and beyond) term prognosis are required to counsel patients and direct secondary prevention. Many studies have addressed the question of medium term prognosis although many were undermined by non-standardised diagnostic criteria, retrospective case identification, incomplete follow up and small numbers of cases.[72] However, three prospective, population-based studies of the medium term prognosis of TIA have been published from Söderhamn, Sweden (97 patients, follow up over 3 years),[73] Perugia, Italy (94 patients, follow up over 9 years)[74] and Oxfordshire, UK (184 patients, follow up over 3.7 years).[75]

In the Söderhamn cohort, the risk of stroke was approximately 5% per year and the overall mortality was 24.7% over a mean of three years. In the Perugia cohort, the annual risk of stroke after TIA was 2.4% (0.7-4.7). The actuarial risk of death was 28.6% (19.2-37.8) at 5 years and 49.5% (38.9-60.0) at 10 years with roughly equal numbers of cerebrovascular, cardiovascular and non-vascular deaths. In the Oxfordshire cohort the annual stroke risk was 4.4% (1.5-7.3) although this was highest in the first year after TIA. The risk of death at five years was 31.3% (23.3- 39.3) and the annual risk of death was 6.3% (4.7- 7.9). The risk of either fatal or non-fatal MI was 12.1% (5.8- 18.4) at 5 years and the approximate annual risk was 2.4%.

Thus, the risks of stroke and other vascular events after TIA are significant in the medium term. However, data on vascular risk in the longer term is limited and whether there is a need for ongoing aggressive secondary prevention is less clear. There are two studies providing reliable data on prognosis up to fifteen years after initial event. In a study of 290 patients with TIA who had participated either in the Oxfordshire Community Stroke Project (OCSP) or a contemporaneous hospital referred cohort study followed up over ten years from 1988, the risk of stroke was 18.8% (13.6-23.7).[76] The risk of MI or death from coronary heart disease was 27.8% (21.8-33.3) and risk of death from any cause was 50.7%. The risk of any first stroke, MI or vascular death was 42.8% (36.4-48.5). Compared to the rates in the general population standardised for age and sex, only the rate of fatal coronary events was significantly higher than expected (standardised mortality ratio 1.47, 1.10-1.93, p=0.009). The risk of major vascular events was found to be constant throughout the follow up. In this study, the median length of follow-up after TIA was 3.8 years (interquartile range (IQR) 2.2-5.8) and mean age at baseline was 69 years.

The Life Long After Cerebral Ischaemia (LILAC) study reported near complete follow up on 2473 participants from the Dutch TIA Trial.[77] Mean age was 65 and 759 patients had a TIA

while the remainder had a minor stroke (defined as mRS score ≤3) at enrolment. At ten years the cumulative risk of recurrent stroke was 18.4% (16.7-20.1) and risk of death was 46.6% (44.2-51.3). Importantly, due to the inclusion criteria of the original trial, only 22% of patients were randomised to different treatment doses of aspirin within a week of initial vascular event and median time to randomisation was 18 days, so much of the very high acute risk described above was missed from these estimates.

1.4 Early recurrent stroke risk prediction after TIA and minor stroke

Patients with TIA and minor stroke are a heterogeneous group in terms of risk factors, symptoms, underlying disorders, and prognosis. Since most patients with TIA will not go on to have an early stroke, the identification of those at high and low risk is needed to enable effective public education, triage to specialist services and tailored secondary prevention. Risk stratification is also needed to make cost-effective decisions about which patients would benefit most from urgent diagnosis and treatment. Several factors have been shown to be independently associated with early recurrent stroke risk, these include; clinical features, vascular territory, underlying aetiology and imaging findings.

1.4.1 Risk prediction by clinical features: the ABCD and ABCD2 scores

In 2000, Johnston et al identified five risk factors independently associated with a high three month risk of recurrent stroke after TIA in a Californian, emergency department based cohort.[64]

Age >60 years (Odds ratio, OR=1.8; 95% CI 1.4-2.9)

Symptom duration greater than 10 minutes (2.3, 1.3 -4.2)

Diabetes mellitus (2.1, 1.1-2.7)

Weakness (1.9, 1.4-2.6)

Speech impairment (1.5, 1.1-2.1)

A simple index with 1 point for each risk factor was useful in estimating recurrent stroke risk at three months. Risk varied from 0% in patients with no risk factors to 34% in those with all five risk factors (Table 1.1). Isolated sensory symptoms were associated with low risk.

Table 1.1 Risk of stroke within 90 days by number of risk factors (age >60 years, symptom duration >10 minutes, diabetes mellitus, and symptoms of weakness or speech impairment) in Johnston cohort of 1707 emergency department attendees with TIA.[64]

Score (number of risk factors)	N (%)	All stroke events (%)	% Risk at 90 days (95% CI)
0	22 (1.3)	0 (0)	0
1	179 (10.5)	5 (2.8)	3 (0-5.2)
2	509 (29.8)	35 (19.4)	7 (4.7-9.1)
3	584 (34.2)	63 (35.0)	11 (8.3-13.3)
4	337 (19.7)	51 (28.3)	15 (11.3-19.0)
5	76 (4.5)	26 (14.4)	34 (23.5-44.9)
Total	1707 (100)	185 (100)	11 (9.1-12.0)

The study found that gender, ethnicity, previous diagnoses of coronary artery disease or hypertension, current cigarette smoking, antiplatelet or anticoagulant use at presentation did not predict early stroke. Other cohorts indentified and validated these independent risk factors which were used to derive the ABCD score, a clinical prediction tool of 7-day stroke risk after TIA.[67] The score is based on 4 clinical features and is out of a total of 6 (Table 1.2).

Table 1.2 The ABCD score.

	Clinical feature	Category	Score
A	Age	≥60 years	1
		< 60 years	0
B	Blood pressure at acute evaluation	SBP≥140 or DBP≥90	1
		Other	0
C	Clinical features	Unilateral weakness	2
		Speech disturbance (no weakness)	1
		Other	0
D	Duration	≥ 60 minutes	2
		10-59 minutes	1
		<10 minutes	0
Total	Total (maximum)		6

Although diabetes was found to be predictive of early recurrent stroke risk, this was not statistically significant and was therefore not included in the score. However, the ABCD score was refined in larger cohorts of patients with the subsequent addition of 1 point for diabetes to give the ABCD2 score, which is out of 7.[78] In a systematic review of validations of the ABCD and ABCD2 scores, including 9808 TIA patients with 456 recurrent strokes at 7-days, the scores were found to have good predictive power, with area under the receiver operating characteristic curve (ROC) of 0.72 (95% CI 0.67-0.77).[79] The predictive power of the score was independent of clinical setting but was greater in two cohorts that included patients with both suspected and confirmed TIA than in cohorts of patients with confirmed TIA only.[79] This suggests that the predictive power of the scores is partly related to its identification of true TIAs although this does not completely explain how the score works.[79]

The ABCD2 score has been incorporated into national clinical guidelines of TIA management in the UK, USA, Australia and New Zealand.[33,39,80,81] The National Institute for Health and

Clinical Excellence (NICE) in the UK recommend using the score to differentiate high-risk (ABCD2 ≥4) from low-risk patients (ABCD2<4).[33]

1.4.2 Risk prediction by vascular territory

The early risk of recurrent stroke also depends on the vascular territory of the TIA (ocular, carotid or vertebrobasilar). Monocular events are associated with a low risk of subsequent cerebral stroke.[60,82] Vertebrobasilar (VB) territory events account for about 15-30% of all TIA and minor strokes,[83-85] they were originally thought to be at low risk of recurrent stroke. This idea was based on findings from a small number of cohort studies from the 1960s and 1970s, many of which do not satisfy modern methodological standards and generally recruited patients after the acute phase.[86] As a consequence, many patients with VB TIAs were managed less aggressively.[86] However, a recent systematic review showed a higher 7-day stroke risk after posterior circulation events than after carotid territory events (OR=1.47, 1.1-2.0, p=0.01).[86] These findings were later confirmed in a prospective cohort study.[87] This high acute risk is comparable to patients with carotid stenosis and suggests a similar underlying pathology. A recent population based study showed that the prevalence of >50% vertebral and basilar stenosis in posterior circulation TIA and stroke was greater than the prevalence of >50% carotid stenosis in anterior circulation events (OR=2.74, 1.67-4.51, p=0.002).[88] Further research is needed to determine the prognosis of patients with isolated TIA-like presentations such as transient isolated diplopia, transient confusion, hemisensory symptoms and transient speech arrest.[89] Thus, apart from monocular events, vascular territory is not particularly useful in risk prediction after TIA or minor ischaemic stroke.

1.4.3 Risk prediction by aetiology

Population based studies of stroke have shown that recurrent stroke risk also depends on underlying aetiology.[90] Clinical trials have driven the need for stroke classification systems, the

most widely used is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[91] This system was devised in 1993 to better characterise a cohort of patients as part of a clinical trial investigating the potential efficacy of danaparoid, a new anticoagulant, in various stroke subtypes.[91] The TOAST investigators defined 11 categories of stroke, which were further collapsed into five groups (Table 1.3). These five groups were used in further clinical research. TOAST classifies ischaemic stroke by identifying the mechanism of vessel occlusion: cardioembolic, artery to artery embolism or in-situ small vessel (lacunar) disease.

It identifies the most probable pathophysiological mechanism on the basis of clinical findings and the result of investigations. The advantages of the TOAST classification are that it

1. has good inter-rater reliability and reproducibility,
2. is easy to use,
3. helps determine prognosis,
4. helps direct secondary prevention.[92]

The limitations of TOAST are that

1. the classification can mask paucity of clinical investigations on one hand and does not account for a very precise work-up on the other.
2. Small vessel (lacunar) stroke is defined by the clinical syndrome and the size of the infarct. Consequently a single small deep infarct due to M1 middle cerebral artery (MCA) stenosis could be classified as SVD if MCA imaging has not been performed.
3. Undetermined cause is the most heterogeneous group in TOAST, those with 2 definite potential causes are classified together with those who have incomplete investigation, negative investigations and those with <50% stenosis.[92]

Table 1.3. The TOAST classification of ischaemic stroke[91,92]

TOAST subtype	Features
Large artery atherosclerosis (LAA)*	• >50% stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis (cortical or cerebellar dysfunction; no lacunar syndrome; cortical, cerebellar, brain stem or subcortical infarct >1.5 cm; stenosis of extracranial internal carotid artery; no other abnormalities on tests); • no cardiac source of embolism; • no subcortical or brainstem infarct <1.5 cm.
Cardioembolism (CE)*	• high-risk (mechanical prosthetic valve, mitral stenosis with atrial fibrillation, atrial fibrillation other than lone AF, left atrial/atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction [<4 weeks], left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, infective endocarditis); • medium risk (mitral valve prolapse, mitral annulus calcification, mitral stenosis without atrial fibrillation, left atrial turbulence (smoke), atrial septal aneurysm, patent foramen ovale, atrial flutter, lone atrial fibrillation, bioprosthetic cardiac valve, nonbacterial thrombotic endocarditis, congestive heart failure, hypokinetic left ventricular segment, myocardial infarction >4 weeks, <6months).
Small vessel occlusion (lacune) (SVD)*	• clinical lacunar syndrome and no evidence of cerebral cortical dysfunction; • a history of diabetes or hypertension supports the diagnosis; • normal CT/MRI scan or a relevant brain stem or subcortical hemispheric lesion with a diameter of <1.5 cm; • should not fulfill criteria for large-artery atherosclerosis or cardioembolism (see above).
Stroke of other determined etiology (OTHER)*	• non-atherosclerotic vasculopathies, hypercoagulable states, hematologic disorders; • cardiac source of embolism or large-artery atherosclerosis should be excluded.
Stroke of undetermined etiology (UND)*	• two or more causes identified (MULTIPLE); • negative evaluation (UNKNOWN); • incomplete evaluation (UNDETERMINED)

* possible or probable depending on results of ancillary studies

Several population based studies have shown that recurrent stroke risk is highest after LAA subtype stroke and lowest in those with lacunar stroke.[90] A pooled analysis of data from 1709 patients with stroke in four population based studies showed that risks of recurrent stroke were highest in patients with large artery disease, reaching 4% (95% CI 0.2-7.8) at 7 days and 12.6% (5.9-19.3) at 30 days.[90] After lacunar stroke, the corresponding risks were 0% and 2% (0-4.2) and after cardioembolic stroke were 2.5% (0.1-4.9) and 4.6% (1.3-7.9) respectively.[90] Although large artery atherosclerosis accounted for only 14% of the 1709 initial strokes, they accounted for 37% of recurrences at 7 days.[90] After TIA, subtype differences in recurrent stroke risk may be smaller, although there is less published data from population-based studies on risks by subtype. Some patients with SVD TIAs can have a very high early risk of stroke, for instance as part of the "capsular warning syndrome".[93] The risk after TIAs of LAA subtype is also high. A population based study of prognosis of patients with TIA or stroke and ≥50% symptomatic carotid stenosis reported recurrent stroke risks of up to 30% during the first month after the presenting event[94] but this risk falls rapidly with time, as does benefit from endarterectomy.[95]

1.4.4 Risk prediction by imaging findings

In TIA and minor stroke, brain imaging is required to

- exclude stroke mimics
- differentiate between ischaemic and haemorrhagic events
- determine aetiology, for example a cardioembolic source with lesions in multiple vascular territories
- identify patients at high risk of early recurrent stroke in order to target treatment.[96]

Some early studies of CT after TIA found the presence of infarction to be associated with increased stroke risk,[97,98] although other studies failed to confirm this.[99,100] Interpretation of these studies is difficult, since the timing of CT differed and new and old infarction was not

differentiated. A more recent study of patients with TIA who had CT scans performed within 48 hours of the event showed that appearances consistent with recent infarction on CT predicted recurrent stroke (OR 4.06, 95% CI 1.16-14.14, p=0.028).[101] Diffusion-weighted MRI (DWI) is a highly sensitive and specific technique for identifying acute cerebral ischaemia. In several studies, DWI hyperintensity after TIA has been shown to be associated with predictors of early stroke risk, such as focal motor weakness, speech disturbance, symptoms lasting longer than one hour and large artery disease.[102-105] In one study of 83 consecutive TIA patients attending the emergency department, symptoms >1 hour and abnormalities on DWI were independent predictors of further strokes (OR=5.02, 1.37-18.3, p=0.015).[106] In a meta-analysis of published and unpublished data from 19 studies, some variables of the ABCD2 score (symptom duration over 1 hour, dysphasia, dysarthria, and motor weakness) were independently associated with the presence of acute infarction on DWI, although diabetes, increasing age, and hypertension were not.[107] As the ABCD2 score was developed to aid triage decisions at initial assessment, it deliberately did not include information from imaging studies. However, recent studies to determine the extent to which the predictive value of the ABCD2 score is improved by the incorporation of brain infarction on imaging have resulted in new scoring systems.[108,109] The ABCDI score combines clinical variables from the ABCD2 score and adds evidence of infarction from CT or MRI.[108] In a multicentre study of 4574 patients with TIA, the ABCD2 score and presence of infarction on DWI or CT were both independently predictive of stroke at 7 days (after adjustment for ABCD2 score, OR for infarction=6.2, 4.2 - 9.0, overall; 14.9, 7.4- 30.2, for DWI; 4.2, 2.6 - 6.9, for CT; all p=0.001).[108] Incorporation of infarction in the ABCD2I score improved predictive power with an optimal weighting of 3 points for infarction on CT or diffusion-weighted imaging.[108] Pooled areas under ROC increased from 0.66 (0.53 to 0.78) for the ABCD2 score to 0.78 (0.72 to 0.85) for the ABCD2I score.[108]

The ABCD3I score is a 13 point score derived from pooled data from 2654 patients with TIA and validated in 1232 patients.[109] To the ABCD2 score, the ABCD3I scoring system adds points for

- dual TIA (an earlier TIA within 7 days of the first TIA, 2 points)
- carotid stenosis of ≥50% on imaging (2 points)
- abnormal DWI (2 points).

The area under the receiver operating characteristic curves for the ABCD3-I score were 0·90 at 2 days (compared with the ABCD² score, p=0·04), 0·92 at 7 days (p=0·001), 0·85 at 28 days (p=0·03), and 0·79 at 90 days (p=0·07).[109]

In comparison to MRI, CT scanning is quick, inexpensive, and widely available, especially in emergency care settings, and remains the predominant neuroimaging modality available for TIA in many centers.[108] However, despite its availability, CT has the disadvantages of reduced sensitivity for early infarction and radiation exposure. Therefore, MRI with DWI remains the imaging modality of choice in TIA.[108]

Findings on intracranial vascular imaging have also been shown to be associated with increased stroke risk. In one study of 73 patients with TIA or minor stroke and recently symptomatic carotid artery stenosis, the presence of solid microembolic signals in the middle cerebral artery detected by transcranial Doppler was a predictor of early recurrent ischaemic events (relative risk, RR=8.7, 2.0-38.2, p=0.0012).[110]

1.5 Secondary prevention after TIA and minor stroke

The aim of treatment after TIA and minor stroke is the secondary prevention of a disabling stroke. A number of treatments have been shown to be effective, including antiplatelet agents, such as aspirin,[111] clopidogrel,[112] and the combination of low-dose aspirin plus dipyridamole;[113,114] blood pressure lowering drugs;[115] anticoagulation for atrial fibrillation;[116] and endarterectomy for symptomatic carotid stenosis≥50%.[95,117] Modelling studies have shown that,

if the effects of these treatments are independent, the combined use of all these interventions in appropriate patients would be predicted to reduce the risk of recurrent stroke by 80-90%.[118] In the acute phase, the evidence base for treatment after TIA and minor stroke comes mainly from a few small randomised trials, extrapolation of results from larger trials in other settings and two non-randomised studies of a combination of preventative treatments started urgently in specialist units,[119] the Early Use of Existing Preventative Strategies for Stroke (EXPRESS) and SOS-TIA studies.[120,121]

1.5.1 Antiplatelet therapy

Aspirin was the first antiplatelet agent used for treatment and prevention of acute ischaemic events. Aspirin is recommended for secondary prevention after cerebral ischaemia of arterial origin. In a meta-analysis of 10 studies comparing aspirin at doses ranging from very low (30–50 mg/day to very high (1000 mg/day or more) with placebo, it was concluded that all aspirin doses above 30 mg/day were equally effective.[122,123] Since then, low dose aspirin has generally been used in secondary prevention studies. The results of a recent meta-analysis evaluating 16 secondary stroke prevention studies involving patients with previous stroke or TIA (10 trials) or MI (6 trials) treated with aspirin, have been published by the Antithrombotic Trialists' Collaboration (ATTC).[124,125] Allocation to aspirin yielded a 22% reduction in ischaemic stroke (RR=0.78, 0.61–0.99) and a 20% reduction in major coronary events (RR=0.8, 0.73-0.88). The ATTC meta-analysis also confirmed the increased risk of haemorrhagic stroke (RR=1.67, 0.97-2.90) and of major extracranial bleeds (RR=2.69, 1.25–5.76).[124] The combination of aspirin and dipyridamole is more effective, the relative reduction in recurrent stroke risk is about 30% compared with aspirin alone.[113,114] In contrast, the combination of clopidogrel and aspirin was not superior to clopidogrel alone in the Management of Atherothrombosis with Clopidogrel in high risk patients with recent TIA or ischaemic stroke (MATCH) trial or to aspirin alone in the Clopidogrel for High Atherothromobtic Risk and Ischaemic Stabilisation, Management and

Avoidance (CHARISMA) trial.[126,127] However, in MATCH there was a non-significant trend towards benefit within the first week of combination treatment.[126] Therefore it is possible that a short course of clopidogrel may be effective in the acute phase after TIA and minor stroke. The risk of life-threatening haemorrhage was significantly higher in the combination group at 18 months, but this difference did not become apparent until three to four months after randomisation.[126] The combination of aspirin and clopidogrel in the acute treatment of TIA and minor stroke is currently being investigated as part of the POINT trial which aims to randomise patients to a loading dose of clopidogrel or placebo with 12 hours of symptoms onset.[128] Treatment then continues with the study drug in addition to aspirin for 90 days.[128]

In the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial in patients with recently symptomatic 50% or greater carotid stenosis, aspirin plus clopidogrel versus aspirin alone reduced microembolic signals and tended to reduce the risk of recurrent stroke. [129] Very similar findings were recently reported in patients with symptomatic intracranial stenosis in the Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR) trial.[130]

The FASTER (Fast Assessment of Stroke and Transient Ischemic Attack to prevent Early Recurrence) pilot trial also reported a trend towards a reduced early risk of stroke with a 90-day course of aspirin plus clopidogrel versus aspirin only in patients with TIA or minor stroke.[131] In a pooled analysis of data from the EXPRESS and FASTER studies, the 90-day risk of major bleeding on aspirin plus clopidogrel was 4.8% (1.6–8.0) in patients who had not previously been on antiplatelet drugs.[132]

Triple antiplatelet therapy in the acute phase may further reduce early recurrence risk, however whether the benefits outweigh the risk of bleeding is uncertain. The TARDIS trial is an ongoing

multicentre, prospective randomised controlled trial which aims to assess the efficacy, safety, tolerability and feasibility of triple antiplatelet therapy (adding clopidogrel to aspirin and dipyridamole) versus dual therapy (aspirin plus dipyridamole) in patients with acute stroke or TIA. The study includes those in the very early phase (within 48 hours of event onset) and patients receive treatment for one month followed by standard therapy. The primary outcome is stroke severity at 90 days assessed with the modified Rankin scale. Secondary outcomes include safety, serious adverse events, vascular events, death, cerebral emboli and platelet function.[133]

Trifusal and Cilostazol are two antiplatelets which have been shown recently to have a lower bleeding risk in randomised trials.[134,135] Trifusal is structurally related to aspirin and has a similar efficacy to aspirin in prevention of vascular events (RR 1.03, 0.89-1.20) but a lower risk of bleeding (0.63, 0.54-0.74).[134] Cilostazol is a phophodiesterase-3 inhibitor which was compared with aspirin in a randomised trial of secondary stroke prevention in Japan.[135] It reduced the risk of both recurrent stroke (Hazard ratio, HR 0.74, 0.56-0.98) and haemorrhagic complications (0.46, 0.30-0.71).[135]

1.5.2 Anticoagulation

In patients with atrial fibrillation (AF) who have a TIA or minor stroke, warfarin reduces the relative risk of recurrent stroke by about 70% (HR 0.34, 0.20-0.57).[136] This benefit needs to be balanced against the risk of major bleeding, in particular the risk of intracerebral haemorrhage which is approximately 0.3-0.6% per year and rises with age, hypertension, use of other antiplatelets and increasing intensity of anticoagulation.[137] Dabigatran, a direct thrombin inhibitor, is a new alternative to warfarin for patients with non-valvular AF.[138] It has the advantages that it does not require regular monitoring, has fewer drug interactions and anticoagulation for a given dose is more predictable.[138] The disadvantages of its use include lack

of a specific reversing agent and that its effects beyond 2 years are unknown.[138] Dabigatran was compared with warfarin in the RE-LY trial in more than 12 000 patients, of which 20% had a prior TIA or stroke.[139] When vascular outcomes, mortality and bleeding events were combined, there was net clinical benefit for the 110mg dose (RR 0.92, 0.84-1.02) and for the 150mg dose (0.9, 0.82-1.00).[139] It has been approved for use in the USA and it is likely that it will be approved in the UK by NICE.[138] Other new anticoagulants include the factor Xa inhibitors rivaroxaban and apixaban. Rivaroxaban has been shown to be non-inferior to warfarin without significant differences in major bleeding risks.[140] In patients with AF unable to take warfarin, apixaban has been shown to be superior to aspirin with no excess in major haemorrhages.[141]

1.5.3 Blood pressure lowering

Blood pressure is often raised after a TIA or stroke, but tends to fall spontaneously during the first few days.[142] Recent trials in patients with major ischaemic stroke have suggested that blood-pressure lowering in the acute phase is unlikely to have major benefits.[143-145] Ischaemic and infarcted brain cannot autoregulate and so increases in cerebral perfusion pressure can cause hyperaemia, cerebral oedema, and haemorrhagic infarction, whereas a fall in pressure can exacerbate ischaemia.[119] In practice, acute blood pressure lowering is generally considered when sustained blood pressure is greater than 220/120 mm Hg in cerebral infarction and greater than 185/105 mm Hg in cerebral haemorrhage.[119] However, falling cerebral perfusion pressure is likely to be of less concern after TIA and minor stroke, and so many clinicians therefore start antihypertensive drugs immediately.[119] This strategy was used in the EXPRESS and SOS-TIA studies and was not associated with a high risk of early recurrent stroke.[119,121] In the sub-acute phase and longer term, the PROGRESS study showed that blood pressure lowering with perindopril and indapamide started weeks to months after TIA and ischaemic stroke reduced the risk of recurrent stroke by about a third.[146] Recent systematic reviews and meta-analyses have shown that blood pressure lowering agents in patients with TIA or stroke significantly reduced

the risk of subsequent stroke and cardiovascular events, although caution must be exercised in the few patients with bilateral severe carotid stenosis and patients with severe basilar artery stenosis.[147-150]

Previous randomised controlled trials (RCTs) have shown the benefit of home blood pressure (BP) monitoring in improving BP control, perhaps due to better adherence to treatment.[151,152] Telemonitoring, whereby home BP readings are relayed to a health care professional who can take appropriate action, has also been shown to be feasible and acceptable to patients.[153] Recently, the role of self management in improving BP control has been shown in the telemonitoring and self-management in the control of hypertension (TASMINH2) study.[154] This RCT of 527 patients in primary care with poor BP control (BP >140/90 despite antihypertensive treatment), showed that home BP telemonitoring combined with self management resulted in better BP control compared with usual care.[154] Self-management consisted self-monitoring of BP, self-titration of antihypertensive drugs, combined with telemonitoring of home BP. Patients in the intervention group with two consecutive months of readings above target were instructed to make medication changes in accordance with a pre-determined titration schedule. At 6 months, mean systolic BP decreased by 12.9mmHg (95% CI 10.4-15.5) in the self management group and by 9.2mmHg (6.7-11.8) in the control group (difference between groups 3.7mmHg, 0.8-6.6, p=0.013). At 12 months, systolic BP decreased by 17.6mmHg (14.9-20.3) in the self-management group and by 12.2mmHg (9.5-14.9) in the control group (difference between groups 5.4mmHg, 2.4-8.5, p=0.004).[154]

1.5.4 Cholesterol-lowering

The Heart Protection Study (HPS) showed that treatment with simvastatin 40mg daily in patients with TIA and stroke reduced the risk of cardiac events but not recurrent stroke.[155] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed a 16%

reduction in stroke recurrence and a 35% reduction in major coronary events in patients with TIA or stroke randomised to atorvastatin 80mg daily versus placebo.[156] A systematic review of four trials showed that in patients with a history of stroke or TIA, statins reduced the risk of ischaemic stroke (pooled RR 0.80, 0.70-0.92) but this benefit was partly lost by an increased risk of hemorrhagic stroke (RR 1.73, 1.19-2.50).[157]

1.5.5 Carotid endarterectomy

The benefit of carotid endarterectomy in patients with TIA or minor stroke with at least 70% stenosis of the symptomatic artery was established from randomised trials from the 1990s, mainly the European Carotid Surgery Trialists Collaborative Group and the North American Symptomatic Carotid Endarterectomy Trial Collaborators.[158,159] Benefit from surgery plus medical treatment over medical treatment alone was greatest in patients randomised within two weeks after their last ischaemic event and fell rapidly with increasing delay. For patients with ≥50% stenosis, the number of patients needed to treat with surgery (NNT) to prevent one ipsilateral stroke in 5 years was 5 for those randomised within 2 weeks after their last ischaemic event, versus 125 for patients randomised >12 weeks. This trend was partly due to the operative risks of endarterectomy in the trials (1% risk of death and 5-6% risk of stroke), which were not increased in patients operated on within one week after their event, with most benefit if done within 2 weeks.[158,159] The relative risk reduction of ipsilateral fatal or non-fatal stroke is about 60% during 3 years,[117] which needs to be balanced against the operative risks of stroke or death. There is uncertainty as to whether any benefit remains beyond 12 weeks.[160]

Recently, the efficacy and safety of carotid artery angioplasty and stenting (CAS) in comparison with endarterectomy has been of interest. The benefits of CAS are that it is less invasive, quicker and has less local complications such as cranial nerve injury or neck haematoma.[161] A systematic review and meta-analysis of 13 randomised controlled trials enrolling 7484 patients, of which 80% had symptomatic disease, found that CAS was associated with an increased risk

of any stroke (RR 1.45, 1.06-1.99).[162] However, CAS may be an alternative when endarterectomy is technically difficult, for instance after previous ipsilateral endarterectomy or previous neck surgery or radiotherapy.[162]

A summary of the effect of acute interventions in secondary prevention, reproduced from a recent systematic review, is shown in Table 1.4.[163]

Table 1.4 Secondary prevention strategies of proven benefit[163]

Secondary prevention	Initial or important study, year	RRR	ARR	NNT
Aspirin	Canadian Co-op Study Group, 1978	13%	1.0%	100
Aspirin plus dipyridamole	Diener, 1996	15.0%	1.9%	53
Clopidogrel	CAPRIE, 1996	10.0%	1.6%	62
Anticoagulants	EAFT, 1993	66.0%	8.0%	11
Blood pressure lowering	PROGRESS, 2001	28.0%	4.0%	97
Cholesterol lowering	SPARCL, 2006	16.0%	2.2%	220
Carotid endarterectomy	NASCET, 1991, ECST, 1991	44.0%	3.8%	26

RRR= relative risk reduction

ARR= absolute risk reduction

NNT= the number needed to treat to prevent one fatal or non-fatal stroke per year

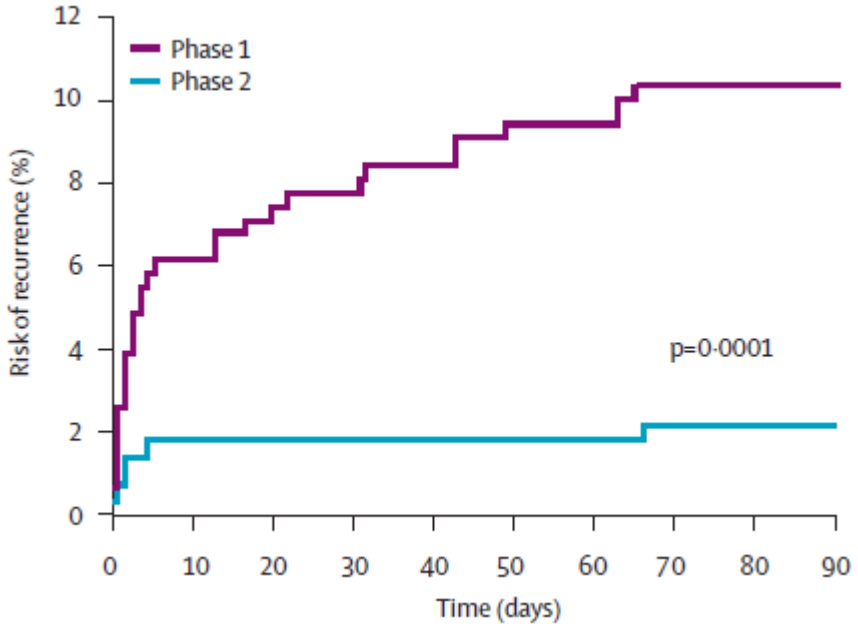
1.6 Optimal service provision after TIA and minor stroke

Early recognition and treatment of TIA and minor stroke provides an ideal opportunity for rapid intervention to prevent disabling recurrence. The benefits of secondary prevention in the acute phase were shown in two studies; the Early use of eXisting PREventive Strategies for Stroke (EXPRESS) study[120] and SOS-TIA study.[121]

The EXPRESS study aimed to determine the effect of more rapid treatment of TIA and minor stroke in patients who were treated in a specialist neurovascular clinic within Oxfordshire.[120] EXPRESS was nested in a prospective population-based study of all TIA and stroke (Oxford Vascular Study) and compared urgent assessment and treatment (phase 2) with appointment-based clinic assessment and primary care-initiated treatment (phase 1). During phase 1, the study clinic offered appointment-based access to patients. Brain imaging (usually CT) and ECG were obtained on the same day as the appointment or shortly thereafter. Also done were carotid ultrasound imaging (all patients) and trans-thoracic or trans-oesophageal echocardiography (when clinically indicated). Treatment recommendations were communicated by fax or telephone to the general practitioner (GP) who would then initiate the prescription. The treatment protocol recommended to the GP was tailored to the individual patient but generally included: aspirin in patients not already on antiplatelet therapy (75 mg daily), or clopidogrel if aspirin was contraindicated; simvastatin (40 mg daily); blood pressure lowering unless systolic blood pressure was below 130 mm Hg on repeated measurement (either by increases in existing medication, or by commencement of perindopril 4 mg daily with or without indapamide 1.25 mg daily); and anticoagulation as required. In patients seen within 48 hours of their event, or those seen within 7 days who were thought to be at particularly high early risk, clopidogrel (75 mg daily, to be stopped after 30 days) was recommended in addition to aspirin. Brain imaging was required before starting combination antiplatelet treatment or anticoagulation after a minor stroke. In Phase 2, patients were sent to the clinic urgently without the need for an appointment and treatment was started immediately in the clinic. The clinic operated at weekdays only. Patients were assessed in the same way as in phase 1, but all those who were considered to have had a TIA or stroke were given aspirin 300 mg to take in the clinic, together with a prescription for a 4-week supply of any other study medication (using the same treatment protocol as in phase 1) to start on the same day. A loading dose of clopidogrel (300 mg) was also prescribed in cases in whom this drug was initiated. A CT brain scan was obtained during the clinic for patients with incomplete resolution of symptoms at the time of assessment to

exclude intracerebral haemorrhage before giving aspirin, clopidogrel, or anticoagulants. Baseline characteristics and delays in seeking of initial medical attention were similar in the two phases, but median delay to assessment in the study clinic fell from 3 days (IQR 2–5) in phase 1 to less than 1 day (IQR 0–3) in phase 2 ($p<0.0001$), and the median delay to first prescription of treatment fell from 20 days (8–53) to 1 day (0–3) ($p<0.0001$). The 90-day risk of recurrent stroke in patients referred to the study clinic was 10.3% (32/310) in phase 1 versus 2.1% (6/281) in phase 2 (HR 0.20, 0.08–0.48, p=0.0001, Figure 1.2).[120]

Figure 1.2 Risk of recurrent stroke after first seeking medical attention in all patients with TIA or stroke who were referred to the EXPRESS study clinic.[120]



The good prognosis associated with urgent, intensive treatment was also shown in the SOS-TIA study.[121] An emergency TIA clinic with 24 hour access for 7 days a week was set up in Paris and local clinicians were invited to refer all TIA patients for urgent investigation and treatment. Patients were assessed by a vascular neurologist within 4 hours of admission with brain, arterial and cardiac imaging. Medical treatment was started immediately, patients were discharged unless they satisfied pre-defined high-risk criteria. Of 629 consecutive patients with definite TIA,

there were only two strokes within 7 days and 12 strokes within 3 months, resulting in risks of 0.3% and 1.9%, respectively. These risks were much lower than those expected from the ABCD2 scores of the patients seen and were attributed to the urgent intervention in the study.[121]

The results of EXPRESS and SOS-TIA have changed clinical guidelines. In the UK, the Royal College of Physicians and NICE guidelines currently recommend that those with suspected TIA who are at high risk of stroke (ABCD2 score≥4) should have specialist assessment and investigation within 24 hours of symptom onset.[33,36] For those with ABCD2 score<4, specialist assessment and investigation are recommended within 1 week.[33,36] For all those with suspected TIA, a 300mg aspirin stat dose, statins, and blood pressure and lifestyle management are advised (Appendix I).[33,36] Brain imaging (preferably with MRI) is recommended for all those with TIA and carotid imaging is advised for those in whom carotid intervention is considered.[33,36] The American National Stroke Association[164] and the American Heart Association[39] both call for initial evaluation within 48 hours for all TIAs and consideration of more rapid evaluation in those felt to be at particularly high risk. Internationally, the setting of acute care delivery for TIA and minor stroke varies, from direct admission of all those with TIA and minor stroke to urgent outpatient clinic evaluation. Admission rates vary widely for TIA with rates of 41-68%[39] reported in the USA and 26% in SOS-TIA.[121] Urgent assessment of TIA in the specialist outpatient clinic has been shown to be cost-effective.[165]

However, the benefit of urgent assessment depends on patients recognising the significance of their symptoms and presenting to medical attention quickly. The advent of thrombolysis has driven interest in improving people's recognition of stroke symptoms and reducing delays in seeking medical attention after major stroke[166-170] but equivalent studies relating to TIA and minor stroke are limited. A nationwide telephone survey of 10,112 adults in the US in 1999 found that only 8.7% correctly understood the definition of a TIA and 8.6% could identify a typical symptom.[52] In Oxfordshire, from 2002-2003, 138 consecutive patients from the Oxford Vascular

Study and 103 consecutive hospital clinic attendees were studied to determine patient behaviour immediately after TIA. 44% of patients sought medical attention within hours of the event but only 10% attended the emergency department.[171] Several tools have been developed to enable correct recognition of stroke and TIA symptoms. In the pre-hospital setting the Face, Arm, Speech Test[172] (FAST), Los Angeles Pre-hospital Stroke Scale (LAPPS)[173] and Cincinnati Pre-hospital Stroke Scale (CPSS)[174] have been developed for use by paramedics to ensure rapid transport of suitable patients to specialist care. In the emergency department setting, the Recognition of Stroke in the Emergency Department (ROSIER)[175] has been developed to improve the diagnosis of stroke and therefore the referral of patients. These clinical tools were designed to increase the numbers of patients with major stroke presenting within 3 hours who were eligible for thrombolysis. However, they may also play a role in improving access to services after TIA and minor stroke by improving symptom recognition.

Table 1.5 Elements of stroke detection tools

LAPSS[173]	**CPSS**[174]	**FAST**[172]
Age >45 years	Facial droop	Facial weakness
No prior seizure history	Arm drift	Arm weakness
Onset within 24 hours	Slurred speech	Speech problems
Patient ambulant previously		
Blood glucose		
Asymmetry of		
Smile/grimace		
Grip strength		
Arm strength		

LAPSS=Los Angeles Pre-hospital Stroke Scale

CPSS=Cincinnati Pre-hospital Stroke Scale

FAST=Face, Arm, Speech Test

1.7 The Oxford Vascular study

The data used in this thesis has been obtained from the Oxford Vascular Study. The following sections detail the methodology used in the study.

The Oxford Vascular Study (OXVASC) is a prospective, population-based cohort study of all incident acute vascular events in all territories (TIA, stroke, acute coronary and peripheral vascular events) in Oxfordshire, UK. The study population is defined by registration with nine general practices (Figure 1.3) and comprises approximately 91,000 individuals of all ages. OXVASC is based on the Oxfordshire Community Stroke Project (OCSP),[176] a similarly designed population based incidence study of stroke and TIA performed in the 1980s in the same population.

Figure 1.3. The nine OXVASC GP practices



OXVASC GP practice

1. Exeter, Kidlington, OX5 1AP
2. Kidlington & Yarnton, Kidlington, OX5 1AP
3. 19, Beaumont Street, Oxford, OX1 2NA
4. Bartlemas surgery, Oxford, OX4 1XD
5. Stert Street, Abingdon, OX14 3LB
6. Malthouse, Abingdon, OX14 3JY
7. Marcham Road, Abingdon, OX14 1BT
8. Berinsfield, OX10 7NE
9. Church Street, Wantage, OX12 9BN

The OXVASC population has an ethnic mix of 94% white, 3.1% Asian, 1.5% Chinese and 1.4% Afro-Caribbean.[177] Based on the Index of Multiple Deprivation (IMD),[178] the population includes a broad range of deprivation.

1.7.1 Case ascertainment and follow-up

After a 3-month pilot, the study started on April 1st 2002 and is ongoing. Multiple methods of "hot" and "cold" pursuit are used to enable near complete case ascertainment. Hot pursuit includes

1) a daily (weekdays only), urgent open-access "TIA clinic" to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital, with alternative on-call review provision at weekends. Patients too frail to attend are assessed at their residence by a study nurse or doctor.

2) Daily searches and case note review of admissions to the medical, stroke, neurology and other relevant wards.

3) Daily searches of the local A&E and eye hospital attendance registers.

4) Daily identification from the bereavement office of patients dead on arrival at hospital or who died soon after.

5) Daily searches of lists of all patients from the study population in whom a troponin level had been requested.

6) Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify prior acute events to estimate the completeness of ascertainment of non-fatal events by our other methods.

Cold pursuit includes

1) monthly computerised searches of GP diagnostic coding and hospital discharge codes (Appendix II).

2) Monthly searches of all cranial and carotid imaging studies performed in local hospitals.

3) Monthly reviews of all death certificates and coroners reports.

4) Monthly searches of practice-specific listings of all ICD-10 death codes registered centrally.

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who were not registered with one of the study practices are excluded. Patients are assessed as soon as possible after the event in hospital or at home by a study clinician. Data is collected using event-specific forms, for TIA and stroke, acute coronary syndrome (Appendix III and IV) or peripheral vascular events. This includes timing, history of presenting condition, diagnostic information, risk factors and subsequent management. Those cases with no typical history or ECG changes but a raised troponin I have core risk factor data recorded. For all deaths that are not recorded as being of clearly non-vascular aetiology that occurred outside hospital and/or prior to assessment, an eyewitness account of the clinical event is obtained and any relevant medical records and the autopsy report are reviewed.

All surviving patients are followed-up face-to-face by a research nurse at 1, 6, 12 and 60 months after the event and all recurrent vascular events were recorded together with the relevant clinical details and investigations. Recurrent events are also recorded as part the ongoing OXVASC ascertainment methods. For those too unwell or unable to have face-to-face follow up, telephone follow-up is performed.

1.7.2 Definitions and diagnosis

The standard definitions of TIA and stroke discussed previously are used in OXVASC. Acute coronary events are defined using published criteria[179] based on available history, ECG findings,

cardiac biomarkers (mainly troponin I), and autopsy or death certificate. Non-ST elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI) are defined using standard criteria.[180] Sudden cardiac deaths are coded according to recent recommendations for epidemiological studies,[181] and required a definite history of preceding symptoms consistent with acute coronary ischaemia, or post-mortem evidence of either significant coronary atherosclerosis or acute thrombosis, or a documented myocardial infarction during the previous 28 days.[179] Sudden deaths were coded as probable cardiac deaths in the absence of the above characteristics if the person had a past history of ischaemic heart disease. Other sudden out-of-hospital deaths were coded as unclassifiable. Acute peripheral arterial events are defined as those affecting a limb or an organ other than the heart or the brain/eye. Aortic events included ruptured or acutely symptomatic aortic aneurysm or dissection. Acute thrombo-embolic events included all documented cases of limb or visceral ischaemia of clearly acute onset. In view of previous data on the inaccuracy of death certification of coronary heart disease and stroke,[179,181] all deaths in the OXVASC population that were recorded and assigned were coded as in Appendix V.

1.7.3 Patient consent and ethical approval

All patients eligible for the study are given an information sheet (Appendix VI). If the patient is willing to decide about participation in the study immediately, then written consent is obtained (Appendix VII). If the patient requests a period of time to consider the decision then this is respected. Study assent is obtained from next of kin if the patient is unable to consent (Appendix VIII). OXVASC is approved by Oxfordshire Clinical Research Ethics committee (OxREC C02.043)

1.8 OXVASC contribution

The study is supervised by Professor Peter Rothwell and the day to day patient ascertainment, assessment and follow up are performed by clinical fellows and research nurses. This thesis

uses data from the first eight years of the study unless otherwise stated. I participated as one of five full-time clinical fellows from 2008-2011. Over the first two and a half years of my fellowship, I was responsible for patient ascertainment and assessment for the study. I therefore performed daily patient searches of the Emergency Department register and appropriate wards at the John Radcliffe Hospital and, with a study nurse, performed monthly searches of computerised patient lists from radiology, cardiology, angiography, hospital coding and public health departments and the study general practices. I assessed and recruited patients whom we had identified as having had an acute vascular event or who were undergoing a vascular intervention. I also participated in the study clinic on a day to day basis, assessing and ascertaining five to six referrals of suspected TIA or minor stroke per week, and supervised the research nurses who ran the weekly TIA follow-up clinic.

I ascertained and assessed a significant proportion of patients whose data are used in this thesis, although I acknowledge the help of other clinical fellows and study nurses in this process. All the data extraction and data entry in this thesis are my own. I acknowledge the help of the study statistician, Dr Ziyah Mehta for her help with data analysis, the help from Dr Ramon Luengo-Fernandez for his help with economic analysis in chapter 6 and the assistance of Professor Peter Rothwell in the preparation and revision of parts of this manuscript.

1.9 Thesis aims

The aim of my thesis is to identify areas of clinical practice during the patient journey after TIA and minor stroke where secondary prevention could be improved, from the acute phase to the long-term, chronic phase.

The first point on the patient journey that I address is prior to the onset of symptoms, regarding factors affecting delays in seeking medical attention such as prior patient knowledge, recognition

of symptoms and the ability to translate knowledge into action. I then address the difficulties surrounding diagnosis and risk stratification after TIA, in particular after recurrent TIA and isolated brainstem symptoms. The ability of public education campaigns to identify those at high risk of recurrence is explored with reference to the FAST test.[172] As the patient presents to medical attention, the safety of the outpatient clinic as a setting for care delivery is investigated. The second half of my thesis explores outcomes after TIA and stroke and opportunities for targeted intervention in relation to timing of recurrent stroke, with particular reference to home blood pressure monitoring in reducing sub-acute risk. Finally, the effect of improvements in secondary prevention on long-term recurrence risk, cardiac events and mortality is assessed in comparison with outcomes from the Oxford Community Stroke Project which studied the same population in the 1980s.

This thesis uses data from OXVASC to determine:

1. Time trends in patient behaviour after TIA and minor stroke.
2. The early recurrent stroke risk after recurrent TIA.
3. The prognosis of transient isolated brainstem symptoms.
4. The utility of FAST test[172] in prediction of early recurrent stroke risk after TIA and minor ischaemic stroke.
5. The feasibility, safety and cost of outpatient management of acute minor ischaemic stroke.
6. The prognosis of TIA and minor stroke in the subacute phase.
7. The feasibility, acceptability and blood pressure control with intensive Bluetooth home BP-monitoring.
8. The long term prognosis after TIA and ischaemic stroke.
9. Changes in late recurrent stroke, fatal stroke and fatal cardiac event risks after TIA and ischaemic stroke in Oxfordshire from 1981- 2010 in a comparison with OCSP.

1.10 References

1. Dahlof B. Cardiovascular disease risk factors: Epidemiology and risk assessment. Am J Cardiol 2010;105 (suppl):3A-9A
2. Fuster V. Epidemic of cardiovascular disease and stroke: the three main challenges. Circulation 1999;99(9):1132-7.
3. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349(9063):1436-42.
4. Ezzati M, Hoorn SV, Rodgers A, Lopez AD, Mathers CD, Murray CJ. Estimates of global and regional potential health gains from reducing multiple major risk factors. Lancet 2003;362(9380):271-80.
5. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation 2001;104(23):2855-64.
6. Yach D, Hawkes C, Gould CL, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. JAMA 2004;291;2616 –2620
7. Hatano S. Experience from a mulitcentre stroke register: a preliminary report. Bulletin WHO 1976;54:541-553.
8. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global burden of disease study. Lancet 1997; 349: 1269-76.
9. Wolfe CDA. The impact of stroke. Br Med Bull 2000;56:275-86
10. Murray CJL, Lopez AD. (eds) The Global Burden of Disease: a comprehensive assessment of mortality and disability from disease, injuries, and risk factors in 1990 and projected to 2020. Boston, MA: Harvard University Press, 1996
11. Bonita R. Epidemiology of stroke Lancet 1992; 339: 342-44
12. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006; 367: 1747–57.
13. Anderson CS, Linto J, Stewart-Wynne E. A population-based assessment of the impact and burden of caring for long-term survivors of stroke. Stroke. 1995;26:843-49.
14. Rothwell PM. Incidence, risk factors and prognosis of stroke and TIA: the need for high-quality, large scale epidemiological studies and meta-analyses. Cerebrovasc Dis. 2003;16(suppl 3):2-10.
15. Stroke Association UK website http://www.stroke.org.uk/media_centre/facts_and_figures/. Accessed November 7th 2011

16. Reducing Brain Damage: Faster access to better stroke care. National Audit Office 2005
17. British Heart Foundation Statistics Database. Coronary heart disease statistics 1998. London: British Heart Foundation.
18. Rothwell PM. The high cost of not funding stroke research: a comparison with heart disease and cancer. Lancet 2001;19:1612-1616
19. National Audit Office. Reducing brain damage: faster access to better stroke care (HC 452 Session 2005-2006). London: NAO, 2005
20. Sudlow CLM, Warlow CP. Comparing stroke incidence worldwide: what makes studies comparable? Stroke. 1996;27:550-58.
21. Feigin VL, Lawes CMM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2003;2:43-53
22. Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systemic review. Lancet Neurol 2009;8:355-69.
23. Wolfe CD, Giroud M, Kolominsky-Rabas P et al. Variations in stroke incidence and survival in 3 areas of Europe. European Registries of Stoke (EROS) Collaboration. Stroke 2000;31:2074-79.
24. Morikawa Y, Nakagawa H, Naruse Y et al. Trends in stroke incidence and acute case fatality in a Japanese rural area: the Oyabe study. Stroke 2000;31:1583-87
25. Stegmayr B, Asplund K. Exploring the declining case fatality in acute stroke: population-based observations in the northern Sweden MONICA Project. J Intern Med 1996;240:143-9
26. The end of the long-term decline in stroke mortality in the United States. Stroke 1997;28:1527-29
27. Reitsma JB, Limburg M, Kleijnen J, Bonsel GJ, Tissen JG. Epidemiology of stroke in The Netherlands from 1992 to 1994: the end of the decline in stroke mortality. Neuroepidemiol 1998;17:121-31
28. Bonita R, Beaglehole R. Increased treatment of hypertension does not explain the decline in stroke mortality in the United States, 1970-1980. Hypertension 1989;13:169-73
29. Thrift AG, Dewey HM, Sturm JW et al. Greater incidence of both fatal and nonfatal strokes in disadvantaged areas: the Northeast Melbourne Stroke Incidence Study. Stroke 2006; 37:877-82
30. Geddes JML, Fear J, Tennant A et al. Prevalence of self reported stroke in a population in Northern England. Journal epidemiology and community health. 1996;50:150-143

31. Bots ML, Looman SJ, Koudstaal PJ et al. Prevalence of stroke in the general population. The Rotterdam study. Stroke 1996;27:1499-1501.
32. Wyller TB, Bautz-Holter E, Holmen J. Prevalence of stroke and stroke-related disability in North Trondelag County Norway. Cerebrovasc Dis 1994;4:421-427.
33. The diagnosis and acute management of stroke and transient ischaemic attacks. National Institute for Health and Clinical Excellence 2008. In: http://guidance.nice.org.uk/CG68
34. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: Assessment, investigation, immediate and secondary prevention (SIGN 108). Edinburgh, 2008 (UK): The Network: www.sign.ac.uk/pdf/sign108.pdf.
35. Department of Health. National stroke strategy, 2007. In: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyandguidance/dh_081062.
36. National Collaborating Centre for Chronic Conditions. Stroke: National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). London: Royal College of Physicians, 2008.
37. Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA et al. National Stroke Association Guidelines for the Management of Transient Ischemic Attacks. Ann Neurol 2006;60:301–313
38. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke 2008;39(5):1647-52.
39. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack :Stroke 2009;40:2276-2293
40. Weisberg LA. Clinical characteristics of transient ischemic attacks in black patients. Neurology 1991;41(9):1410-4.
41. Levy DE. How transient are transient ischemic attacks? Neurology 1988;38(5):674-7.
42. Marx JJ, Mika-Gruettner A, Thoemke F, Fitzek S, Fitzek C, Vucurevic G, et al. Diffusion weighted magnetic resonance imaging in the diagnosis of reversible ischaemic deficits of the brainstem. J Neurol Neurosurg Psychiatry. 2002;72:572–575.
43. Purroy F, Montaner J, Rovira A, Delgado P, Quintana M, Alvarez-Sabin J. Higher risk of further vascular events among transient ischemic attack patients with diffusion-weighted imaging acute ischemic lesions. Stroke. 2004;35:2313–2319.
44. Inatomi Y, Kimura K, Yonehara T, Fujioka S, Uchino M. DWI abnormalities and clinical characteristics in TIA patients. Neurology. 2004; 62:376 –380.

45. Ay H, Koroshetz WJ, Benner T, Vangel MG, Wu O, Schwamm LH, Sorensen AG. Transient ischemic attack with infarction: a unique syndrome? Ann Neurol. 2005;57:679–686.
46. Daffertshofer M, Mielke O, Pullwitt A, Felsenstein M, Hennerici M. Transient ischemic attacks are more than “ministrokes.” Stroke. 2004;35:2453–2458.
47. Pendlebury S, Giles MF, Rothwell PM. Transient ischaemic attack and stroke. Cambridge University Press 1999. p 1-2
48. Sempre AP, Duarte J, Cabezas C et al. Aetiopathogenesis of transient ischaemic attacks and minor ischaemic stroke: a community-based study in Segovia, Spain. Stroke 1998;29:40-45.
49. Fischer U, Baumgartner A, Arnold M, Nedeltchev K, Gralla J, de Marchis GM et al. What is a minor stroke? Stroke 2010;41:661-666
50. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Recombinant tissue plasminogen activator for minor strokes: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Experience. Ann Emerg Med. 2005;46:243–252.
51. Giles MF, Rothwell PM. Substantial underestimation of the need for outpatient services for TIA and minor stroke. Age Ageing 2007;36:676-680
52. Johnston SC, Fayad PB, Gorelick PB, Hanley DF, Shwayder P, van Husen D, Weiskopf T. Prevalence and knowledge of transient ischemic attack among US adults. Neurology. 2003;60:1429 –1434.
53. Lemesle M, Milan C, Faivre J, Moreau T, Giroud M, Dumas R. Incidence trends of ischemic stroke and transient ischemic attacks in a well-defined French population from 1985 through 1994. Stroke 1999;30(2):371-7.
54. Dennis MS, Bamford JM, Sandercock PA, Warlow CP. Incidence of transient ischemic attacks in Oxfordshire, England. Stroke 1989;20(3):333-9.
55. Brown RD, Jr., Petty GW, O'Fallon WM, Wiebers DO, Whisnant JP. Incidence of transient ischemic attack in Rochester, Minnesota, 1985-1989. Stroke 1998;29(10):2109-13.
56. Feigin VL, Shishkin SV, Tzirkin GM, Vinogradova TE, Tarasov AV, Vinogradov SP, et al. A population-based study of transient ischemic attack incidence in Novosibirsk, Russia, 1987-1988 and 1996-1997. Stroke 2000;31(1):9-13.
57. Correia M, Silva MR, Magalhaes R, Guimaraes L, Silva MC. Transient ischemic attacks in rural and urban northern Portugal: incidence and short-term prognosis. Stroke 2006;37(1):50-5.

58. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005;36(4):720-3.
59. Rothwell PM, Coull AJ, Giles MF, et al., Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004; 363:1925–1933.
60. Hankey GJ, Slattery JM, Warlow CP. The prognosis of hospital-referred transient ischaemic attacks. JNNP 1991;54:793-802.
61. Gubbitz G and Sandercock P. Prevention of ischaemic stroke. BMJ 2000;321:1455-1459.
62. Rothwell PM, Warlow CP. Timing of transient ischaemic attacks preceding ischaemic stroke. Neurology 2005;64:817-20.
63. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004;62:2015-20.
64. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901-6.
65. Lisabeth LD, Ireland JK, Risser JM, Brown DL, Smith MA, Garcia NM, Morgenstern LB. Stroke risk after transient ischemic attack in a population-based setting. Stroke 2004;35:1842-6.
66. Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. Stroke 2003;34:138-40.
67. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, Mehta Z. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet 2005;366:29-36.
68. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328:326-30
69. Giles MF, Rothwell PM. Risk of stroke early after transient ischemic attack: a systematic review and meta-analysis. Lancet Neurol. 2007; 6(12):1063-1072.
70. Chandratheva A, Mehta Z, Geraghty OC, Marquardt L, Rothwell PM. Population-based study of risk and predictors of stroke in the first few hours after a TIA. Neurology 2009;72:1941-1947
71. Elkins JS, Sidney S, Gress DR et al. Electrocardiographic findings predict short-term cardiac morbidity after transient ischaemic attack. Arch Neurol 2002;59:1437-41.

72. Kernan WN, Feinstein AR, Brass LM. A methodological appraisal of research on prognosis after transient ischemic attacks. Stroke 1991;22:1108-16.
73. Terent A. Survival after stroke and transient ischemic attacks during the 1970's and 1980's. Stroke 1990;21:848-853.
74. Ricci S, Cantisani AT, Righetti E, Duca E, Spizzichino L. Long term follow up of TIAs: the SEPIVAC Study. Neuroepidemiology 1998;17:54.
75. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischaemic attacks in the Oxfordshire Community Stroke Project. Stroke 1990;21:1320-1326.
76. Clark TG, Murphy MFG, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in "low risk" patients with a non-recent transient ischaemic attack. J Neurol Neurosurg Psychiatry 2003;74:577-580.
77. Van Wijk I, Kappelle LJ, van Gijn J, Koudstaal PJ, Franke CL, Vermeulen M, Gorter JW, Algra A, for the LILAC study group. Long-term survival and vascular event risk after transient ischaemic attack or minor stroke: a cohort study. Lancet 2005;365:2098-104
78. Johnston SC, Rothwell PM, Nguyen-Huynh MN et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;368:283-292.
79. Giles MF, Rothwell PM. Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD2 transient ischaemic attack scores. Stroke 2010; 41:667-73.
80. Clinical guidelines for stroke management 2010. National stroke foundation 2010. http://www.strokefoundation.com.au/news/welcome/clinical-guidelines-for-acute-stroke-management.
81. Stroke foundation of New Zealand. New Zealand guideline for the assessment and management of people with recent transient ischaemic attack (TIA). 2008. www.stroke.org.nz. Accessed May 3 2011
82. Benavente O, Eliasziw M, Streifler JY et al. for the NASCET Collaborators: Prognosis after transient monocular blindness associated with carotid artery stenosis. NEJM 2001; 345:1084-1090.
83. Cartlidge NE, Whisnant JP, Elveback LR. Carotid and vertebral-basilar transient cerebral ischemic attacks. A community study, Rochester, Minnesota. Mayo Clin Proc 1977;52(2):117-20.
84. Savitz SI, Caplan LR. Vertebrobasilar disease. N Engl J Med 2005;352(25):2618-26.
85. Wiebers DO, Whisnant JP, O'Fallon WM. Reversible ischemic neurologic deficit (RIND) in a community: Rochester, Minnesota, 1955-1974. Neurology 1982;32(5):459-65.

86. Flossmann E, Rothwell PM. Prognosis of vertebrobasilar TIA and minor ischaemic stroke. Brain 2003; 126:1940-54
87. Flossmann E, Touze E, Giles MF et al. The early risk of stroke after vertebrobasilar TIA is higher than after carotid TIA. Cerebrovasc Dis 2006:21 (suppl 4):6.
88. Marquardt L, Kuker W, Chandratheva A, Geraghty O, Rothwell PM. Incidence and prognosis of > or = 50% symptomatic vertebral or basilar artery stenosis: prospective population-based study. Brain 2009;132(Pt 4):982-8.
89. Rothwell PM. Lack of epidemiological data on secondary stroke prevention. Lancet Neurol 2005;4(9):518-9.
90. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischaemic stroke in population based incidence studies. Neurology 2004;62:569-573.
91. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, 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):35-
92. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. Cerebrovasc Dis. 2009;27(5):493-501.
93. Donnan GA, O'Malley HM, Quang L et al. The capsular warning syndrome: pathogenesis and clinical features. Neurology 1993:43:957-962.
94. Fairhead JF, Mehta Z, Rothwell PM. Population-based study of delays in carotid imaging and surgery and the risk of recurrent stroke. Neurology 2005;65(3):371-5.
95. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004;363:915-24.
96. Pendlebury S, Giles MF, Rothwell PM. Transient ischaemic attack and stroke. Cambridge University Press 1999. p 91
97. Evans GW, Howard G, Murros KE et al. Cerebral infarction verified by cranial computed tomography and prognosis for survival following transient ischaemic attack. Stroke 1991;22:431-436
98. Dutch TIA Trial Study Group. Predictors of major vascular events in patients with a transient ischaemic attack or nondisabling stroke; the Dutch TIA Trial Study group. Stroke 1993;24:527-531
99. Davalos A, Matias-Guiu J, torrent O et al. Computed tomography in reversible ischaemic attacks: clinical and prognostic correlations in a prospective study. J Neurol 1988;235:155-158

100. Dennis M. Bamford, Sandercock P et al. Computed tomography in patients with transient ischaemic attacks: when is a transient ischaemic attack not a transient ischaemic attack but a stroke? J Neurol 1990;237:257-261.

101. Douglas VC, Johnston CM, Elkins J, Sidney S, Gress DR, Johnston SC. Head computed tomography findings predict short-term stroke risk after transient ischemic attack. Stroke. 2003;34:2894 –2898

102. Calvet D, Touze E, Oppenheim C, Turc G, Meder J-F, Mas J-L. DWI lesions and TIA etiology improve the prediction of stroke after TIA. Stroke. 2009;40:187–192.

103. Sciolla R, Melis F. SINPAC Group. Rapid identification of high-risk transient ischemic attacks: prospective validation of the ABCD score. Stroke. 2008;39:297–302.

104. Coutts SB, Eliasziw M, Hill MD, Scott JN, Subramaniam S, Buchan AM, Demchuk AM. VISION Study Group. An improved scoring system for identifying patients at high early risk of stroke and functional impairment after an acute transient ischemic attack or minor stroke. Int J Stroke. 2008;3:3–10.

105. Ay H, Arsava EM, Johnston SC, Vangel M, Schwamm LH, Furie KL, Koroshetz WJ, Sorensen AG. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack. The CIP model. Stroke 2009; 40:181–186.

106. Purroy F, Montaner J, Rovira A, Delgado P, Quintana M, Alvarez-Sabin J. Higher risk of further vascular events among transient ischemic attack patients with diffusion-weighted imaging acute ischemic lesions. Stroke 2004;35(10):2313-9.

107. Redgrave JN, Coutts SB, Schulz UG, et al. Systematic review of associations between the presence of acute ischemic lesions on diffusion-weighted imaging and clinical predictors of early stroke risk after transient ischemic attack. Stroke 2007;38:1482–88

108. Giles MF, Albers GW, Amarenco P, Arsava MM et al. Addition of brain infarction to the ABCD2 score (ABCD2I): a collaborative analysis of unpublished data on 4574 patients. Stroke 2010;41:1907-1913.

109. Merwick A, Albers GW, Amarenco P, Arsava EM, Ay H et al. Addition of brain and carotid imaging to the ABCD^2 score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study.. Lancet Neurol. 2010 ;11:1060-9

110. Valton L, Larrue V, le Traon AP. Microembolic signals and risk of early recurrence in patients with stroke or TIA. Stroke 1998;29:2125-2128.

111. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomized controlled trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86

112. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin inpatients at risk of ischaemic events. (CAPRIE). Lancet 1996; 348:1329-39

113. Diener HC, Cunha L, Forbes C et al. European secondary prevention study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1-13

114. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT) randomized controlled trial. Lancet 2006; 367: 1665-73

115. PROGRESS Collaborative Group. Randomised trial of a perindopril- based blood pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358: 1033-41

116. European Atrial Fibrillation Trial Study Group. Secondary prevention in non- rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993: 342: 1255-62

117. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomized controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003: 361: 107-16

118. Hackam DG, Spence JD. Combining multiple approaches for the secondary prevention of vascular events after stroke: a quantitative modeling study. Stroke 2007;38:1881-1885.

119. Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. Lancet 201;377:1681-92.

120. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN 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;370:1432-42.

121. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): Feasibility and effects. Lancet Neurol. 2007; 6: 953–960.

122. Algra A, van Gijn J. Aspirin at any dose above 30mg offers only modest protection after cerebral ischaemia. J Neurol Neurosurg Psychiatry 1996;60:197–9.

123. Algra A, Van Gijn J, Algra A, Koudstaal PJ. Secondary prevention after cerebral ischaemia of presumed arterial origin: is aspirin still the touchstone? J Neurol Neurosurg Psychiatry 1999; 66:557–9.

124. Antithrombotic Trialists' (ATT) Collaboration. Baigent C, Blackwell L et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 30:1849–60.

125. Inzitari D, Piccardi B, Sarti C. A critical review of aspirin in the secondary prevention of noncardioembolic ischaemic stroke. Int J stroke 2010;5:306-318

126. Diener HC, Bougousslavsky J, Brass LM et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high risk patients (MATCH): randomised, double- blind, placebo-controlled trial. Lancet 2004; 364(9431):331-7

127. Bhatt DL, Flather MD, Hacke W et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. JACC 2007;49:1982-88.

128. Poisson S and Johnston SC. Prevention of stroke following transient ischaemic attack. Curr Atheroscler Rep 2011;13:330-337.

129. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic detection signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005; 111: 2233–40.

130. Wong KSL, Chen C, Fu J, et al, for the CLAIR study investigators. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol 2010; 9: 489–97

131. Kennedy J, Hill MD, Ryckborst KJ, et al, for the FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomized controlled pilot trial. Lancet Neurol 2007; 6: 961–69.

132. Geraghty OC, Kennedy J, Chandratheva A, Marquardt L, Buchan AM, Rothwell PM. Preliminary evidence of a high risk of bleeding on aspirin plus clopidogrel in aspirin-naive patients in the acute phase after TIA or minor ischaemic stroke. Cerebrovasc Dis 2010; 29: 460–67.

133. http://www.tardistrial.org/TardisProtocolV12.pdf. Accessed 7th July 2012

134. Costa J, Ferro JM, Matias-Guiu J et al. Trifusal for preventing serious vascular events in people at high risk. Cochrane Database Syst Rev 2005;3:CD004296.

135. Shinohara Y, Katayama Y et al for the CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double blind, randomized non-inferiority trial. Lancet Neurol 2010;9:959-68.

136. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) study group. Lancet 1993; 342: 1255–62.

137. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. Stroke 2005; 36: 1588–93.

138. Pink J, Lane S, Pirmohammed M, Hughes DA. Dabigatran etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit-harm and economic analyses. BMJ 2011;343: at http://www.bmj.com/highwire/filestream/504057/field_highwire_article_pdf/0.pdf

139. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361: 1139–51.

140. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883-91

141. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011; 364: 806–17.

142. Tikhonoff V, Zhang H, Richart T, Staessen JA. Blood pressure as a prognostic factor after acute stroke. Lancet Neurol 2009; 8: 938–48

143. Robinson TG, Potter JF, Ford GA, et al, on behalf of the COSSACS Investigators. 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: 767–75.

144. Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. Lancet Neurol 2009; 8: 48–56.

145. Sandset EC, Bath PMW, Boysen G, et al, on behalf of the SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet 2011; 377: 741–50.

146. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358: 1033–41.

147. MacMahon S, Rodgers A et al. The lowering of blood pressure after stroke. Lancet 2001, 358:1994-1995

148. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events. Stroke 2003; 34:2741-49

149. Lakhan SE, Sapko MT. Blood pressure lowering treatment for preventing stroke recurrence: a systematic review and meta- analysis. International archives of Medicine 2009, 2:30

150. Rothwell PM, Howard SC, Spence JD; Carotid Endarterectomy Trialists' Collaboration. Relationship between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease. Stroke. 2003; 34: 2583-90

151. Bray EP, Holder R, McManus RJ. Does self monitoring reduce blood pressure? Meta-analysis with meta-regression of randomized controlled trials. Ann Med 2010;42:371-86.

152. Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence. J Clin Hypertens 2006;8:174-80

153. Pare G, Jaana M, Sicotte C. Systematic review of home telemonitoring for chronic diseases: the evidence base. J AM Med Inform Assoc 2007;14:269-77

154. McManus RJ, Mant J, Bray EP, Holder R, Jone MI, Greenfield S, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. Lancet 2010;376:163-172

155. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; 361: 2005–16.

156. Amarenco P, Bougousslavsky J, Callahan 3rd, et al. High dose atorvastatin after stroke or transient ischaemic attack. N Engl J Med 2006 Aug 10; 355(6): 549-59

157. Vergouwen MD, de Haan RJ, Vermeulen M, et al. Statin treatment and the occurrence of haemorrhagic stroke in patients with a history of cerebrovascular disease. Stroke 2008 Feb; 39(2): 497-502

158. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325: 445–53.

159. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991; 337: 1235–43.

160. Rothwell PM. Risk modeling to identify patients with symptomatic carotid stenosis most at risk of stroke. Neurol Res 2005; 27: S18–28.

161. Perkins WJ, Lanzino G, Brott TG. Carotid stenting vs Endarterectomy: New results in perspective. Mayo Clin Proc 2010;85:1101-1108

162. Murad MH, Shahrour A, Shah ND, Montori, Ricotta JJ. A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs stenting. J Vasc Surg 2011; 53:792-7

163. Donnan GA, Fisher M, Macleod, Davis SM. Stroke. Lancet 2008;317:1612-23

164. Johnston SC, Nguyen-Huynh MN, Schwartz et al. National stroke association guidelines for the management of transient ischaemic attacks. Ann Neurol 2006;60:301-13.

165. Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. Lancet Neurol 2009;8:235-43.

166. Evenson KR, Rosamond WD, Morris DL. Prehospital and in-hospital delays in acute stroke care. Neuroepidemiology 2001;20(2):65-76.

167. Harraf F, Sharma AK, Brown MM, Lees KR, Vass RI, Kalra L. A multicentre observational study of presentation and early assessment of acute stroke. BMJ 2002;325(7354):17.

168. Lacy CR, Suh DC, Bueno M, Kostis JB. Delay in presentation and evaluation for acute stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (S.T.R.O.K.E.). Stroke 2001;32(1):63-9.

169. Salisbury HR, Banks BJ, Footitt DR, Winner SJ, Reynolds DJ. Delay in presentation of patients with acute stroke to hospital in Oxford. QJM 1998;91(9):635-40.

170. Smith MA, Doliszny KM, Shahar E, McGovern PG, Arnett DK, Luepker RV. Delayed hospital arrival for acute stroke: the Minnesota Stroke Survey. Ann Intern Med 1998;129(3):190-6.

171. Giles MF, Flossman E, Rothwell PM. Patient behavior immediately after transient ischemic attack according to clinical characteristics, perception of the event, and predicted risk of stroke. Stroke 2006;37(5):1254-60.

172. Nor AM, McAllister C, Louw SJ et al. Agreement between ambulance paramedic-and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. Stroke 2004;35:1355-9

173. Kidwell CS, Starkman S, Eckstein M et al. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke 2000;31:71-76

174. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati prehospital stroke scale: reproducibility and validity. Ann Emerg Med. 1999; 33:373–378.

175. Nor AM, Davis J, Sen B et al. The Recognition of Stroke in the Emergency Department (ROSIER) scale: development and validation of a stroke recognition instrument. Lancet Neurol 2005;4:727-734.

176. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. 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 haemorrhage. J Neurol Neurosurg Psychiatry 1990;53(1):16-22.

177. 2001 Census area statistics. London. Stationary Office 2001.

178. Department of the Environment. Transport and the regions. Indices of deprivation. London, UK. Office of the Deputy Prime Minister. 2000.

179. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation 2003;108(20)**:**2543-9.

180. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 2000;21(18)**:**1502-13.

181. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke 2004;35(9)**:**2041-5.

CHAPTER 2

Time trends in patient behaviour after TIA and minor stroke

2.1 Introduction 51

2.2 Methods 52

2.2.1 Analysis 53

2.3 Results 54

2.4 Discussion 64

2.5 References 68

2.1 Introduction

The advent of thrombolysis and acute stroke units prompted interest in the delays between symptom onset and treatment for major acute ischaemic stroke,[1-5] and in knowledge of stroke among the general public and at risk populations.[6-9] In contrast, equivalent studies of TIA and minor stroke are lacking, perhaps because there has previously been less concern about delays to treatment. However, with data on the high risk of stroke during the hours and days after a TIA,[10-12] the ability to identify very high risk individuals with simple clinical scores,[13,14] and the evidence that early instigation of preventive treatments is highly effective,[15-17] it is essential to better understand patient perceptions and behaviour after TIA and minor stroke and hence the barriers to rapid presentation. Existing studies have shown that knowledge of TIA among the general public is poor and delays to seeing a physician after TIA are common.[18-20] There has been only one previous prospective population based study of behaviour of patients immediately after TIA, but only 138 patients were assessed, delay was assessed categorically, minor strokes were excluded and the characteristics of patients who had a TIA but only sought medical attention after an early recurrent stroke were not analysed in detail.[21] A recent systematic review of delays to seeking medical attention after TIA[22] highlighted the lack of high-quality data and the need for more research. To determine the feasibility of targets requiring patients with TIA or minor stroke to be assessed within 24 hours of their event,[23-28] I studied the initial perceptions and actions of patients with incident and recurrent TIA and stroke in a population based study of all incident and recurrent TIA and stroke in Oxfordshire, UK (Oxford Vascular Study). My aim was to identify potential factors associated with delays in seeking medical attention, so that appropriate action may be instigated to achieve shorter delays. In view of public stroke awareness campaigns such as the face arm speech test (FAST),[29-31] which was introduced in the UK in 2005, I also sought to determine whether patient delays in seeking medical attention have changed over time.

2.2 Methods

The Oxford Vascular Study (OXVASC) is a prospective, population based study of all acute vascular events, including stroke and TIA in approximately 91,105 individuals of all ages registered with 63 general practitioners in Oxfordshire, UK. This sub-study includes the first 1357 consecutive incident or recurrent TIA and minor stroke cases, (1st April 2002 to 31st March 2009). The OXVASC study methods have been described in chapter 1 and elsewhere.[32 33] Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke.[32-34] These include:

1) A daily, rapid access "TIA clinic" to which participating general practitioners (GPs) and the local accident and emergency department (A&E) refer all individuals with suspected TIA or stroke whom they would not normally admit directly to hospital.
2) Daily searches of admissions to the medical, stroke, neurology and other relevant wards.
3) Daily searches of the local A&E and emergency eye hospital attendance registers.
4) Monthly searches of GP diagnostic coding and hospital discharge codes.
5) Monthly searches of all cranial and carotid imaging studies performed in local hospitals

Thus the final analysis included inpatients, emergency department and eye hospital attendees, those who were assessed at home and those who attended the OXVASC dedicated daily hospital clinic.

All patients were consented and seen by study physicians as soon as possible after initial presentation to determine:

1) Their initial perception of the cause of their symptoms.
2) Their immediate response.
3) Dates and times of symptom onset, when medical attention was sought and the first contact with medical services. In a minority of patients for whom precise timing was

not known, such as those presenting late or with cognitive impairment, timings were derived from ambulance sheets, general practitioner referral letters and consultation notes.

Baseline characteristics were recorded in all patients and assessments were made for severity of event (using National Institute of Health Stroke Scale, NIHSS). Minor stroke was defined as NIHSS ≤5. Demographic data, risk factors, and symptomatology were also recorded, including the main known independent risk factors for early recurrent stroke.[13, 14, 35] Social class was coded using the standard occupational classification scheme[36] and educational level was stratified into basic (compulsory standard education up to age 16), further (education to age 18) and higher (university degree). All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA or stroke, or other condition using standard definitions.[23-25] All patients presenting with stroke were asked about recent symptoms of TIA. In patients with multiple TIAs, the most recent event prior to presentation was studied. The Face Arm and Speech test (FAST)[29] was applied to symptoms of the first TIA or minor stroke. A positive FAST requires the presence of one of unilateral face weakness (F), arm weakness (A) or speech difficulty (S).

2.2.1 Analysis

I determined the delay from symptom onset to first seeking medical attention in relation to whether the patients correctly identified the cause of their symptoms, demographic data, risk factors, symptomatology and the day on which the presenting TIA occurred. Delay was also related to the predicted early risk of stroke using the ABCD2 score.[13] A separate analysis was performed of those patients who did not seek medical attention for their initial symptoms and only presented to medical attention after their recurrent stroke (within three months). To determine if behaviour had changed over the duration of the study period, I performed a separate analysis of delays to presentation, first medical contact and recognition of symptoms by year of the study.

2.3 Results

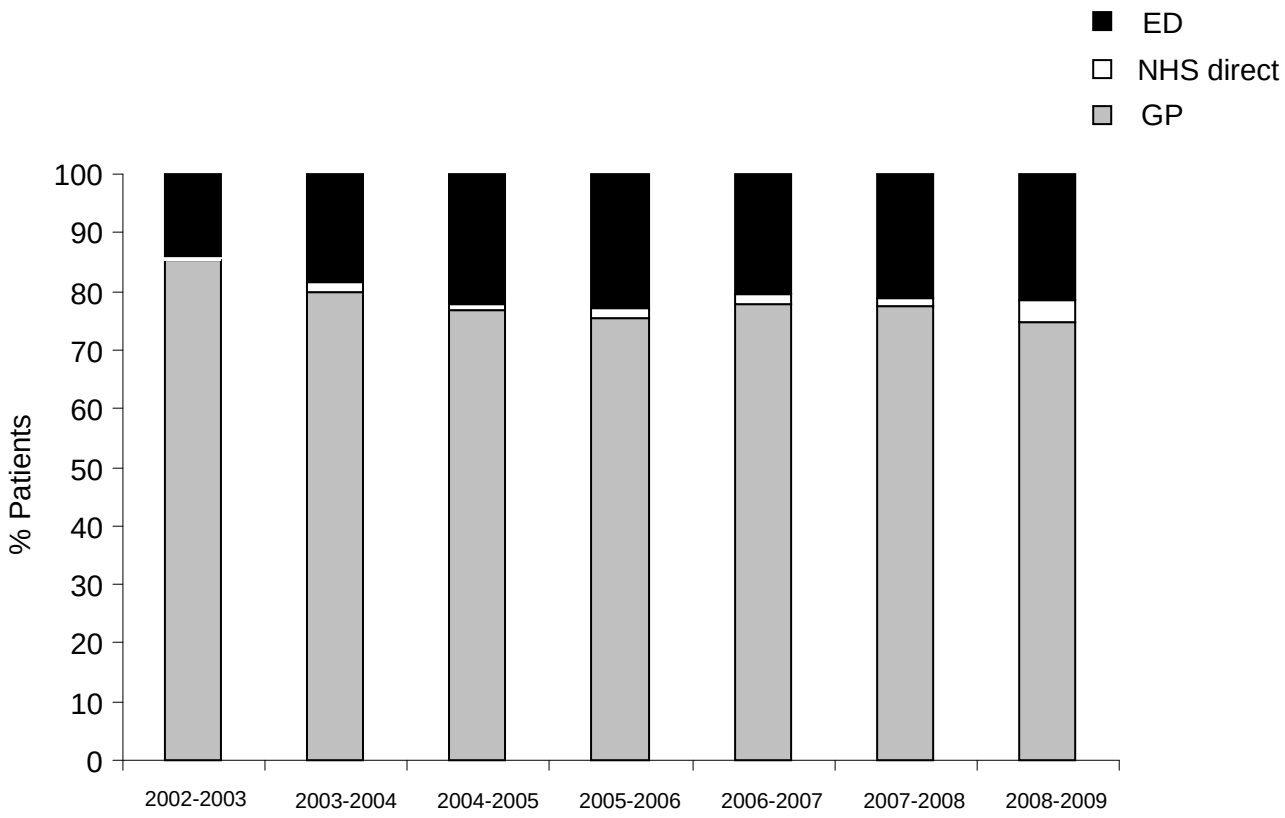
Of 1357 consecutive eligible patients, 654 presented after TIA and 703 after minor stroke. Data were available on all cases on first medical provider. The first healthcare provider contacted by patients after the event (Table 2.1) was the general practitioner in 507 (78%) TIA and 500 (71%) minor stroke patients, the main hospital emergency department in 104 (16%) TIA and 144 (21%) minor stroke patients, and NHS Direct (a 24-hour national telephone advice service) in 11 (1.7%) TIA and 11 (1.6%) minor stroke patients.

Table 2.1: The first contact with healthcare services in patients with TIA or minor stroke.

	TIA (n=654)	Minor stroke (n=703)
	Patients (%)	Patients (%)
GP	507 (78.0)	500 (71.0)
Emergency department	104 (15.9)	144 (20.5)
NHS direct	11 (1.7)	11 (1.6)
District nurse	0	1 (0.2)
Eye hospital	10 (1.5)	6 (0.9)
Inpatient at time of event	8 (1.2)	27 (3.8)
Other physician clinic	13 (2.0)	7 (1.0)
Ships doctor	0	2 (0.3)

The proportions of patients first seeking medical attention from their GP did not change significantly during the study period (p trend=0.08, Figure 2.1)

Figure 2.1 First medical attention call in patients with TIA and minor stroke by year of study (2002-2009), n=1277

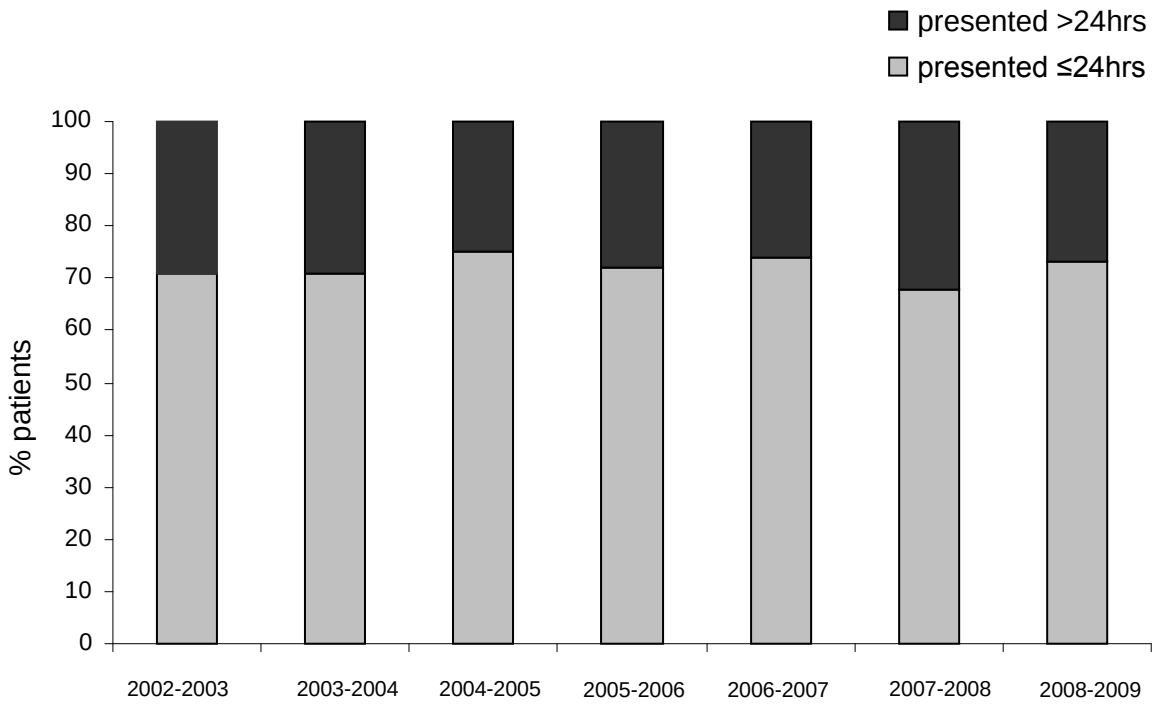


In 36 (2.7%) TIA patients and 46 (3.4%) minor stroke patients not seen in the OXVASC clinic (i.e. seen by the GP only, by doctors out of area, in the eye hospital, or admitted direct to hospital), the exact time to call for attention had not been recorded and could not be recalled by the patient on subsequent questioning. Data were available on all remaining 1275 patients (618 TIA, 657 minor stroke). Mean (SD) age of these patients was 72 (13.1) years, and 433 (34%) were aged over 80 years. 63 patients presented with a stroke but had had a TIA (47 cases) or minor stroke (16 cases) during the previous 90 days for which they had not sought medical attention, accounting for 31% of all patients with recurrent stroke within 90 days of a TIA or minor stroke in the whole study population.

There were 424 (68.1%) patients with TIA and 493 (75%) patients with minor stroke who sought medical attention within 24 hours. The proportions of patients who sought medical

attention within 24 hours did not change significantly over the course of the study period (p trend= 0.99, Figure 2.2).

Figure 2.2 Patients with TIA and minor stroke who sought medical attention within 24 hours by year of study (2002-2009), n=1275



There were 281 (45%) patients with TIA and 303 (46%) patients with minor stroke who sought medical attention within 3 hours. In the first 5 years of the study the proportions of patients seeking medical attention within 3 hours remained similar (p trend=0.25). However, in years 6 and 7, significantly fewer patients sought medical attention in 3 hours (p trend=0.05, Figure 2.3).

Figure 2.3 Patients with TIA and minor stroke presenting within 3 hours by year of study (2002-2009), n=1275

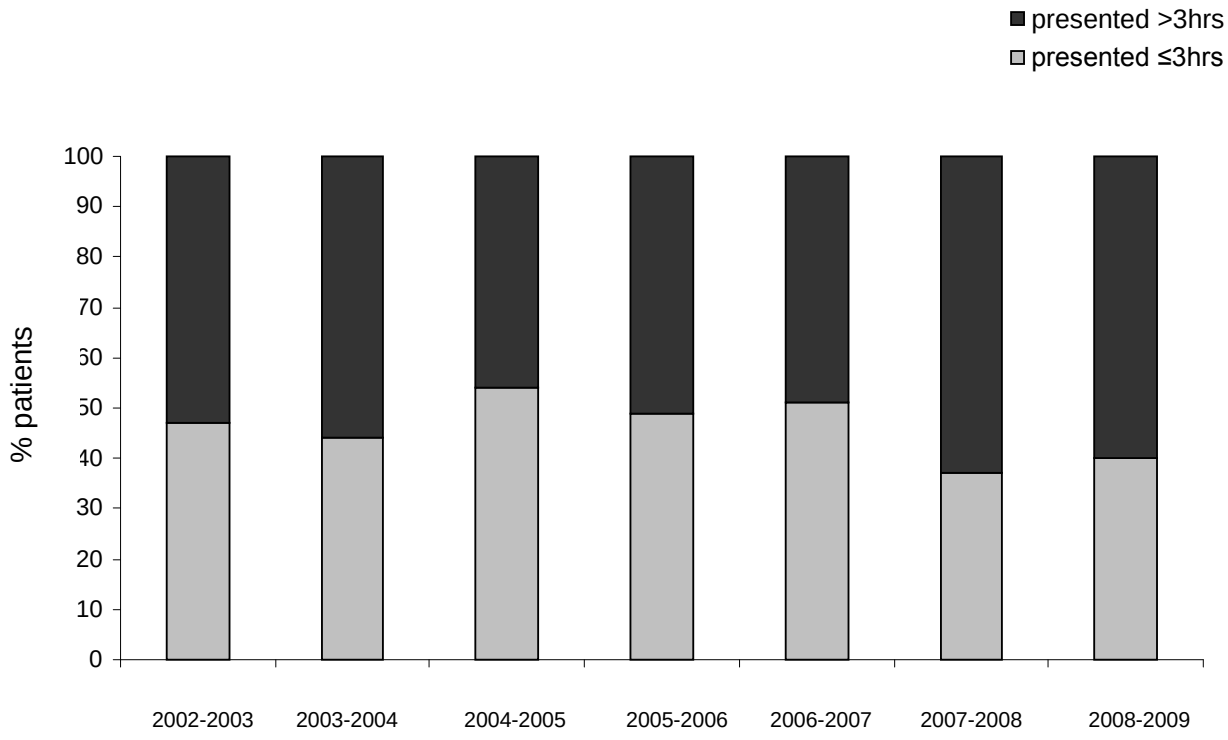


Table 2.2 shows median delay to seeking medical attention in relation to patient demographics, perceptions, risk factors for early stroke and other vascular risk factors. Patients with TIA with a lower predicted early risk of stroke were more likely to delay than those at higher risk, particularly those with absence of motor symptoms ($p<0.001$) and speech symptoms ($p=0.002$) and duration of event <60 minutes ($p<0.001$). There was no association between the other components of the ABCD2 score. Patients with TIA who had a positive FAST test had shorter delays in seeking medical attention (3.0 hours vs 13.5 hours, $p<0.001$) however in those with minor stroke, FAST test result was not associated with delay ($p=0.41$). In those with TIA, prior stroke ($p=0.001$) and atrial fibrillation ($p=0.006$) were associated with less delay, but prior TIA, myocardial infarction and hypertension were not. In those with minor stroke, prior history of atrial fibrillation ($p<0.001$) and history of myocardial infarction ($p=0.05$) were associated with shorter delays in seeking medical attention.

Interestingly, both TIA and minor stroke patients with cognitive impairment (MMSE ≤24) sought medical attention more quickly (p=0.01 for TIA, p=0.04 for minor stroke). Although, those with TIA who had MMSE ≤24 were less likely to be alone at the time of their event (10/81 vs 83/375, p=0.05). However, this was not the case for those with minor stroke and cognitive impairment, in these patients, being alone at the time of event was not related to delay (49/155 vs 102/337, p=0.83).

Table 2.2: Delay to seeking medical attention stratified by demographic, clinical characteristics and vascular risk factors

		TIA (n=618)			Minor Stroke (n=657)		
		Patients (%)	Median (IQR) delay hrs,	p-value	Patients (%)	Median (IQR) delay, hrs	p-value
Mean age		72.0 (13.3)			72.5 (13.0)		
Male		278 (45%)	4.00 (0.50-45.50)	0.665	344 (52%)	4.00 (0.75-24.00)	0.598
Correct recognition	Y	189 (31%)	2.25 (0.50-21.4)	**<0.0001**	180 (27%)	4.00 (0.96-23.88)	0.928
	N	429 (69%)	11.0 (1.0-48.6)		477 (73%)	4.50 (0.67-24.63)	
Age <60		107 (17%)	11.8 (0.75-54.1)	0.24	106 (16%)	9.75 (0.98-31.75)	0.067
Age 60-79		306 (50%)	5.75 (1.0-43.0)		323 (49%)	4.50 (0.75-24.00)	
Age ≥80		205 (33%)	3.25 (0.68-30.0)		228 (35%)	3.01 (0.68-19.59)	
BP <140/90		235 (38%)	4.0 (0.65-43.0)	0.812	218 (33%)	3.46 (0.60-23.75)	0.322
≥140/90		383 (62%)	6.0 (0.83-43.0)		439 (67%)	5.00 (0.75-24.75)	
Motor symptoms	Y	264 (43%)	1.88 (0.44-19.4)	**<0.001**	389 (59%)	3.50 (0.68-22.88)	0.107
	N	354 (57%)	15.8 (1.31-62.0)		268 (41%)	6.71 (0.85-29.63)	
Speech symptoms	Y	252 (41%)	2.50 (0.50-24.9)	**0.002**	269 (41%)	4.00 (0.69-22.13)	0.334
	N	366 (59%)	10.8 (1.00-48.6)		388 (59%)	5.00 (0.75-25.00)	
FAST positive		371 (60%)	3.0 (0.5-27.0)	**<0.001**	430 (65%)	4.00 (0.75-24.00)	0.41
FAST negative		247 (40%)	13.5 (1.0-49.0)		227 (35%)	6.00 (0.75-25.00)	
TIA duration	<10 mins	122 (20%)	16.3 (2.0-63.1)	**<0.001**			
	10-59 mins	211 (34%)	10.3 (0.68-49.0)				
	≥60 mins	285 (46%)	2.4 (0.50-23.0)				
Diabetes:	Y	73 (12%)	10.0 (0.58-65.0)	0.701	81 (12%)	6.00 (0.96-35.47)	0.441
	N	545 (88%)	4.5 (0.75-41.8)		576 (88%)	4.00 (0.75-24.00)	
ABCD2 ≥5:	Y	229 (37%)	2.0 (0.5-18.00)	**<0.001**	436 (66%)	4.50 (0.73-24.00)	0.535
	N	389 (63%)	14.0 (1.00-52.5)		221 (34%)	4.00 (0.75-27.00)	
Previous TIA	Y	95 (15%)	11.8 (1.00-48.8)	0.196	56 (9%)	7.90 (1.13-24.50)	0.341
	N	523 (85%)	4.3 (0.75-41.0)		601 (91%)	4.00 (0.73-24.25)	
Previous Stroke	Y	61 (10%)	1.0 (0.50-11.5)	**0.001**	98 (15%)	3.09 (0.58-20.88)	0.251
	N	557 (90%)	6.0 (0.91-45.8)		559 (85%)	5.00 (1.00-24.67)	
Hypertension	Y	317 (51%)	4.3 (0.7-41.6)	0.473	373 (57%)	4.00 (0.75-23.50)	0.847
	N	301 (49%)	5.25 (1.0-45.8)		284 (43%)	4.88 (0.69-25.00)	
Previous MI	Y	57 (9.2%)	2.00 (0.50-31.4)	0.094	71 (11%)	1.75 (0.50-19.50)	0.045
	N	561 (91%)	5.00 (0.97-43.5)		586 (89%)	5.00 (0.99-24.54)	
Atrial Fibrillation	Y	97 (16%)	2.00 (0.50-20.0)	**0.006**	111 (17%)	1.75 (0.50-10.42)	**<0.001**
	N	521 (84%)	6.23 (0.99-46.0)		546 (83%)	5.83 (1.00-25.75)	
MMSE*: ≤24		87 (18%)	2.00 (0.25-23.5)	**0.010**	159 (31%)	2.83 (0.58-20.50)	**0.041**
>24		402 (82%)	6.00 (0.81-46.0)		361 (69%)	7.00 (1.00-27.50)	
Educational level**	Basic	393 (71%)	4.00 (0.50-42.0)	0.619	421 (73%)	5.00 (0.96-25.00)	0.582
	Further	87 (16%)	4.50 (1.00-25.5)		101 (17%)	5.33 (0.50-25.50)	
	Higher	74 (13%)	5.21 (0.97-50.1)		59 (10%)	2.50 (0.50-20.00)	
Social Class***	1	52 (9%)	11.0 (1.00-29.8)	0.103	76 (13%)	4.25 (0.88-24.38)	0.159
	2	127 (23%)	10.3 (1.00-62.0)		132 (22%)	2.04 (0.50-20.88)	
	3	224 (40%)	4.00 (0.83-25.3)		244 (41%)	5.00 (0.88-24.50)	
	4	97 (17%)	2.00 (0.50-47.0)		68 (11%)	9.75 (1.00-28.56)	
	5	56 (10%)	14.8 (1.0-63.3)		76 (13%)	8.46 (1.04-46.50)	

*266 patients had no MMSE recorded **140 patients had no educational level recorded ***123 patients no social class recorded

In patients with TIA, occurrence at the weekend was associated with the longest delays in seeking medical attention (median delay 23.0 vs 3.5 hours p=0.001, Table 2.3).

Table 2.3: Delay to seeking medical attention stratified by weekday on which event occurred

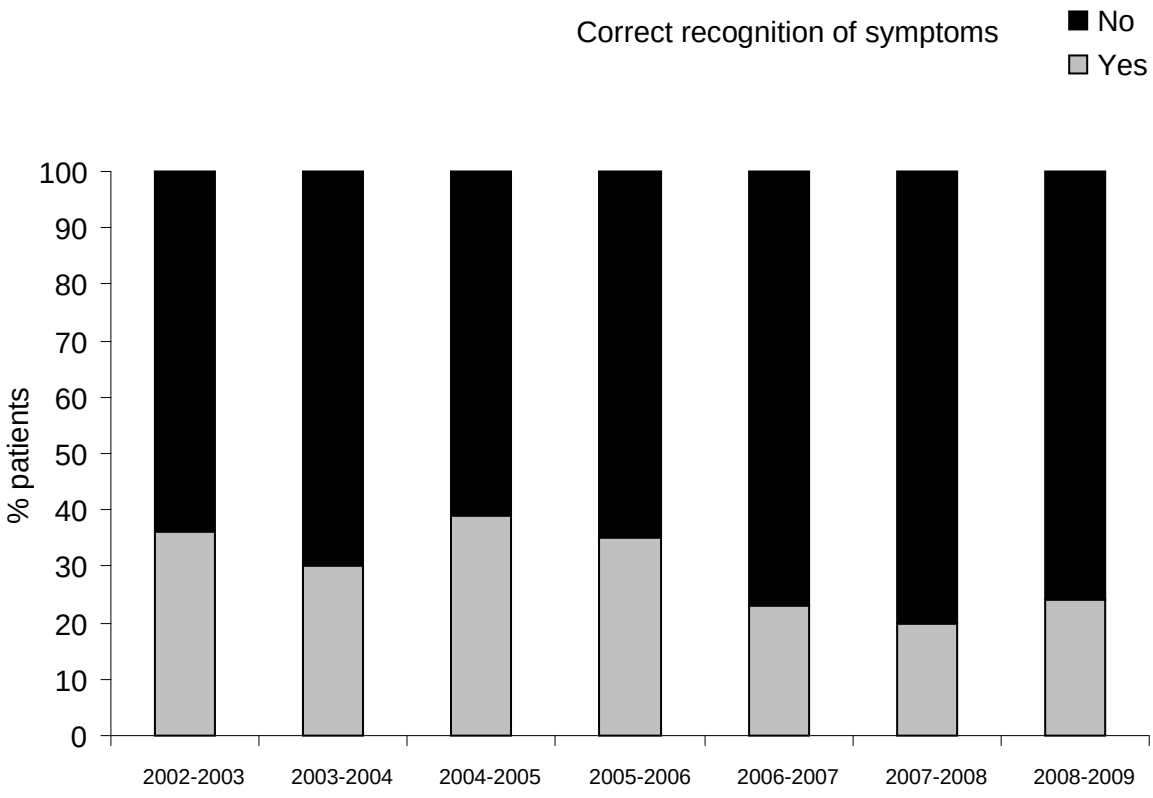
	TIA (n=618)		Minor Stroke (n=657)	
Day of event	Patients (%)	Median Delay (hours)	Patients (%)	Median Delay (hours)
Monday	95 (15%)	11.0 (1.00-40.00)	98 (15%)	3.17 (1.00-22.75)
Tuesday	100 (16%)	1.31 (0.50-18.75)	103 (16%)	2.83 (0.50-23.67)
Wednesday	77 (13%)	3.00 (0.50-22.25)	92 (14%)	3.46 (0.69-16.88)
Thursday	102 (17%)	3.75 (1.00-22.00)	94 (14%)	7.25 (1.69-20.06)
Friday	81 (13%)	4.75 (1.00-94.5)	93 (14%)	5.00 (0.75-47.75)
Saturday	85 (14%)	24.5 (0.71-62.00)	93 (14%)	3.00 (0.55-45.75)
Sunday	78 (13%)	21.00 (1.60-48.00)	84 (13%)	9.45 (0.67-24.50)

Among those patients who did seek medical attention, 638/645 (98%) TIA and 692/703 (98.4%) minor stroke patients were able to recall their initial perception of the cause of their symptoms or were with a spouse or carer who was able to. In 192 (31%) TIA and 189 (27%) minor stroke patients, their initial impression was correct. The remaining 446 (70%) TIA and 503 (73%) minor stroke patients did not know the cause of their symptoms or assumed incorrect causes.

Incorrect recognition of symptoms in patients presenting with TIA was associated with longer median (IQR) delays to seeking medical attention (11.0 vs 2.0 hours, p<0.001), but no significant association was seen in patients with minor stroke. TIA patients who did not correctly recognise their symptoms were less likely to call emergency services (52/419 vs 42/189 p=0.002). However, in TIA patients with low-risk characteristics, such as absence of

motor or speech symptoms, shorter duration of event and ABCD2 score <5, who tended as a group to respond slower, incorrect recognition of symptoms was not associated with any additional delay. Thus, when adjusted for clinical characteristics correct recognition of symptoms was not a significant determinant of delay in seeking attention after either a TIA or a minor stroke. The proportion of patients who were able to correctly identify the cause of their symptoms did not change significantly from 2002 to 2007 (p trend=0.09). However from 2007 to 2009, significantly fewer patients were able to correctly identify their symptoms (p trend< 0.001, Figure 2.4).

Figure 2.4 Patients with correct recognition of symptoms by year of study (2002-2009), n=1330



There were 801 (59%) of patients with TIA and minor stroke who had a positive FAST result. The proportion of patients with FAST positive events remained similar throughout the study period, (p trend= 0.12, Figure 2.5).

Figure 2.5 Patients with TIA and minor stroke by FAST result and year of study, n=1275

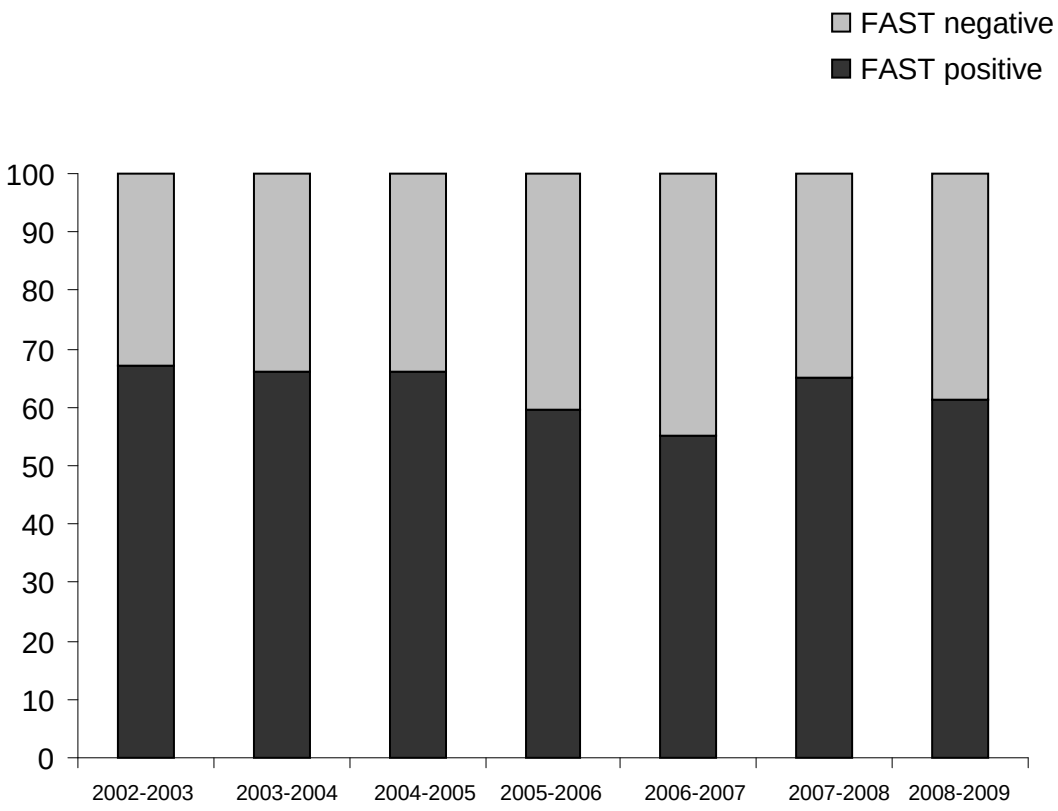


Table 2.4 shows clinical and demographic characteristics of the 63 patients who presented with a stroke but had a recent preceding TIA or minor stroke for which they did not seek medical attention. These patients were more likely to have had a TIA ($p<0.001$), shorter duration event ($p=0.01$), higher post event BP ($p=0.04$) and past history of TIA ($p=0.05$) but less likely to have motor symptoms ($p=0.03$) compared to those who sought attention for their initial TIA or minor stroke. The number of patients who correctly recognised their initial symptoms was not systematically recorded in these cases as they were ascertained at the point of their recurrent stroke.

Table 2.4: Demographics, clinical characteristics and vascular risk factors in stroke patients who did not seek medical attention for a preceding TIA or minor stroke.

	Presented to hospital with stroke but had preceding TIA or minor stroke for which medical attention was not sought n=63	TIA and minor stroke n=1357	p-value
Age (mean (SD))	73 (14.1)	72 (13.1)	0.66
TIA	47 (75%)	654 (48%)	**<0.001**
Minor stroke	16 (25%)	703 (52%)	**<0.001**
Male sex	31 (49%)	660 (48%)	1.00
Systolic BP (mean (SD))	160.7 (26.5)	153.0 (28.7)	**0.04**
Diastolic BP (mean (SD))	88.1 (13.3)	82.4 (14.6)	**0.003**
ABCD2 score (TIA)			
0	0	5 (0.8%)	0.86
1	3 (6%)	43 (6%)	
2	8 (17%)	85 (13%)	
3	12 (25%)	130 (20%)	
4	10 (21%)	151 (23%)	
5	9 (19%)	129 (20%)	
6	4 (8.5%)	99 (15%)	
7	1 (2.1%)	12 (1.8%)	
Duration TIA: <10 minutes	18 (38%)	134 (21%)	**0.01**
10-59 minutes	15 (32%)	223 (34%)	0.87
≥60 minutes	14 (30%)	297 (45%)	**0.05**
Diabetes	11 (18%)	167 (12%)	0.24
Motor symptoms	23 (37%)	688 (51%)	**0.03**
Speech symptoms	19 (30%)	545 (40%)	0.11
Previous Myocardial Infarction	2 (3%)	138 (10%)	0.08
Previous Angina	5 (8%)	209 (15%)	0.15
Previous TIA	13 (21%)	165 (12%)	**0.05**
Previous Stroke	6 (10%)	164 (12%)	0.69
Hypertension	36 (57%)	737 (54%)	0.70
Current smoker	11 (18%)	193 (14%)	0.46
Social class*			
1	0	139 (12%)	0.13
2	6 (16%)	273 (23%)	
3 manual	10 (27%)	252 (21%)	
3 non manual	10 (27%)	234 (19%)	
4	6 (16%)	171 (14%)	
5	5 (14%)	140 (12%)	

* 174 patients did not have a social class recorded

2.4 Discussion

In a telephone survey of randomly sampled US adults, Johnston and colleagues found that only 8.6% could identify a typical symptom of a "TIA"[18] and in a Swiss urban community survey even less (2.8%) identified TIA as a disease requiring urgent medical attention.[20] Given that public knowledge of the symptoms of "stroke" is much better,[6,8,9] it is likely that this low level of knowledge was at least partly due to poor recognition of the term "TIA" itself. Indeed, the same study found that among those with a history of TIA, 64% recalled seeing a physician within 24 hours,[18] although only a third of patients who had a TIA during follow-up in the Asymptomatic Carotid Artery Study in the early 1990's reported it to medical attention within three days.[19] I found that about 70% of patients in this population did not correctly recognise their TIA or minor stroke and about 30% delayed seeking medical attention for over 24 hours. Higher risk patients tended to contact health services most quickly, but 30% of early recurrent strokes still occurred prior to any attempt to do so.

Correct recognition of symptoms was associated with seeking medical attention more quickly in TIA patients, but not in patients with minor stroke. I did not collect detailed data on the severity of events at onset, but it is possible that severe initial deficits were more common in patients who recovered quickly than in those with persisting minor stroke. Presence of weakness and shorter duration of event was associated with shorter delays to calling for medical attention in those TIA patients who did not correctly recognise their symptoms, although TIA patients at highest predicted stroke risk were more likely to respond quickly.

Despite correct recognition of TIA being associated with shorter delays to seeking medical attention in this study, the low proportion of patients attending the ED (TIA 16%, minor stroke 20%) indicates a lack of public awareness that a TIA is a medical emergency and also perhaps the longstanding emphasis on primary care lead services in the UK. Public education should therefore emphasise the need to seek urgent medical attention in addition to symptom recognition. A systematic review of 9 studies of delays in seeking medical

attention after TIA found that many patients do not recognise their symptoms but those that do may still fail to seek urgent help.[22] The lack of perception of urgency in this study is perhaps best illustrated by patient behaviour after events occurring on Fridays and weekends. Whether the same patterns of behaviour following TIA would be observed in other populations or healthcare systems is uncertain.

More encouraging was the observation that patients at higher predicted stroke risk were more likely to act as in an emergency due apparently to the influence of weakness and prolonged symptom duration on behaviour. As expected, these symptoms were also particularly frequent in those patients who had an early recurrent stroke prior to seeking medical attention. However, even in patients with ABCD2 scores <4, about 20% have pathology that might require urgent treatment,[37] highlighting the importance of public education campaigns focusing on seeking urgent medical attention rather than purely symptom recognition.

During the 7-year study period, the median delay in seeking medical attention after TIA and minor stroke did not change. The proportion of patients seeking medical attention within 24 hours remained around 70%. During the later years of the study, delay in seeking medical attention did not decline, in fact the proportion of patients who delayed longer than 3 hours to seek medical attention increased slightly in years 6 and 7 (2007-2009) from 51% to 62%. Since the proportion of FAST positive events remained static throughout the study period, it is unlikely that changes in event symptomatology over time are related to the increased delay in recent years. Also the proportion of TIA and minor strokes in each year of the study remained constant so it is unlikely that changes in event type are implicated. I found that for those with TIA, a positive FAST was associated with shorter delays however for those with minor stroke, the FAST result was not associated with delay. The FAST poster campaign was introduced in 2005, it maybe that an unintended consequence of the FAST campaign is that people with symptoms that fail to fit the FAST criteria are less likely to attribute their

symptoms to a stroke or TIA and so are more likely to delay seeking medical attention. The impact of FAST on delays in seeking medical attention will be explored in detail in chapter 5.

Although I think that these observations are valid, the methods did have some potential shortcomings. First, I will undoubtedly have under-estimated the extent of the lack of awareness of the need to seek medical attention by studying cohorts all of whom did eventually report their symptoms. An unknown proportion of patients with TIA never seek medical attention. Second, it is possible that some patients' reporting of initial perceptions and actions was influenced by the knowledge that they were attending a TIA clinic or were participating in a study of TIA. However, such knowledge would probably have tended to lead to exaggeration of my estimates of correct recognition of symptoms and emergency action. Moreover, I was able to validate much of the reported behaviour against what was documented by primary care and the ED and found very few inconsistencies. Third, the setting of the study, Oxfordshire, UK, is a county with slightly lower social deprivation and slightly higher educational levels on average than the rest of the UK, although such differences would be expected to lead to higher rates of health awareness and a greater propensity to use emergency services. Fourth, I did not have exact data on timings of event and on delays to seeking medical attention in all patients because of factors such as dysphasia and cognitive impairment. Reliable data, were however available in 94% of patients, of whom over 34% were aged >80, and so there is unlikely to have been substantial inclusion bias. Fifth, from a clinical point of view it could be argued that the results of TIA and minor stroke patients should be pooled as they have similar early risk, receive similar treatment and the majority will be managed in the outpatient setting in the UK, but importantly they do appear to behave differently and I felt these striking differences merited separate evaluation. Moreover, although there have been many previous studies of delays in seeking attention after acute stroke, very few have studied TIA separately. Finally, TIAs and minor strokes before major disabling strokes might have been under-reported as some patients were unable to give an account of previous TIA or minor stroke and corroborative accounts were not always available.

These findings suggest a need for more public education, although awareness campaigns have not always had predictable effects.[38] The most appropriate content of public education campaigns is also uncertain. To date most campaigns have focused on symptom recognition, but I found that even when patients correctly recognised the event they often did not seek attention urgently, suggesting that public education should focus more strongly on the need to seek medical attention as soon as possible. Targeting of public education might be also informed by the finding that delays in seeking medical attention were unrelated to age, sex, social class or educational level.

In conclusion, patients with TIA or minor stroke often delay seeking medical attention. The clinical impact of such delay is counterbalanced partly by the fact that TIA patients at higher predicted risk of stroke tend to present more urgently, but many patients still have a recurrent stroke prior to seeking medical attention after a TIA or minor stroke. Without more effective public education the full potential of acute prevention will not be realised.

2.5 References

1. Evenson KR, Rosamond WD, Morris DL. Prehospital and in-hospital delays in acute stroke care. Neuroepidemiology 2001;20(2):65-76.
2. Harraf F, Sharma AK, Brown MM, Lees KR, Vass RI, Kalra L. A multicentre observational study of presentation and early assessment of acute stroke. BMJ 2002;325(7354):17.
3. Lacy CR, Suh DC, Bueno M, Kostis JB. Delay in presentation and evaluation for acute stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (S.T.R.O.K.E.). Stroke 2001;32(1):63-9.
4. Salisbury HR, Banks BJ, Footitt DR, Winner SJ, Reynolds DJ. Delay in presentation of patients with acute stroke to hospital in Oxford. QJM 1998;91(9):635-40.
5. Smith MA, Doliszny KM, Shahar E, McGovern PG, Arnett DK, Luepker RV. Delayed hospital arrival for acute stroke: the Minnesota Stroke Survey. Ann Intern Med 1998;129(3):190-6.
6. Pancioli AM, Broderick J, Kothari R, Brott T, Tuchfarber A, Miller R, et al. Public perception of stroke warning signs and knowledge of potential risk factors. JAMA 1998;279(16):1288-92.
7. Parahoo K, Thompson K, Cooper M, Stringer M, Ennis E, McCollam P. Stroke: awareness of the signs, symptoms and risk factors--a population-based survey. Cerebrovasc Dis 2003;16(2):134-40.
8. Reeves MJ, Hogan JG, Rafferty AP. Knowledge of stroke risk factors and warning signs among Michigan adults. Neurology 2002;59(10):1547-52.
9. Carroll C, Hobart J, Fox C, Teare L, Gibson J. Stroke in Devon: knowledge was good, but action was poor. J Neurol Neurosurg Psychiatry 2004;75(4):567-71.
10. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328(7435):326.
11. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004;62(11):2015-20.
12. Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. Stroke 2003;34(8):e138-40.
13. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369(9558):283-92.

14. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet 2005;366(9479):29-36.
15. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004;363(9413):915-24.
16. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol 2007;6(11):953-60.
17. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2007;6(12):1063-72.
18. Johnston SC, Fayad PB, Gorelick PB, Hanley DF, Shwayder P, van Husen D, et al. Prevalence and knowledge of transient ischemic attack among US adults. Neurology 2003;60(9):1429-34.
19. Castaldo JE, Nelson JJ, Reed JF, 3rd, Longenecker JE, Toole JF. The delay in reporting symptoms of carotid artery stenosis in an at-risk population. The Asymptomatic Carotid Atherosclerosis Study experience: a statement of concern regarding watchful waiting. Arch Neurol 1997;54(10):1267-71.
20. Nedeltchev K, Fischer U, Arnold M, Kappeler L, Mattle HP: Low awareness of transient ischemic attacks and risk factors of stroke in a Swiss urban community. J Neurol 2007;254:179-184.
21. Giles MF, Flossman E, Rothwell PM. Patient behavior immediately after transient ischemic attack according to clinical characteristics, perception of the event, and predicted risk of stroke. Stroke 2006;37(5):1254-60.
22. Sprigg N, Machili C, Otter ME, Wilson A, Robinson TG. A systematic review of delays in seeking medical attention after transient ischaemic attack. J Neurol Neurosurg Psychiatry 2009;80(8):871-5.
23. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: Assessment, investigation, immediate and secondary prevention (SIGN 108). Edinburgh (UK): The Network: www.sign.ac.uk/pdf/sign108.pdf, 2008.
24. Department of Health. National stroke strategy. In: dh.gov.uk/stroke w, 2007.
25. National Institute for Health and Clinical Excellence TIA and Stroke Guidelines. In: www.nice.org.uk, 2008.
26. Clinical guidelines for acute stroke management. In: www.nhmrc.gov.au/publications, 2009
27. Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA et al. National Stroke Association guidelines for the management of transient ischaemic attack.

Ann Neurol 2006;60:301-313

28. European Stroke Organization (ESO) Executive committee, ESO Writing Committee. Guidelines for the management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457-507
29. Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians and ambulance staff using the face arm speech test. Stroke 2003;34:71-76
30. Nor AM, McAllister C, Louw SJ et al. Agreement between ambulance paramedic-and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. Stroke 2004;35:1355-9
31. Whitely WN, Wardlaw J, Dennis M, Sandercock PG. Clinical scores for the identification of stroke and transient ischaemic attack in the emergency department: a cross-sectional study. JNNP 2011; online doi:10.1136/jnnp2010.235010
32. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363(9425):1925-33.
33. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, 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). Lancet 2005;366(9499):1773-83.
34. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke 2004;35(9):2041-5.
35. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284(22):2901-6.
36. OPCS (1980) Classification of Occupation 1980. London. HMSO
37. Amarenco P, Labreuche J, Lavallee PC, Meseguer E, Cabrejo L, Slaoui T, Guidoux C, Olivot JM, Abboud H, Lapergue B, Klein IF, Mazighi M, Touboul PJ: Does ABCD2 score below 4 allow more time to evaluate patients with a transient ischemic attack? Stroke 2009;40:3091-3095.
38. Marx JJ, Nedelmann M, Haertle B, Dieterich M, Eicke BM. An educational multimedia campaign has differential effects on public stroke knowledge and care-seeking behavior. J Neurol 2008;255(3):378-84.

CHAPTER 3

Population-based study of capsular warning syndrome and prognosis after early recurrent TIA

3.1 Introduction 72

3.2 Methods 72

3.2.1 Analysis 73

3.3 Results 74

3.4 Discussion 81

3.5 References 84

3.1 Introduction

The risk of stroke after TIA is highest within the first seven days.[1-8] Individual risk can be predicted to some extent by the use of clinical scores such as the ABCD2 score.[9] Recurrent or 'dual' TIA has been proposed as an addition to the ABCD2 score in the ABCD3I score, to improve early stroke risk prediction after TIA.[10] Many guidelines also recommend urgent intervention for patients with 2 or more TIAs within 7-days,[11-17] perhaps in recognition of the capsular warning syndrome. In the classical description of capsular warning syndrome, multiple, stereotyped motor TIAs precede capsular infarction,[18,19] probably as a consequence of haemodynamic compromise or thrombosis within a small, single penetrating artery or proximal middle cerebral artery (MCA) stenosis.[19-21] It is uncertain whether all patients with recurrent TIA are at high early risk of stroke or whether the capsular warning syndrome mainly accounts for the overall increased risk. Moreover, the prognosis of capsular warning syndrome itself may have changed since the original hospital-based studies of patients presenting in the 1980s and 1990s,[18-19] and may also be systematically different in population-based studies. It is also uncertain to what extent other treatable underlying pathologies, such as carotid stenosis or atrial fibrillation, are over-represented in patients with multiple TIAs. I addressed these issues in the first prospective, population-based study of the incidence, prognosis and outcomes of all incident and recurrent TIA and stroke in Oxfordshire, UK (Oxford Vascular Study).

3.2 Methods

The Oxford Vascular Study (OXVASC) is a prospective, population based study of all stroke and TIA in approximately 91,100 individuals of all ages registered with 63 general practitioners (GPs) in Oxfordshire, UK. The study methods have been described in chapter 1 and elsewhere.[22,23] Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke [22-24]

All patients were consented and seen by study physicians as soon as possible after their initial presentation. All patients presenting with TIA were asked about symptoms of TIA within the previous 90-days. Event characteristics and risk factors were recorded and patients underwent brain imaging with CT or MRI as appropriate. All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA or other condition using standard definitions.[21,22] I excluded stroke patients in whom it was impossible to obtain a definite history of preceding TIAs because they were aphasic, confused, or unconscious. Patients were followed up face-to-face at 30 days and 6 months by a study nurse or physician, recurrent symptoms were recorded and disability was assessed with the modified Rankin scale (mRS). All recurrent events that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. All patients with recurrent events were reassessed by a study physician and reviewed by PMR. Aetiological classification of events was performed according to the TOAST classification once investigations were complete.[25] This sub-study includes the first 1000 consecutive patients with TIA from 1st April 2002 to 15th August 2011.

3.2.1 Analysis

I restricted analysis to the risk of recurrent events after the first TIA in the study period (index TIA). I determined the risk of recurrent TIA and stroke within 90 days of the index TIA, including patients who did not seek medical attention for the initial symptoms but presented after a recurrent TIA or stroke. A recurrent TIA was defined as a new neurological symptom of less than 24 hours duration in a patient whom the initial symptoms had completely recovered. In patients who had multiple recurrent events, the end point was the first recurrence following the index TIA. A recurrent stroke was defined as a new persistent neurological symptom in a patient in whom the initial symptoms had already substantially or fully recovered. The 7-day risk of recurrent TIA was determined in relation to ABCD2 score and TOAST subtype. After recurrent TIA, the 7-day

stroke risk was determined in relation to the index TIA. A lacunar (or SVD) TIA was diagnosed if the following criteria were fulfilled:

(1) the presence of either

a) unilateral motor or sensory disturbance of at least two of three body parts (face, arm, leg) in the absence of cortical dysfunction presumed due to subcortical ischemia,

b) ataxic hemiparesis,

c) clumsy hand dysarthria syndrome,

(2) and/or the presence of lacunar infarct on DWI,

(2) absence of other TOAST aetiologies.

3.3 Results

Complete baseline data and follow up to 90 days were available on all 1000 consecutive, first TIAs (Table 3.1). The mean (range) age was 73 (24-99) years, with 327 (33%) patients aged over 80. 940 patients were referred to secondary care (32 patients had their event on holiday and 28 were managed by their GP only). Of 871 cases with cerebral TIA referred to secondary care, 828 (95%) had brain imaging, the majority had CT (703, 85%) as first line imaging and 125 (15%) had MRI. In those without brain imaging, reasons were being too unwell (n=22), diagnostic uncertainty at initial assessment (n=12) and patient refused (n=9).

246 (25%) cases had a recurrent event at 7 days (Table 3.2), the first recurrence was a TIA in 170 cases (17.0%, 95% CI 14.6-19.4) and a recurrent stroke in 76 cases (9.2%, 7.2-11.2). Patients with recurrent TIA were younger (p=0.007, Table 3.1), less likely to have had a previous stroke (p=0.02) or to be taking anti-hypertensives (p=0.04), but no more likely to have atrial fibrillation or ≥50% symptomatic carotid stenosis (17/90 vs 186/442, p=1.0, in those with carotid territory events) than those with single TIA. Of all recurrent TIAs within 7 days, 105 (62%) occurred within 24-hours and 136 (80%) occurred within 48-hours. The second TIA occurred

before the patient sought medical attention in 141 cases (83%). TOAST subtype and vascular territory were not associated with risk of recurrent TIA (Table 3.1).

Table 3.1 Baseline characteristics of all patients, n=1000

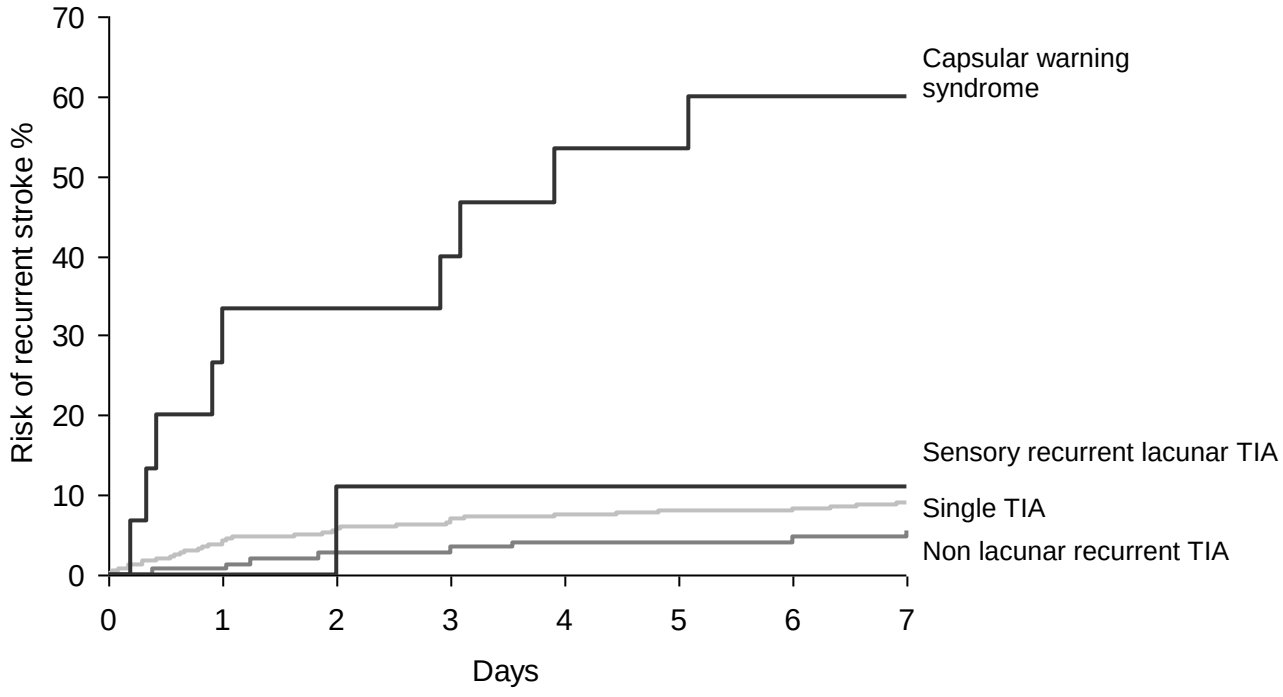
		Single TIA (n=830)	Recurrent TIA (n=170)	p
Age (mean (SD))		72.8 (13.4)	69.7 (13.7)	**0.007**
Male Sex		384 (46.3)	89 (52.4)	0.15
Closest systolic BP after TIA (mean (SD))		151.3 (28.0)	151.7 (23.6)	0.87
Closest diastolic BP after TIA (mean (SD))		82.0 (14.1)	83.3 (12.6)	0.26
Hypertension		460 (55.4)	84 (49.4)	0.18
Diabetes		107 (12.9)	27 (15.9)	0.32
Angina or myocardial infarction		152 (18.3)	29 (17.1)	0.74
Peripheral vascular disease		42 (5.1)	5 (2.9)	0.32
Atrial fibrillation		131 (15.8)	25 (14.7)	0.82
Current Smoker		103 (12.4)	23 (13.5)	0.70
Previous TIA		110 (13.3)	19 (11.2)	0.53
Previous stroke		86 (10.4)	8 (4.7)	**0.02**
Prior antiplatelet/anticoagulant		319 (38.4)	58 (34.1)	0.30
Prior statin		203 (24.5)	45 (26.5)	0.63
Prior antihypertensive		460 (55.4)	79 (46.5)	**0.04**
Carotid territory		513 (61.8)	98 (57.6)	0.31
TOAST	CE	136 (16.4)	22 (12.9)	0.30
	LAA	106 (12.8)	30 (17.6)	0.11
	SVD	85 (10.2)	24 (14.1)	0.09
	UND	391 (47.1)	78 (48.9)	0.80
	UNK/MULT/OTHER	16 (9.4)	112 (13.5)	0.17

Table 3.2. 7-day stroke risk after single and recurrent TIA stratified by ABCD2 score and TOAST classification, % risk (95% CI)

	Single TIA	Strokes	7-day stroke risk	Recurrent TIA	Strokes	7-day stroke risk	p
ABCD2 score							
0	3	0	0	2	0	0	0
1	48	3	6.2 (0 – 13.1)	18	0	0	0.28
2	115	7	6.1 (1.8 - 10.4)	38	3	7.9 (0 – 16.5)	0.69
3	152	10	6.6 (2.7 - 10.5)	35	3	8.6 (0 – 17.8)	0.70
4	187	14	7.5 (3.8 – 11.2)	34	3	8.8 (0 - 18.4)	0.75
5	173	14	8.1 (4.0 – 12.2)	27	6	22.2 (6.5 – 37.9)	0.02
6	133	26	19.5 (12.8 – 26.2)	14	3	21.4 (0 – 43.0)	0.87
7	19	2	10.5 (0 – 24.2)	2	1	50.0 (0-119.4)	0.06
ABCD<4	318	20	6.3 (3.6 – 9.0)	93	6	6.5 (1.6-11.4)	0.97
ABCD≥4	512	56	10.9 (8.2 – 13.6)	77	13	16.9 (8.5 – 25.3)	0.11
TOAST							
CE	136	16	11.8 (9.8 - 13.8)	22	2	9.1 (0 – 21.12)	0.74
LAA	106	13	12.3 (6.0 – 18.6)	30	4	13.3 (1.1 – 25.5)	0.89
SVD	85	17	20.0 (11.6 – 28.4)	24	10	41.7 (21.9 – 61.5)	0.03
Undetermined	391	15	3.8 (1.8 – 5.8)	78	1	1.3 (0 – 3.8)	0.26
Unknown	74	8	10.8 (3.7 -17.9)	6	1	16.7 (0-46.5)	0.63
Multiple/Other	38	7	18.4 (6.1- 30.7)	10	1	10.0 (0-28.6)	0.50
Total patients	830	76	9.2 (7.2 – 11.2)	170	19	11.2 (6.5 - 15.9)	0.41

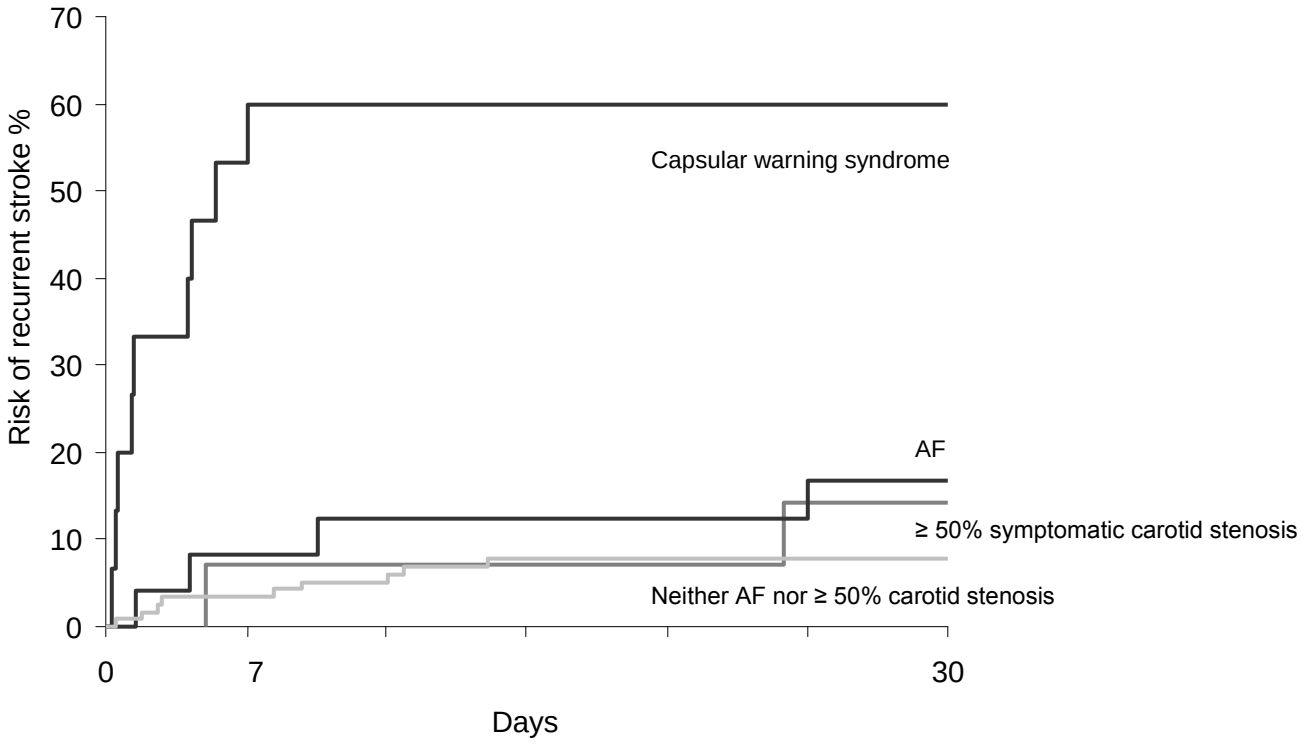
In those with recurrent TIA, stroke risk after the first TIA was 5.9% (2.4-9.4, 10 cases) in the first 48-hours, 10.6% at 7-days (5.9-15.3, n=18), 14.1% at 30-days (8.8-19.4, n=24) and 14.7% (9.4-20, n=25) at 90-days. The 7-day stroke risk after recurrent TIA was similar to risk after a single TIA (18/170 vs 76/830 p=0.56) and risks were also similar when stratified by ABCD2 score (Table 3.2). In contrast to the risk of recurrent TIA, which did not vary according to TOAST subtype, the 7-day stroke risk was highest after recurrent TIAs of small vessel disease (SVD) subtype (10/24 vs 8/146, OR=12.3, 3.7-41.9, p<0.0001). For all other TOAST subtypes, 7-day stroke risk was no different after recurrent TIAs compared to after a single TIA (8/146, 5.5% vs 76/830, 9.2%, OR 0.58, 0.25-1.3, p=0.20). Thus, recurrent TIAs of small vessel disease type were associated with a particularly high 7-day stroke risk of 42% (10/24, 21.9 - 61.5) and risks were highest after recurrent motor compared to recurrent sensory TIAs (9/15, 60% vs 1/9, 11.1%, p=0.03, Figure 3.1). However, if strokes secondary to TIAs of SVD aetiology are excluded, the 7-day stroke risk after recurrent TIA is low (8/146, 5.5%, 1.8-9.2, Figure 3.1).

Figure 3.1: 7-day stroke risk after the first TIA in single and recurrent TIA of lacunar and non-lacunar type



At 30-days, the risk of stroke in those with recurrent TIA and ≥50% symptomatic carotid/vertebral stenosis or atrial fibrillation tended to be higher than in non-SVD cases of undetermined aetiology (9/41 22.0%, 9.3-34.7 vs 6/114, 5.3%, 1.2-9.4, p=0.002, Figure 3.2).

Figure 3.2: 30-day stroke risk after the first TIA in those with recurrent TIA and capsular warning syndrome, ≥50% symptomatic carotid stenosis, AF or neither of these aetiologies.



Of 24 patients with recurrent TIAs of SVD subtype, the main features were motor weakness in 15 cases (12 hemiparesis, 2 ataxic hemiparesis, 1 slurred speech) and hemi-numbness in 9 cases. Of 146 patients with recurrent TIAs of non-SVD subtype, only 7 had hemi-weakness without cortical symptoms, the aetiologies in these cases were LAA (n=3), CE (n=2), multiple (n=1) and other (n=1).

Of 10 patients with stroke after recurrent lacunar SVD TIAs, all had the recurrent TIA within 24 hours after the first TIA (median time to recurrent TIA=2.3 hours, SD 9.4, Table 3.3). The subsequent stroke occurred within 24-hours of the second TIA in five cases, and within 72-hours in nine cases (median time to stroke=29.5 hours, SD 37.7). Nine of the 10 patients had motor weakness as a feature of the recurrent TIA (8 hemiparesis, 1 slurred speech) and only one had heminumbness, such that the ABCD2 score of all TIAs prior to stroke was ≥4 in 9 cases.

Of 15 cases of recurrent motor lacunar TIAs (capsular warning syndrome), the 7-day stroke risk was 60% (35.3-84.7, n=9), with no strokes at 8-90 days. 10/15 cases presented to medical attention prior to any stroke (5 to GP, 4 to A+E and 1 to a doctor whilst on holiday) and 5 presented after a subsequent stroke. Among the 10 patients who presented prior to any stroke, the risk of progression to stroke appeared to be lower in those given an immediate loading dose of an antiplatelet drug (0/4 vs 4/6, p=0.08), either starting aspirin (n=3) or adding clopidogrel to premorbid aspirin (n=1). Of the 9 cases of capsular warning syndrome stroke, the median mRS at 1 month after stroke was 2 (range 1-4).

Table 3.3 Characteristics of stroke within 7 days of second TIA

	Stroke after recurrent lacunar TIAs, n=10	Stroke after recurrent non-SVD TIAs, n=9	p
Age (mean, (SD))	70.7 (13.4)	67.9 (19.4)	0.71
Male sex	7	4	0.37
Recurrent TIA within 24 hours	10	6	0.09
Stroke within 24 hours of 2nd TIA	5	4	1.0
Median time to recurrent stroke after 2nd TIA (IQR)	29.5 (7-68.1)	27.0 (20.5-126.5)	0.51
Presented to medical attention after TIAs	4	4	1.00
Presented to medical attention after stroke	6	5	1.00
ABCD2 score of 2nd TIA ≥4	9	4	0.06
Clinical Features of 2nd TIA			
Motor weakness	8	4	0.17
Speech difficulty only	1	2	0.58
Sensory symptoms only	1	1	1.00
Prior antiplatelet	4	3	1.00
Prior statin	1	1	1.00
Prior antihypertensive	4	5	0.66
Acute post-stroke SBP	169.5 (33.1)	160.9 (26.3)	0.76
Acute post-stroke DBP	90.6 (12.5)	86.4 (10.2)	0.51

3.4 Discussion

Recurrent TIA has been incorporated into guidelines as an indication for urgent secondary prevention,[11-17] and it has been proposed that it should be included as a variable in prognostic scores.[10] However, there are limited published data on whether all those with multiple TIAs are at high risk of recurrent stroke or whether this group differs in terms of treatable underlying pathologies. I have shown that recurrent TIA has a similar early stroke risk to that after a single TIA in this population, other than in the case of capsular warning syndrome, and that the prevalence of atrial fibrillation and large artery stenosis is no greater. Indeed, in patients with multiple non-SVD TIAs the early risk of stroke tended to lower than after a single TIA.

In this sub-study, the 7-day risk of recurrent TIA was high at 17%, which appears to be consistent with previous studies.[10,27,28] However, reports of the prognostic significance of recurrent TIA have been less consistent. In an emergency department cohort of 1707 patients, the 90-day stroke risk after recurrent TIA was not greater than after a single TIA.[26] In another hospital-based study of 113 patients with TIA, progression or fluctuation of symptoms was an independent predictor of stroke.[27] However, when patients with multiple attacks at presentation were analysed separately, there was no significant difference in stroke risk.[27] In a recent analysis of pooled data from 2654 patients with TIA, two or more TIAs within 7-days occurred in 19.4% and was associated with higher stroke risk (OR 5·0, 95% CI 2·76 – 9·06).[10] However, no previous studies have determined the extent to which prognostic significance is dependent on the underlying aetiology of recurrent TIAs.

In this study, early stroke risk was highest after single or recurrent TIAs of SVD aetiology. Previous studies have shown that large artery stenosis subtype is associated with high recurrent stroke risk after TIA or stroke,[28-30] but have tended to underestimate the risk of stroke after SVD

events by including patients presenting with lacunar stroke rather than lacunar TIA. Although capsular warning syndrome is rare (only 1.5% of TIA presentations in my study), the early risk of stroke in previous studies has been very high.[18-19] My results show that this poor prognosis still applies today. In contrast to capsular warning syndrome, however, the risk of stroke after recurrent TIAs of other aetiologies was much lower in this study. The current emphasis in guidelines on greater urgency of assessment of all patients with multiple versus single TIA may not be justified by their stroke risk.

The emphasis on recurrent TIA in management guidelines and in prognostic scores could still be justified, however, if they were particularly associated with treatable pathologies. However, I found no excess of atrial fibrillation or carotid stenosis in cases with multiple TIA. Moreover, specific treatments for capsular warning syndrome are lacking, although thrombolysis, hydration, BP elevation, dual antiplatelets and anticoagulants have been shown to be beneficial in case reports.[31-35]

My results show that despite improvements in processes of care, the prognosis of capsular warning syndrome is similar to when it was first described in the 1980s. The trend towards a reduced risk of early stroke in patients given an immediate loading dose of antiplatelet drugs is encouraging and this approach is probably justified despite the lack of trial data.

In this study, less than half of capsular warning syndrome cases presented to medical attention prior to recurrent stroke, highlighting the continued need for public education on TIA. However, I also found that the high risk of stroke persists beyond 48-hours, such that randomized treatment trials might be feasible nevertheless.

This study had some potential limitations. First, my estimate of stroke risk in the acute phase may not be completely precise because an unknown proportion of patients with TIA and minor stroke will never seek medical attention. However, this bias is likely to be somewhat smaller after a second event, with patients probably being less likely to ignore two events. Second, my analysis of stroke risk after recurrent TIA was based on only 18 stroke outcomes. Although this is more than the 12 stroke outcomes following multiple TIAs in the Californian cohort[26], further studies would help confirm or refute my findings. Third, the intensity and timing of secondary prevention may have varied according to treatment setting, causing a difference in the timing of recurrent events. The cases included patients seen in the EXPRESS clinic in which secondary prevention was initiated at time of assessment.[36] Fourth, rates of intracranial vascular imaging in this study were low (36% of cases) and I was not therefore able to identify the subset of patients with capsular warning syndrome due to proximal middle cerebral artery stenosis.[20,21]

In summary, recurrent TIA is not associated with a greater stroke risk than after a single TIA, other than in capsular warning syndrome, and has a similar prevalence of other underlying pathologies.

3.5 References

1. Giles MF, Rothwell PM. Substantial underestimation of the need for outpatient services for TIA and minor stroke. Age Ageing 2007;36:676-80.
2. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005;36:720-3.
3. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004;62:2015-20.
4. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901-6.
5. Lisabeth LD, Ireland JK, Risser JM, Brown DL, Smith MA, Garcia NM, Morgenstern LB. Stroke risk after transient ischemic attack in a population-based setting. Stroke 2004;35:1842-6.
6. Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. Stroke 2003;34:138-40.
7. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, Mehta Z. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet 2005;366:29-36.
8. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328:326-30
9. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283-92.

10. Merwick A, Albers GW, Amarenco P, Arsava EM, Ay H, Calvet D et al Addition of brain and carotid imaging to the $ABCD^2$ score to identify patients at high early stroke risk after transient ischaemic attack. Lancet Neurol 2010:1060-9
11. The diagnosis and acute management of stroke and transient ischaemic attacks. National institute for health and clinical excellence, 2008. In: http://guidance.nice.org.uk/CG68
12. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: Assessment, investigation, immediate and secondary prevention (SIGN 108). Edinburgh, 2008 (UK): The Network: www.sign.ac.uk/pdf/sign108.pdf.
13. Department of Health. National stroke strategy, 2007. In: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyandguidance/dh_081062.
14. National Collaborating Centre for Chronic Conditions. Stroke: National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). London: Royal College of Physicians, 2008.
15. Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA et al. National Stroke Association Guidelines for the Management of Transient Ischemic Attacks. Ann Neurol 2006;60:301–313
16. The Stroke Prevention and Educational Awareness Diffusion (SPREAD) Collaboration. The Italian Guidelines for stroke prevention. Neurol Sci. 2006;21:5-12.
17. Gomman J, Barber PA, Fink J. Preventing strokes: the assessment and management of people with transient ischemic attack. N Z Med J 2009;122:3556-3567.
18. Donnan GA, O'Malley RN, Quang L, Hurley S, Bladin PF. The capsular warning syndrome: pathogenesis and clinical features. Neurology 1993;43:957-962
19. Hankey GJ and Warlow CP. Lacunar transient ischaemic attacks: a clinically useful concept. Lancet 1991; 337:335-38

20. Yoon W, Seo J, Cho KH, Kim MK, Kim BC, Park MS et al. Symptomatic middle cerebral artery stenosis treated with intracranial angioplasty: Experience in 32 patients. Radiology 2005; 237:620-626.
21. Cho KH, Kang DW, Kwon SU, Kim JS. Location of single subcortical infarction due to middle cerebral artery atherosclerosis: proximal versus distal arterial stenosis. JNNP 2009:48-52
22. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;363:1925-1933.
23. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE 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). Lancet. 2005;366:1773-1783.
24. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke. 2004;35:2041-2045.
25. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL 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;24:35-41.
26. Johnston SC, Sidney S, Bernstein A, Gress D. A comparison of risk factors for recurrent TIA and stroke in patients diagnosed with TIA. Neurology 2003;60:280-285
27. Nakajima M, Hirano T, Naritomi H, Minematsu K. Symptom progression or fluctuation in transient ischaemic attack patients predicts subsequent stroke. Cerebrovasc Dis 2010;29:221-227
28. Purroy F, Montaner J, Molina C, Delgado P, Ribo M, Alvarez-Sabin J. Patterns and predictors of early risk of recurrence after transient ischaemic attack with respect to aetiologic subtypes. Stroke 2007;38:3225-3229
29. Kim SH, Han SW, Heo J. Predictive implications of recurrent transient ischaemic attacks in large artery atherosclerosis. Cerebrovasc Dis 2006; 22:240-244

30. Lovett JK, Coull A, Rothwell PM, on behalf of the Oxford Vascular Study. Early risk of recurrent stroke by aetiological subtype: implications for stroke prevention. Neurology 2004; 62: 569-74.
31. Caporale CM, Notturno F, Caulo M, Uncini A. Capsular warning syndrome mimicking a jacksonian sensory march. J Neurol Sci 2009; 262-264.
32. Teng T, Hong CT. Capsular warning syndrome: Report of a case. Acta Neurol Taiwan 2008;17:248-52.
33. Vivanco-Hidalgo RM, Rodriguez-Campello A, Ois A, Cucurella G, Pont-Sunyer C, Gomis M et al. Thrombolysis in capsular warning syndrome. Cerebrovasc Dis 2008;25:508-510.
34. Fahey CD, Alberts MJ, Bernstein RA. Oral clopidogrel load in aspirin-resistant capsular warning syndrome. Neurocrit. Care 2005;2:183-184.
35. Lalive PH, Mayor I, Sztajzel R. The role of blood pressure in lacunar stroke preceded by TIAs. Cerebrovasc Dis 2003;16:88-90.
36. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty OC, Redgrave JNE, et al. Effect of urgent treatment of transient ischemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370:1432-1442.

CHAPTER 4

Population-based study of NINDS-defined TIA: evidence of substantial under-diagnosis of posterior circulation events

4.1 Introduction……89

4.2 Methods 90

4.3 Results ……..91

4.4 Discussion ……98

4.5 References ……101

4.1 Introduction

The diagnosis of TIA is often based purely on the description of the symptoms of the event, particularly in vertebrobasilar (VB) cases where positive diffusion weighted imaging is less common.[1,2] There is therefore significant observer variability in clinical diagnosis, even amongst experienced neurologists.[3,4] A false-positive diagnosis of TIA can adversely affect patient confidence, lifestyle, and insurance eligibility and can result in unnecessary preventative treatments. On the other hand, missing the diagnosis may mean that the opportunity to prevent a disabling stroke is lost. Transient isolated "brainstem" symptoms are not defined as TIAs by the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) diagnostic criteria (Appendix IX).[5] The NINDS criteria provide specific examples of isolated attacks that are not to be considered a TIA, these include vertigo, dysarthria, dizziness or wooziness, focal symptoms associated with migraine, confusion and amnesia.[5] It is emphasized that VB TIA should not be diagnosed on the history of a few minutes of vertigo alone but only with concurrent weakness, sensory deficit or loss of vision.[5] The prevalence of dizziness presenting to an emergency department in a population based study was 5.3 per 1000 population although only 0.7% were diagnosed as TIA or stroke.[6] Transient neurological attacks (TNAs), defined as "attacks of sudden neurological symptoms that completely resolve within 24 hours, with no clear evidence for the diagnosis of migraine, epilepsy, Ménière's disease, hyperventilation, cardiac syncope or orthostatic hypotension" have been shown to be associated with an increased risk of stroke, cardiovascular events and vascular dementia.[7-9] However, whether TNAs signify brainstem ischaemia is uncertain and there are too few data on their prognosis to be confident of their nature. In addition, subsequent stroke territory has not been reported and whether events are associated with carotid or vertebral artery stenosis is not known. If some of these events are VB TIAs, then they should be common during the days and weeks prior to definite VB ischaemic events. The temporal relationship between preceding TNAs and ischaemic events can be estimated because the majority of patients who go on to have a definite ischaemic

event after a TNA will present to medical attention.[10] I aimed to assess the frequency of TNAs preceding VB and carotid territory events in a prospective, population based study of all incident and recurrent TIA and stroke in Oxfordshire, UK (Oxford Vascular Study).

4.2 Methods

This study was nested within the Oxford Vascular Study (OXVASC), a prospective, population based study of all stroke and TIA in approximately 91 000 individuals of all ages registered with 63 general practitioners in Oxfordshire, UK. The study methods have been described in chapter 1 and elsewhere.[11,12] Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke.[11,12] All patients were consented and seen by study physicians as soon as possible after their initial presentation. A detailed history was obtained from each patient with a standardised questionnaire. This included date of symptom onset, duration and type of symptoms, baseline characteristics and time of first seeking medical attention.

Definite events were defined as those with either a stroke or a NINDS-defined TIA with ≥50% symptomatic stenosis on MRA, CTA or angiography as reported by the study neuroradiologist (Dr W Küker). All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA, stroke or other condition using standard definitions.[11] Assessments were made for severity of event using the National Institute of Health Stroke Scale (NIHSS)[13] and clinical features. Events were classified as minor stroke if there was a focal neurological deficit lasting more than 24 hours and an NIHSS score ≤5 at time of assessment by a study physician. Vascular territory (carotid or VB) of definite events was assigned by using the NINDS criteria applied to clinical features of the event.[5] Definite events of uncertain vascular territory were excluded.

All patients were asked in detail about TIA/TNA symptoms during the previous 90 days. In those cases ascertained via cold pursuit, clinic letters, hospital notes and GP records were also searched for TIA or TNA symptoms in the previous 90 days. TNAs were prospectively

classified using a pre-defined, diagnostic classification system specifically constructed for the study (Appendix X). Isolated vertigo, vertigo with other symptoms, isolated double vision, transient generalised weakness and binocular visual disturbance were classified as VB territory TNAs. Atypical amaurosis fugax and limb-shaking episodes (presumed to be due to low flow in the ipsilateral carotid artery) were classified as carotid territory TNAs. Isolated slurred speech, migraine variants, transient confusion and hemisensory tingling symptoms were classified as uncertain territory TNAs. All TNAs were further classified according to whether they fulfilled NINDS TIA criteria.[5] I restricted analysis to patients with a first definite event presenting to medical attention in the study period. The frequency of TNAs 90 days prior to definite events was analysed. This sub-study includes all cases with events from the 1st April 2002 to 31st March 2010.

4.3 Results

The vascular territory of 1926 consecutive patients presenting to medical attention with ischaemic events is shown in Table 4.1.

Table 4.1 Territory of all ischaemic events presenting to medical attention, n=1926

	Carotid	Vertebrobasilar	Both	Unknown	Total
TIA	491 (39.3)	227 (45.2)	20 (30.3)	47 (43.5)	785 (40.7)
Minor stroke	504 (40.3)	238 (47.4)	25 (37.9)	44 (40.7)	811 (42.1)
Major stroke	255 (20.4)	37 (7.4)	21 (31.8)	17 (15.7)	330 (17.1)
Total	1250 (100)	502 (100)	66 (100)	108 (100)	1926 (100)

There were 1224 (64%) patients with definite events. Of these, the vascular territory could be determined in 1117 (91%) cases. There were 83 (7.4%) patients with TIA and associated stenosis, 742 (66.4%) with minor stroke and 292 (26.1%) with major stroke. Amongst these, there were 308 (28%) with VB events and 809 (72%) with carotid territory events, Table 4.2)

Table 4.2 Territory of all definite ischaemic events, n= 1117

	Carotid	Vertebrobasilar	Total
TIA ≥50% symptomatic stenosis	50 (6.2)	33 (10.7)	83 (7.4)
Minor stroke	504 (62.3)	238 (77.3)	742 (66.4)
Major stroke	255 (31.5)	37 (12.0)	292 (26.1)
Total	809 (100)	308 (100)	1117 (100)

Patients with carotid events were older than those with VB events (75.8 vs 72.6 years, p<0.001) and were more likely to have had previous stroke (16.7% vs 11.7%, p=0.041), other baseline characteristics were similar in both territories (Table 4.3).

Table 4.3 Baseline characteristics, vascular risk factors and premorbid medication of definite ischaemic events by territory, n=1117

	Carotid (n=809)	Vertebrobasilar (n=308)	p
Age (mean (SD))	75.8 (11.6)	72.6 (13.5)	**<0.001**
Male Sex	401 (49.6)	155 (50.3)	0.841
Hypertension	482 (59.6)	189 (61.4)	0.632
Diabetes	98 (12.6)	41 (13.3)	0.408
Angina or myocardial infarction	165 (20.4)	67 (21.8)	0.621
Peripheral vascular disease	71 (8.8)	29 (9.4)	0.726
Previously diagnosed atrial fibrillation	161 (19.9)	56 (18.2)	0.554
Current Smoker	120 (14.8)	37 (12.0)	0.248
Previous TIA	74 (9.1)	21 (6.8)	0.232
Previous stroke	135 (16.7)	36 (11.7)	**0.041**
Prior antiplatelet	359 (44.4)	121 (39.3)	0.137
Prior statin	189 (23.4)	69 (22.4)	0.751
Prior antihypertensive	481 (59.5)	185 (60.1)	0.892

TNAs or TIAs were more common in the 90 days preceding VB events than before carotid events (79/308 vs 87/809, OR 2.86, 95% CI 2.04-4.02, p<0.001). Of 308 patients with definite VB events, 79 (25.6%, 20.7-30.5) had at least one TNA/TIA within the preceding 90 days (median=7.0 days) of which only 9 (11.4%) fulfilled the NINDS criteria for TIA. The other 70 cases were isolated vertigo (n=25), non-NINDS binocular visual disturbance (16), vertigo with non-focal symptoms (12), isolated slurred speech (4), isolated hemisensory tingling (4), transient confusion (3), transient generalised weakness (2), isolated diplopia (2), and migraine variant (2). Most non-NINDS TNAs (70%, 49/70) occurred prior to minor stroke, however almost 50% (16/33, 48.5%) of TIAs with stenosis had a preceding TNA within 90 days. Vertigo was a feature of all non-NINDS TNAs prior to major VB stroke and was present in 58% (28/49) before minor stroke. Isolated vertigo was more common prior to VB stroke than TIA with stenosis (23/54 vs 2/16, OR 5.19, 1.18-22.3, p=0.04). However, binocular visual disturbance was more common prior to VB TIA than stroke (7/16 vs 9/54, OR 3.89, 1.18-12.9, p=0.04).

TNAs of probable VB origin were twelve times more likely before definite VB events than carotid events (57/308 vs 14/809, OR 12.9, 7.12-23.3, p<0.001, Table 4.4).

TNAs of probable carotid territory origin, such as atypical amaurosis fugax and limb shaking episodes, only occurred prior to definite carotid events. Of 809 patients with definite carotid territory events, 87 (10.8%, 8.6-13.0) had at least one TNA/TIA within the preceding 90 days (median=7.0 days) of which 45 (51.7%) fulfilled the NINDS criteria for TIA (Table 4.4). Most TNAs prior to carotid events occurred before minor stroke (52%, 22/42).

Table 4.4. TNA/TIA in 90 days preceding definite event by territory

	Definite events			
	Vertebrobasilar n=308	Carotid n=809	OR (95% CI)	p
Event in preceding 90 days				
Carotid territory TNA[1]	0	9 (1.1)	0 (0-1.11)	0.07
VB territory TNA[2]	57 (18.5)	14 (1.7)	**12.9 (7.12-23.3)**	**<0.001**
Uncertain territory TNA[3]	13 (4.2)	19 (2.3)	1.83 (0.91-3.71)	0.11
Definite TIA	9 (2.9)	45 (5.6)	0.51 (0.25-1.04)	0.09
No TIA/TNA	229 (74.4)	722 (89.2)	0.35 (0.25-0.49)	<0.001

1. Atypical amaurosis fugax, Limb shaking/low flow

2. Isolated vertigo, Vertigo plus other symptoms, Isolated double vision, Transient generalized weakness, Binocular visual disturbance

3. Isolated slurred speech, Migraine variant, Transient confusion, Isolated hemi-tingling

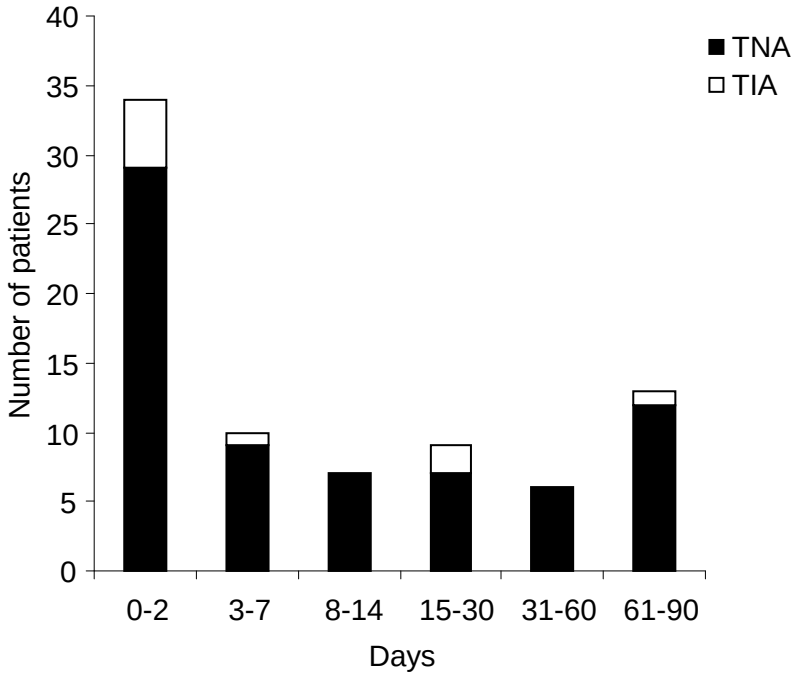
The majority of TNAs occurred in the 2 days prior to a definite ischaemic event (40/112, 36%) and the temporal relationship between TNA and definite ischaemic events was similar to that of TIA and definite events (Figure 4.1). Of those with TIAs/TNAs prior to definite VB events, few (13/79, 16%) sought medical attention after the TNA, of these over two thirds (9/13, 69%) had vertigo as a symptom. The other 4 cases were isolated double vision, binocular visual disturbance, isolated slurred speech and transient confusion. A vascular cause was suspected in only 2 cases (isolated slurred speech and vertigo with facial droop), in the remainder the diagnoses at time of seeking medical attention was documented as peripheral vestibular disturbance (3), postural hypotension (3), sepsis (2), migraine (2), cranial nerve palsy (1).

13/70 (16.5%) cases had multiple TNAs prior to definite VB events, in whom vertigo was the most common TNA (7/13, 54%). In all 7 cases, the vertigo occurred suddenly and without provocation, unlike the pattern characteristic of benign paroxysmal, positional vertigo. Binocular visual disturbance was also common in those with multiple TNAs prior to VB events (4/13 cases).

Among 180 patients (58%) with definite VB territory events who had VB arterial imaging, preceding TNAs were particularly associated with the presence of ≥50% symptomatic stenosis (27/72 vs 23/108, OR=2.21, 1.15-4.28, p=0.03) (Table 4.5).

Figure 4.1. Distribution of time from TIA/TNA to definite events in those with TIA/TNA in preceding 90 days

a) Vertebrobasilar events



b) Carotid events

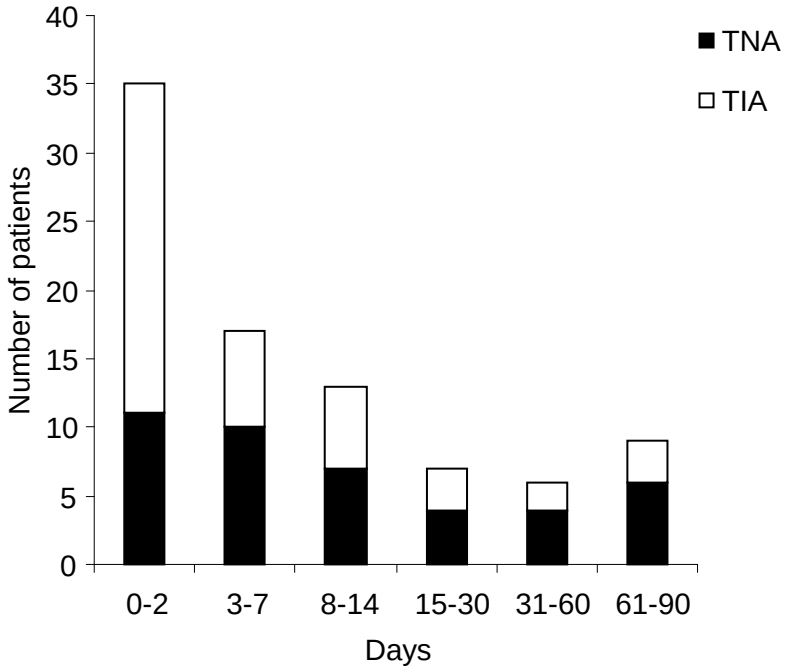


Table 4.5. Presence of VB stenosis and TNA within preceding 90 days in those with definite VB events and VB imaging, n=180

	Definite VB event n=180			
	No stenosis	Stenosis	OR (95% CI)	p
Nature of preceding event				
NINDS TIA	1 (0.9)	5 (6.9)	7.99 (1.20-52.4)	**0.038**
TNA	23 (21.3)	27 (37.5)	**2.21 (1.15-4.28)**	**0.027**
No TIA/TNA	84 (77.8)	40 (55.6)	0.36 (0.19-0.68)	**0.002**
Total	108 (100)	72 (100)		

Of 776 patients (96%) with definite carotid events who had carotid arterial imaging, preceding TNAs were associated with the presence of ≥50% symptomatic stenosis (12/95 vs 28/681, OR=3.37, 1.67-6.81, p=0.002) (Table 4.6).

Table 4.6. Presence of ≥50% symptomatic internal carotid artery stenosis and TNA within preceding 90 days in those with definite carotid events and carotid imaging, n=776

	Definite carotid event n=776			
	No stenosis	Stenosis	OR (95% CI)	p
Nature of preceding event				
NINDS TIA	27 (4.0)	17 (17.9)	5.27 (2.78-10.0)	**<0.001**
TNA	28 (4.1)	12 (12.6)	**3.37 (1.67- 6.81)**	**0.002**
No TIA/TNA	626 (91.9)	66 (69.5)	0.20 (0.12-0.33)	**<0.001**
Total	681 (100)	95 (100)		

4.4 Discussion

The high early risk of recurrence after VB TIA and minor stroke and the association between ≥50% symptomatic VB stenosis and multiple TIAs at presentation has been shown in previous studies.[14,15] This study adds information on patients with definite VB TIA or stroke, in whom preceding transient isolated “brainstem” symptoms occurred in 26%, with vertigo being the most common. Despite this close temporal link and the association with ≥50% symptomatic VB stenosis, only 11% of preceding events satisfied the NINDS definition of TIA.

In this study, 26% of patients with VB events had preceding isolated brainstem symptoms within 90 days. Even including the 9 cases that could be considered as TIAs, the proportion of TNAs that would satisfy the NINDS definition of TIA is still low. That 89% of warning events may be missed by current diagnostic criteria provides support for broadening the definition of posterior circulation TIA.

However, I also found that most patients with such symptoms fail to present to medical attention at the onset of such symptoms but present only after a further more disabling event. Therefore public education to improve recognition and awareness of the significance of such symptoms may be needed.

In those who did present to medical attention, most were not managed as vascular events. It may be that a broader TIA definition including such cases would aid recognition and diagnosis of these episodes so that the opportunity to prevent a disabling recurrence is not lost. Since these cases may not be identified by TIA triage scoring systems such as the ABCD2 score, my data may also help in risk stratification.

In those with TNAs prior to VB events, isolated vertigo was the most common symptom, occurring in 8% in the 90 days prior to the event. A prospective study of patients hospitalized with isolated vertigo found a threefold increase in stroke risk compared with controls up to 4 years after hospital discharge.[16] A retrospective study of patients with vertigo identified from MRI requests performed after emergency department attendance found 9.2% had acute stroke. Gait instability and subtle neurological examination findings were associated with increased stroke risk.[17] Studies using MRA or catheter angiography have found that isolated vertigo can be the only manifestation of vertebrobasilar ischaemia.[17-19] In a study of 29 hospitalised patients with VB TIA, isolated vertigo was present in 21%.[18] Other studies have found an increased cardiac risk in patients with TNAs, it has been suggested this may indicate that symptoms may be due to cardiac dysfunction rather than cerebrovascular disease.[8] In this study, the close temporal relationship between vertigo and definite VB events suggests that it is likely these TNAs are secondary to verterobasilar ischaemia.

The main strengths of the present study are its population-based design, rigorous ascertainment and follow-up. The possibility of selection and misclassification bias was minimised since all patients presenting for medical attention in the study population were prospectively recruited, and preceding TNA symptoms were assessed by assessors blinded to the study hypotheses.[11,12] However, this study has also limitations. First, the prevalence of TNAs prior to events may be inaccurate since some TNAs may have been missed if patients failed to report them during direct questioning and recall bias could have increased recollection and reporting of TNAs. I may have missed TNAs in patients who were unable to give a clear history due to aphasia or reduced consciousness after an event. Second, I may have attributed territory incorrectly since distinguishing clinically between carotid and VB events can be difficult and intra-observer agreement between neurologists is only moderate.[3] However, all cases were assessed by a neurologist and later reviewed by a study neurologist. Third, by looking only at

the 90 days prior to definite events, I have not included all those with TNAs but only those that sought medical attention and were referred. Some patients with TNA may never present to medical attention, and of those that do present, not all will be referred to a specialist clinic, therefore my findings may only be applicable to patients seen in general practice and then referred as possible ischaemic events. A previous study of TNAs referred to clinic suggested that GPs seeing patients with TNAs tend to refer those with vascular risk factors to a specialist neurology clinic leading to a referral bias.[20] Since the prevalence of TNAs in the OXVASC study population is not known, I am unable to provide an estimate of stroke risk after all TNAs. Fourth, by including only those TIAs with ≥50% stenosis I may have overestimated the relationship between TNAs prior to definite events and VB stenosis. However, when patients with TIA were excluded the relationship between prior TNA and VB events remained.

In conclusion, this sub-study shows a temporal relationship between vertebrobasilar events and preceding TNAs. Many patients with TNA do not present to medical attention and those that do may not be assessed urgently as they do not satisfy the NINDS definition of TIA. Improvements in public education and broadening of the definition of posterior circulation TIA may improve access to secondary prevention in those with isolated brainstem symptoms.

A high index of suspicion on the part of clinicians will also improve diagnosis of these patients. This is particularly important given the short time window available for prevention of disabling recurrence.[14] It also has implications for the type of patients that could be included in secondary prevention trials, such as trials of vertebral artery stenting[21] as these trials will need a high number of patients to establish the effect of treatment over standard medical care. Further prospective studies of TNAs are needed to establish reliable estimates of stroke risk and the particular clinical features, such as the type of vertigo, associated with increased stroke risk.

4.5 References

1. Schulz U, Briley et al Diffusion-weighted MRI in 300 patients presenting late with subacute transient ischaemic attack or minor stroke. Stroke 2004;35:2459-2465
2. Schulz U, Briley D et al Abnormalities on diffusion weighted magnetic resonance imaging performed several weeks after a minor stroke or transient ischaemic attack. JNNP 2003;74:734-738
3. Kraaijeveld CL, van Gijn J, Schouten HJ, Staal A. Interobserver agreement for the diagnosis of transient ischemic attacks. Stroke 1984;15:723-5.
4. Flossmann E, Redgrave JN, Briley D, Rothwell PM. Reliability of clinical diagnosis of the symptomatic vascular territory in patients with recent transient ischemic attack or minor stroke. Stroke 2008;39:2457-60.
5. The Ad Hoc Committee on the classification and outline of cerebrovascular disease II. Stroke 1975;6:566-616.
6. Kerber KA, Brown DL, Lisabeth LD, Smith MA, Moregenstern LB. Stroke among patients with dizziness, vertigo and imbalance in the emergency department. Stroke 2006;37:2484-2487.
7. Grimley Evans J. Transient neurological dysfunction and risk of stroke in an elderly English population: The different significance of vertigo and non-rotatory dizziness. Age and ageing 1990;19:43-49.
8. Koudstaal PJ, Algra A, Pop GAM, Kappelle LJ, van Latum JC, van Gijn J. Risk of cardiac events in atypical transient ischaemic attack or minor stroke. Lancet 1992;340:630-33.
9. Bos MJ, van Rijn MJE, Witteman JCM, Hofman A, Koudstaal PJ, Breteler MMB. Incidence and prognosis of transient neurological attacks. JAMA 2007;298:2877-2885.
10. Rothwell PM and Warlow CP. Timing of TIAs preceding stroke: time window for prevention is very short. Lancet 2005;366:29-36

11. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363(9425):1925-1933.
12. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE 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). Lancet 2005;366:1773-83.
13. Brott T, Adams HP Jr., Olinger CP, Marler JR, Barsan WG, Biller J et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864-70.
14. Flossmann E, Rothwell PM. Prognosis of vertebrobasilar transient ischaemic attack and minor stroke. Brain 2003;126:1940-1954
15. Marquardt L, Kuker W, Chandratheva A, Geraghty O, Rothwell PM. Incidence and prognosis of ≥50% symptomatic vertebral or basilar artery stenosis: prospective population-based study. Brain 2009;132:982-988.
16. Lee C-C, Su Y-C, Ho H-C, Hung S-K, Lee M-S, Chou P, Huang Y-S. Risk of stroke in patients hospitalized for isolated vertigo-a four year follow-up study. Stroke 2011;42:48-52.
17. Chase M, Joyce NR, Carney E, Salciccioli JD, Vinton D, Donnino MW, Edlow JA. ED patients with vertigo: can we identify clinical factors associated with acute stroke? Am J Emerg Med. 2011 Apr 25. [Epub ahead of print]
18. Gomez CR, Cruz-Flores S, Malkoff MD, Sauer CM, Burch CM. Isolated vertigo as a manifestation of vertebrobasilar ischaemia. Neurology 1996;47:94-97
19. Moubayed SP and Saliba I. Vertebrobasilar insufficiency presenting as isolated positional vertigo or dizziness: a double-blind retrospective cohort study. Laryngoscope 2009; 119:2071-2076
20. Dennis M, Warlow C. Migraine aura without headache: transient ischaemic attack or not? JNNP 1992;55:437-440

21. St George's, University of London. Vertebral artery ischaemic stenting trial study protocol. http://www.vist.sgul.ac.uk/vist-protocol-version-4.0-02dec09.pdf. Accessed September 16th 2011

CHAPTER 5

Utility of FAST test in prediction of early stroke risk after TIA and minor ischaemic stroke: implications for public education

5.1 Introduction 105

5.2 Methods 106

5.2.1 Analysis 107

5.3 Results 108

5.3.1 FAST and 7-day recurrent stroke risk 111

5.3.2 FAST and 90-day recurrent stroke risk 115

5.3.3 FAST in those who did not seek medical attention at the time of event ..115

5.3.4 FAST in those who delayed seeking medical attention 115

5.4 Discussion 120

5.5 References 123

5.1 Introduction

The reduction in recurrent stroke risk that can be achieved by early use of secondary prevention after TIA and minor ischaemic stroke (MIS) is dependent on patients seeking medical attention promptly. However, 30% of patients delay seeking medical attention for over 24 hours and around 30% of early recurrent strokes occur after a TIA or MIS for which attention was not sought.[1] The advent of thrombolysis and acute stroke units has driven the effort to improve knowledge of stroke among the general public and at risk populations[2-6] to reduce delays in seeking medical attention after symptom onset.[7-10] Even though high risk patients tend to contact medical services more quickly, likely due to the influence of weakness and duration of symptoms on behaviour, failure to seek medical attention urgently could account for a treatment gap in up to 1/3 of patients with TIA. Educational campaigns have focussed on symptom recognition and urgency in seeking medical attention. The face arm speech test (FAST) is a clinical, stroke recognition tool with high sensitivity that has been validated in pre-hospital and acute hospital settings.[11-13] A positive FAST requires the presence of one of unilateral face weakness (F), arm weakness (A) or speech difficulty (S) and patients are advised to call emergency services (T). The test is quick, easy to use and has been part of national public awareness campaigns in the UK since 2005 (Figure 5.1).[14] An 18-month nationwide campaign was launched on 6/10/2005 with posters on public transport and wallet-cards.[14] The campaign was revised in 2009 with the T in FAST standing for 'time to call 999' rather than 'test all 3'. National television advertisements ran for six weeks from 9/2/2009-30/3/2009.[14] FAST was designed primarily to identify major stroke in order to facilitate acute treatment. However, it is uncertain how well the test identifies those with TIA and minor stroke, particularly those with a high early risk of stroke in whom acute prevention is required. Furthermore, whether FAST could encourage those who do not present and those who delay seeking medical attention to present more quickly is not known. To determine the utility of FAST in patients with TIA and MIS, I modelled FAST in those who did

and did not present within 24 hours and determined the early stroke risk in a population based study in Oxfordshire, UK (Oxford Vascular Study).

Figure 5.1 Act FAST stroke awareness poster[14]



5.2 Methods

This study was nested within the Oxford Vascular Study (OXVASC), a prospective, population based study of all acute vascular events, including stroke and TIA in approximately 91,000 individuals of all ages registered with 63 general practitioners in Oxfordshire, UK. I included the first 1000 consecutive incident and recurrent TIA cases, (April 2002 to August 2011) and 775 MIS cases (April 2002 to March 2010). The OXVASC study methods have been described in

chapter 1 and elsewhere.[15-16] Briefly, multiple overlapping methods of “hot” and “cold” pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke.[15-17]

All patients were consented and seen by study physicians as soon as possible after initial presentation. Baseline characteristics, demographic data, risk factors, and symptomatology were recorded in all patients. All patients presenting with stroke were asked about recent symptoms of TIA. The FAST test was applied to symptoms of the first TIA or MIS. In patients with multiple TIAs, the most recent event prior to presentation was studied. MIS was defined as a focal neurological deficit lasting greater than 24 hours of ischaemic origin and an NIHSS score ≤5 at time of assessment by a study physician. Vascular territory (carotid or vertebrobasilar) was assigned by using the NINDS criteria applied to clinical features of the event.[18] Patients were followed up face-to-face at 30-days, 6 months, 1 year and 5 years by a study nurse or physician, recurrent symptoms were recorded. All recurrent events that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. All patients with recurrent events were reassessed by a study physician and reviewed by the senior study neurologist. Aetiological classification of events was performed according to the TOAST classification once investigations were complete.[19]

5.2.1 Analysis

I restricted analysis to the risk of recurrent stroke after the first TIA or MIS in the study period (index event). I analysed the risk of recurrent stroke within 7 and 90 days of the index event, including patients who did not seek medical attention for their first event but presented after a recurrent TIA or stroke. In patients who presented with recurrent TIAs, the 7-day stroke risk was determined in relation to the second TIA. A recurrent stroke was defined as a new, persistent neurological symptom in a patient in whom the initial symptoms had already substantially or fully recovered. The 7-day recurrent stroke risk was determined in relation to FAST result, duration of

TIA and TOAST subtype using Kaplan–Meier analysis.

5.3 Results

The baseline characteristics of 1775 patients (1000 TIA and 775 MIS) are shown in Table 5.1. Median age was 72.9 years, 625 cases (35.2%) were over 80 years. FAST was positive in 1044 cases (58.8%, 539 TIA and 505 MIS). The 'speech' component of the score identified the most events, being positive in 39.4% versus 31.1% for the 'arm' component and 19.7% for the 'face' component. Vascular territory was determined in 1628 (91.7%) cases. FAST performed best in carotid territory events, being positive in 765/1089 (70.2%) but identified only 186/538 (34.6%) of vertebrobasilar (VB) territory events (Table 5.2). A negative FAST was four times more likely after a VB event than after a carotid event (352/538, 65.4% vs 324/1089, 29.8%, OR 4.47 (3.6-5.6), $p<0.0001$). Almost half of FAST negative TIAs affected the VB territory (352/731, 48.2%). A positive FAST was associated with ABCD2≥4 and cardioembolic subtype ($p<0.0001$, Table 5.2).

Table 5.1: Baseline characteristics of all patients with TIA, n =1000 and MIS, n=775

		TIA, n=1000 (%)	MIS n=775 (%)
Age (mean (SD))		72.3 (13.4)	73.5 (12.7)
Male Sex		473 (47.3)	394 (50.8)
Hypertension		456 (45.6)	444 (57.2)
Diabetes		134 (13.4)	97 (12.5)
Angina or myocardial infarction		181 (18.1)	157 (20.2)
Peripheral vascular disease		47 (4.7)	60 (7.7)
Atrial fibrillation		156 (15.6)	130 (16.8)
Current Smoker		126 (12.6)	108 (13.9)
Previous TIA		129 (12.9)	58 (7.5)
Previous stroke		94 (9.4)	111 (14.3)
Prior antiplatelet		377 (37.7)	318 (41.0)
Prior statin		248 (24.8)	174 (22.4)
Prior antihypertensive		539 (53.9)	441 (56.8)
TOAST	UND	469 (46.9)	261 (33.7)
	CE	158 (15.8)	149 (19.2)
	LAA	136 (13.6)	83 (10.7)
	SVD	109 (10.9)	151 (19.5)
	MULT/UNK/OTHER	128 (12.8)	131 (16.9)
FAST positive		539 (53.9)	505 (65.2)
Carotid territory		611 (61.1)	478 (61.6)
Vertebrobasilar territory		310 (31.0)	228 (29.4)

Table 5.2. Vascular territory, ABCD2 score and TOAST subtype of all patients with TIA and MIS by FAST (n=1775)

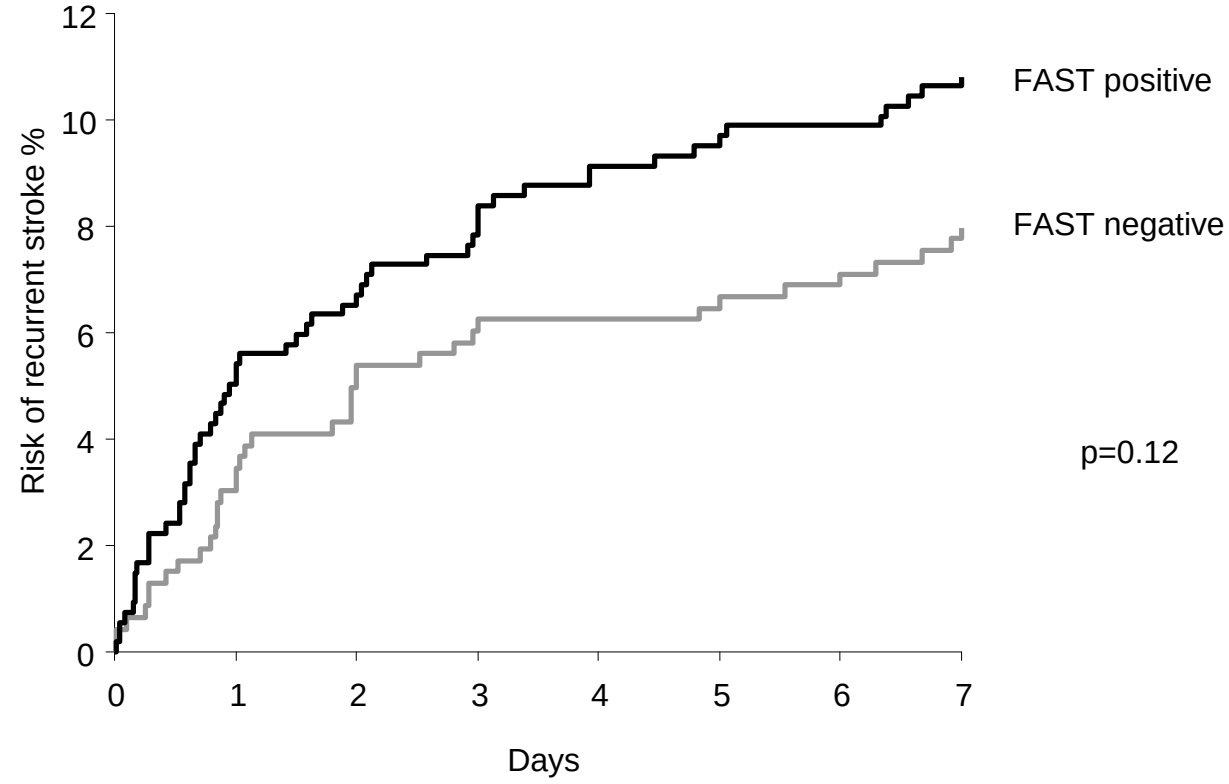
	FAST positive n=1044	FAST negative n=731	OR (95% CI)	p
Territory				
Carotid	765 (73.3)	324 (44.3)	3.44 (2.81-4.23)	**<0.0001**
Vertebrobasilar	186 (17.8)	352 (48.2)	0.23 (0.19-0.29)	**<0.0001**
Unknown	93 (8.9)	55 (7.5)	1.20 (0.84-1.73)	0.34
ABCD2<4	92 (17.1)	319 (69.2)	0.09 (0.07-0.13)	**<0.0001**
ABCD2≥4	447 (82.9)	142 (30.8)	10.9 (8.1-14.4)	**<0.0001**
TOAST				
CE	209 (20.0)	98 (13.4)	1.62 (1.24-2.12)	**<0.0001**
LAA	126 (12.1)	93 (12.7)	0.94 (0.70-1.27)	0.71
SVD	166 (15.9)	94 (12.9)	1.28 (0.97-1.70)	0.08
UND	381 (36.5)	349 (47.7)	0.62 (0.52-0.77)	**<0.001**
UNK	106 (10.2)	66 (9.0)	1.14 (0.8-1.59)	0.46
MULTIPLE/OTHER	56 (5.4)	31 (4.2)	1.28 (0.8-2.1)	0.32

5.3.1 FAST and 7-day recurrent stroke risk

At 7-days, 127 patients (95 TIA, 32 MIS) had a recurrent stroke (recurrence risk 7.2%, 95% CI 6.02-8.38). After FAST positive TIA, the 7-day recurrent stroke risk was 10.8 % (8.4-13.8, 58 cases) which was similar to the risk after FAST negative TIA (8.0% (5.3-10.2) 37 cases, p=0.12, Figure 5.2a). Similarly after MIS, there was no difference in 7-day recurrent stroke risk after FAST positive and negative events (21/505, 4.2% (2.2-5.8) vs 11/270, 4.1% (1.7-6.5), p=0.97, Figure 5.2b). After TIA and MIS, the sensitivity of FAST in predicting recurrent stroke at 7-days was 62.2% (53.1-70.7) and specificity was 41.4% (39.1-43.9). The positive predictive value (PPV) of FAST for predicting stroke at 7-days was 7.6% (6.0-9.3) and negative predictive value (NPV) was 93.4% (91.4-95.1).

After FAST positive TIA, the 7-day recurrent stroke risk increased with increasing duration of TIA (p=0.05, Figure 5.3). However, after FAST negative TIA, duration was not related to risk of recurrent stroke, even after very short events: those with TIAs lasting <1 minute had a similar recurrent stroke risk to those with duration >1 minute (2.7% (0-8.0) vs 8.0% (5.5-10.6), p=0.25).

Figure 5.2. 7-day risk of stroke by FAST after a) TIA, n=1000



b) MIS, n=775

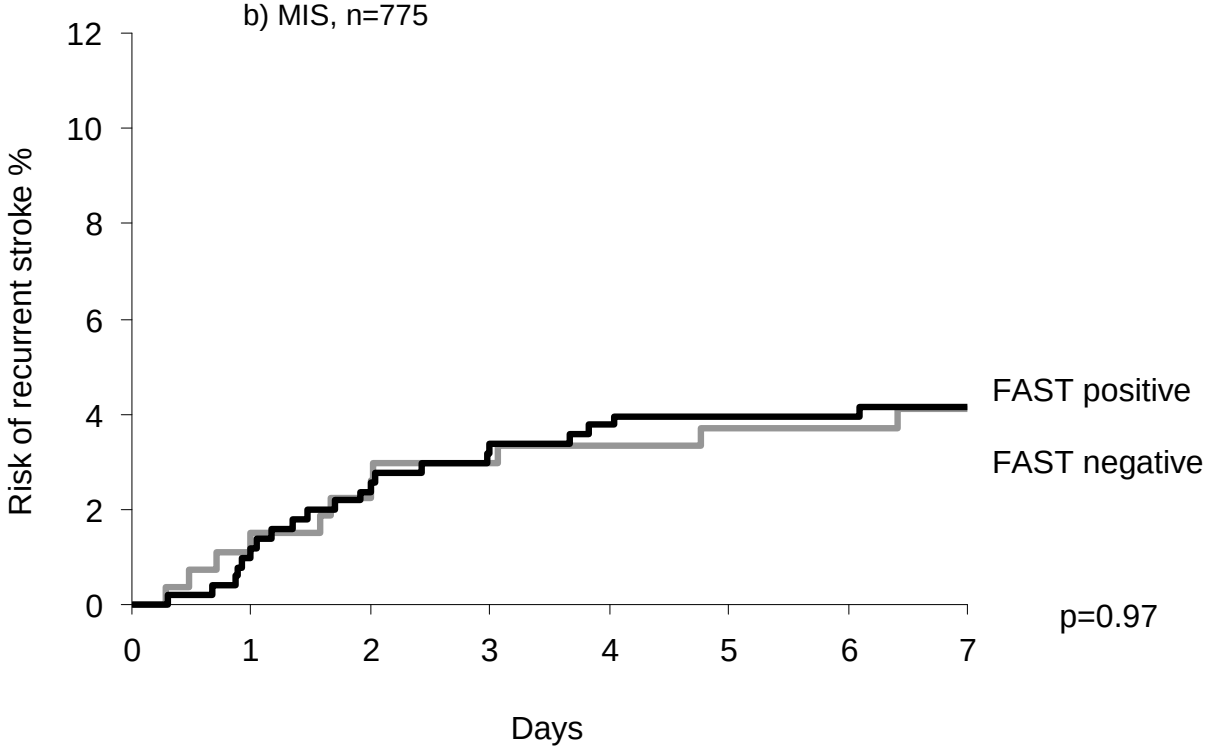
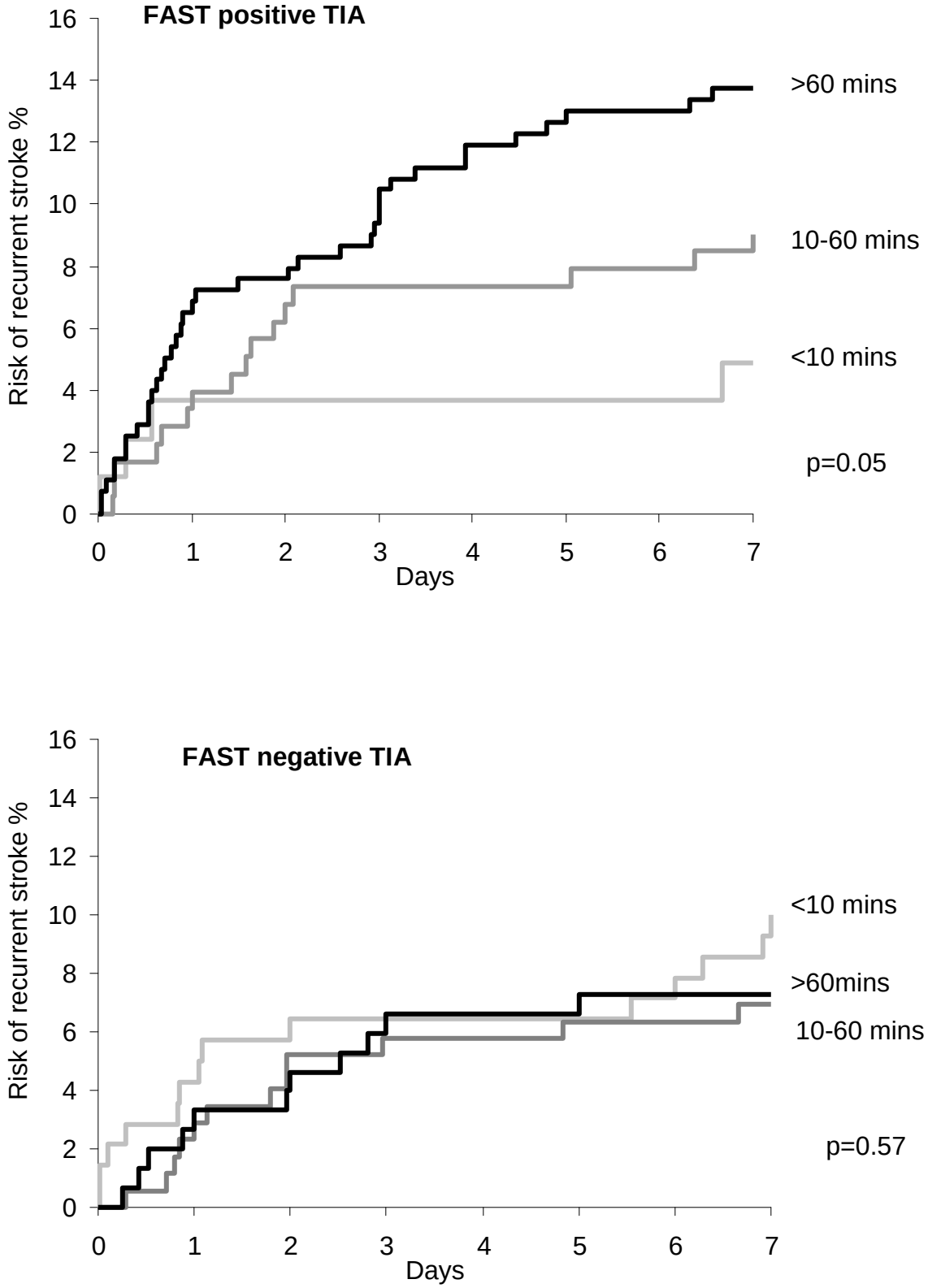
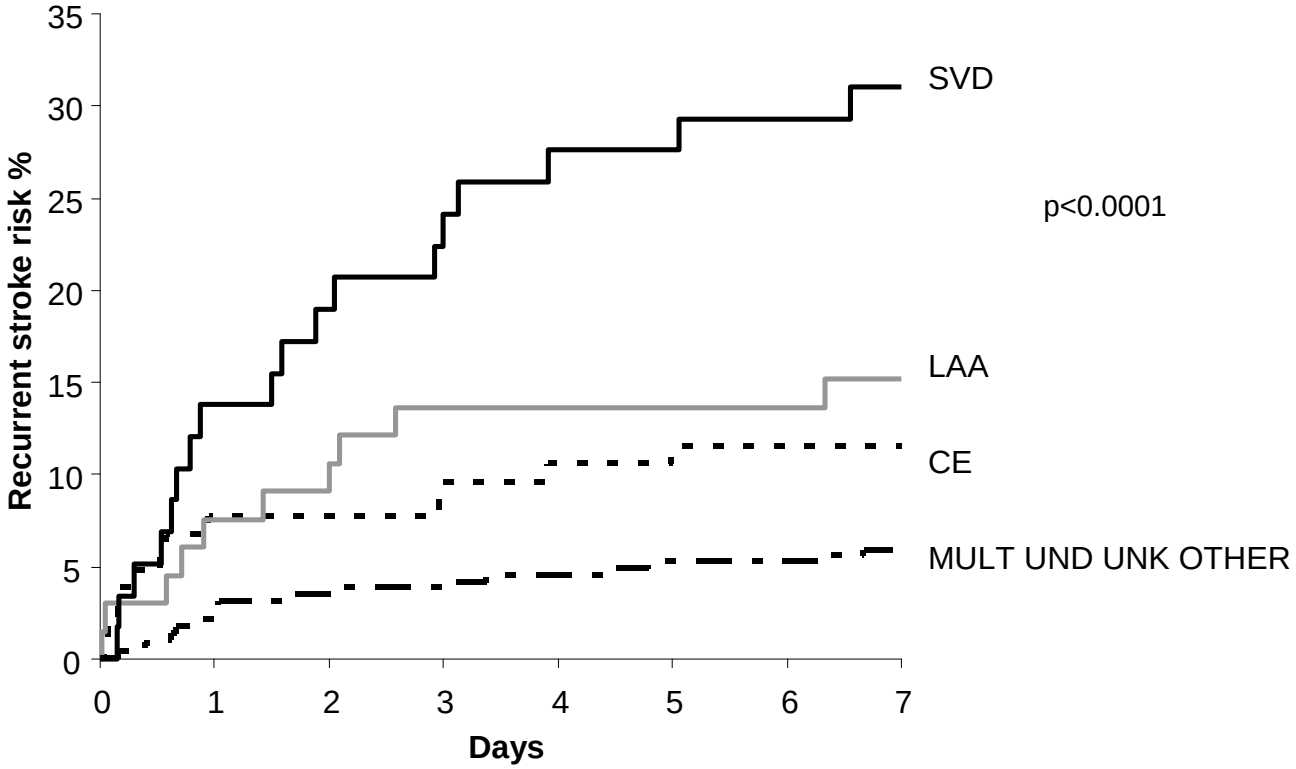


Figure 5.3. 7-day risk of stroke after TIA by FAST test and duration



After FAST positive TIA, the 7-day recurrent stroke risk was highest after TIA of SVD subtype (31% (19.0-43.0) vs 8.8% (6.3-11.3), p<0.0001, Figure 5.4). After FAST negative TIA, the 7-day recurrent stroke risk did not vary with stroke subtype.

Figure 5.4. 7-day risk of stroke after FAST positive TIA by TOAST



5.3.2 FAST and 90-day recurrent stroke risk

At 90 days after event onset, recurrent stroke risk was 11.8% (10.2-13.4, n=210) and risks were similar amongst those who were FAST positive and FAST negative (13% (11-15) vs 10.1% (7.9-12.3) p=0.07). After TIA and MIS, the sensitivity of FAST in predicting recurrent stroke at 90-days was 64.8% (57.8-71.2) and specificity was 42% (39.5-44.5). The PPV of FAST for predicting stroke at 90-days was 13.0% (11.0-15.2) and NPV was 89.9% (87.5-92.0).

5.3.3 FAST in those who did not seek medical attention at the time of event

Of 210 patients with recurrent stroke at 90-days, 81 (38.6%, 67 TIA, 14 MIS) did not seek medical attention at the time of event but presented only after the recurrent stroke. In these cases, the recurrent event was more likely to be a minor stroke than a major stroke (57/81 vs 54/129, p<0.0001, Table 5.3). Patients who did not seek medical attention at the time of initial event were more likely to be FAST negative (46/81 vs 685/1694, p=0.005), less likely to have speech symptoms (p=0.002) and had shorter duration TIAs (p=0.004, Table 5.3). Most of these differences were accounted for by patients with TIA who presented after the recurrent stroke (Table 5.3). From a crude modelling point of view, FAST had the potential to identify 35 patients who, in the best case scenario, would have presented if they had known, remembered and acted upon the FAST test. However, set against that, there are 46 patients who did not seek medical attention who were FAST negative who might have been falsely reassured by a negative FAST. It is likely that the number of patients falsely reassured by a negative FAST would have been small but this is important to acknowledge.

5.3.4 FAST in those who delayed seeking medical attention

One third of patients with TIA (309/933) delayed seeking medical attention >24 hours (Table

5.4). These cases were also less likely to be FAST positive ($p<0.0001$). However 68% (210/309) had TIA duration ≥10 minutes. For those who delayed >24 hours to present, the addition of duration ≥ 10 minutes to FAST would have identified an extra 108/309 (35.0%) TIAs. Therefore the inclusion of duration ≥10 minutes to a FAST positive test would have identified 76% of those who delayed > 24 hours to present to medical attention versus 41% identified by FAST alone.

There were 296 FAST negative patients (218 TIA, 78 MIS) who delayed seeking medical attention >24 hours or who presented only after a recurrent stroke (Table 5.5). The presenting symptoms in these cases were visual disturbance (141, 47.6%), sensory disturbance (28.4%), vertigo (15.5%), leg weakness (9.1%), transient confusion (2.7%) and dyspraxia (0.3%). Of those with TIA, 45/296 (20.1%) had an ABCD2 score≥4.

Table 5.3: Characteristics of patients who did not seek medical attention at time of TIA or MIS but presented after a recurrent stroke within 90-days

	TIA		MIS		Total		
	Presented after recurrent stroke n=67	Presented after TIA n=933	Presented after recurrent stroke n=14	Presented after MIS n=761	Presented after recurrent stroke n=81	Presented after TIA or MIS n=1694	p
Age (mean (SD))	70.3 (15.5)	72.4 (13.3)	70.9 (17.6)	73.6 (12.6)	70.3 (15.5)	72.4 (13.3)	0.21
Male Sex	35 (52.2)	438 (46.9)	5 (35.7)	389 (51.0)	40 (49.4)	827 (48.8)	1.0
FAST positive	28(41.8)	511 (54.8)	7 (50)	498 (65.4)	35 (43.2)	1009 (59.6)	**0.005**
Carotid territory	38 (56.7)	573 (61.4)	11 (78.6)	467 (67.4)	49 (60.5)	1040 (61.4)	0.91
Vertebrobasilar territory	23 (34.3)	287 (30.8)	3 (21.4)	226 (32.6)	26 (32.0)	513 (30.2)	0.71
Weakness	28 (41.8)	370 (39.8)	6 (61.0)	465 (61.0)	34 (42.0)	835 (49.3)	0.21
Speech difficulty	16 (23.9)	364 (39.0)	3 (21.4)	317 (41.6)	19 (23.5)	681 (40.2)	**0.002**
Sensory symptoms	15 (22.3)	213 (24.2)	4 (28.6)	213 (28.0)	18 (22.2)	426 (25.1)	0.60
Duration of TIA <10 minutes	25 (37.3)	197 (21.1)			25 (37.3)	197 (21.1)	**0.004**
≥10 minutes	42 (62.7)	736 (78.9)			42 (62.7)	736 (78.9)	**0.004**
Duration ≥10 minutes and FAST positive	22 (52.4)	432 (58.7)			22 (52.4)	432 (58.7)	0.43
Duration ≥10 minutes and FAST negative	20 (47.6)	304 (41.3)			20 (47.6)	304 (41.3)	0.43
Recurrent stroke at 90 days	67	70	14	59	81	129	
Minor stroke (NIH 0-3)	49 (73.1)	34 (48.6)	8 (57.1)	20 (33.9)	57 (70.3)	54 (41.9)	**<0.0001**
Major stroke (NIH>3)	18 (26.9)	36 (51.4)	6 (42.9)	39 (66.1)	24 (29.6)	75 (58.1)	**<0.0001**

Table 5.4. Characteristics of patients who presented to medical attention after TIA by delay to presentation, n=933

	Presented ≤24 hours n=624	Presented >24 hours n=309	p
Age (mean (SD))	70.2 (15.5)	72.4 (13.3)	0.21
Male Sex	292 (46.8)	146 (47.2)	0.94
FAST positive	381 (61.1)	130 (42.1)	**<0.0001**
Carotid territory, n=573	394 (69.1)	179 (61.7)	**0.03**
Vertebrobasilar territory, n=287	176 (30.9)	111 (38.3)	**0.03**
Weakness	295 (47.3)	75 (24.3)	**<0.0001**
Speech	274 (43.9)	90 (29.1)	**<0.0001**
Duration of TIA <10 minutes	98 (15.7)	99 (32.0)	**<0.0001**
≥10 minutes	526 (84.3)	210 (68.0)	**<0.0001**
FAST positive	332 (63.1)	102 (48.6)	**0.0003**
FAST negative	194 (36.9)	108 (51.4)	**0.0003**
ABCD2 ≥ 4	424 (68.1)	129 (41.7)	**<0.0001**

Table 5.5: Presenting symptoms of FAST negative patients who did not seek medical attention at time of event but presented after a recurrent stroke (39 TIA, 7 MIS) and of those with delay in seeking medical attention > 24 hours (179 TIA, 71 MIS)

	TIA or MIS presenting after recurrent stroke	TIA or MIS presenting after delay >24 hours	Total
Visual	14 (30.4)	127 (50.8)	141 (47.6)
Binocular visual disturbance	4 (8.7)	29 (11.6)	33 (11.1)
Visual field disturbance	5 (10.9)	16 (6.4)	21 (7.1)
Visual field loss	3 (6.5)	27 (10.8)	30 (10.1)
Amaurosis fugax	1 (2.2)	40 (16)	41 (13.9)
Diplopia	1 (2.2)	15 (6)	16 (5.4)
Sensory	14 (30.4)	70 (28)	84 (28.4)
Vertigo	10 (21.7)	36 (14.4)	46 (15.5)
Leg weakness	8 (17.4)	19 (7.6)	27 (9.1)
Transient confusion	0	8 (3.2)	8 (2.7)
Dyspraxia	0	1 (0.4)	1 (0.3)
Total	46	250	296

5.4 Discussion

This study shows that FAST does not reliably identify patients with TIA or MIS at high early risk of recurrent stroke. The sensitivity for predicting stroke at 7-days was 62% and specificity was 41%, the PPV was very low at 7.6%.

The FAST test was developed in 1998 based on the Cincinnati Pre-Hospital Stroke Scale.[20] It was designed for use by paramedics as a screening tool to identify patients with major stroke to be transported quickly to hospital.[11,12] It is quick, simple to use and has good inter-observer reliability.[12] It has become part of public education campaigns in the UK to improve awareness of stroke symptoms and to encourage people to seek medical attention promptly. Patients with TIA and MIS may not require thrombolysis however urgent medical attention is needed to access investigation and early secondary prevention. In this study, 39% of patients with a stroke at 90 days after TIA or MIS did not present at the time of the initial event but only sought medical attention after a recurrent stroke. These patients were less likely to be FAST positive, therefore such patients although at high risk, may not be encouraged to seek help by current campaigns.

I found the 7-day and 90-day recurrent stroke risks after FAST negative TIA or MIS to be just as high as risks after FAST positive events. Whilst FAST is good at identifying major disabling stroke and directing patients towards thrombolysis, one unintended consequence of the FAST campaign is that patients with TIA and minor stroke may be falsely reassured by resolving symptoms or a negative result and may not present to medical attention. Current media campaigns imply that FAST negative events are low risk when in fact the risk is just as high. It has previously been shown that FAST performs poorly in identifying posterior circulation events.[13] A study of stroke symptoms that prompt a call to emergency services found that weakness, speech/language difficulty, confusion/decreased level of consciousness, headache,

dizziness, vertigo or in-coordination increased the odds of a 911 call.[21] Whereas, numbness and visual changes were less likely to result in a 911 call.[21] The authors concluded that the public appear to respond differently based on the type of stroke symptoms and that numbness and visual symptoms may need to form part of public educational campaigns.[21] However, the advantages of FAST are that it is a quick, easily memorable mnemonic that can be used by patients and witnesses and incorporates action. Adding extra features to the test may limit its acceptability, memorability and therefore its usefulness. The addition of visual symptoms and duration≥10 mins to FAST could identify more of those at high risk of recurrence. For example, a FAST-ER test could be used where E= eye/visual symptoms and R=remaining symptoms >10 minutes but this might cause those with stroke to delay > 10 minutes before seeking help. Such a mnemonic may also be less memorable and has the disadvantage of being less specific, identifying more stroke mimics. As I have shown that patients with FAST positive TIA and those with FAST negative TIA lasting >10minutes are at similarly high risk of recurrent stroke, ideally both groups should be directed to seek urgent medical attention. Patients with FAST positive lacunar type TIA are at particularly high risk and providers of secondary care should be aware of this high risk group.

A previous population-based study found that FAST identified 89% of 3824 patients with TIA and stroke and 92% of those with ischaemic events.[22] However, this study included numbness as a symptom within the FAST test.[22] If numbness was excluded, FAST identified 83% of patients. The impact of excluding numbness was greatest for TIA, where 21% cases would be missed by FAST. In their study, the 30-day mortality in those who were FAST negative was similar to those who were FAST positive (9.0% vs 11.6%, p=0.15) which supports my finding that patients missed by FAST do not have a benign outcome.[22] A cross-sectional study of 170 consecutive hospitalised stroke cases (median NIHSS=5) found that FAST identified 84% cases.[23] Of the 16% FAST negative cases in their study, the most common symptom was leg weakness

(50%).[23] The authors proposed 'FLASH' (Face, Leg, Arm, Hospital) as an alternative acronym.[23]

This study has some limitations. First, I may have overestimated the recurrent stroke risk in those with FAST negative TIA. The true denominator of patients with short duration, FAST negative symptoms who do not present to medical attention is unknown and is likely to be higher than those with FAST positive symptoms who generally do seek medical attention. Second, much of my study was conducted prior to the introduction of FAST into public education campaigns, therefore I looked at the potential of the test rather than its actual use. Third, although I have shown the FAST test is poor predictor of early stroke risk after TIA and MIS, it was not designed for this purpose. However, I feel my conclusions are valid and relevant since the campaign may have unintended consequences in this population. As I have shown in chapter 2, the proportions of patients with correct recognition of their symptoms declined in 2007-2009. The proportion of patients seeking medical attention within 3 hours also declined in 2007-2009. Further work is needed to determine if this could potentially be an unintended consequence of the FAST campaign. Fourth, although patients were asked whether they had face, arm or speech symptoms at event onset, the test was not performed at presentation. However, by using the FAST result from reported symptoms, we have shown the risk predicted by the test in the best case scenario, as many patients with a positive FAST would not have realised or acted upon the result. Fifth, my study has only looked at the impact of the FAST campaign one year after the television (TV) campaign was introduced in February 2009, which may be too soon to see the effects. Although the impact of TV advertising is maximal in the first year, its impact on patient behaviour will need to be monitored in further studies.

In summary, the FAST does not reliably identify patients with TIA or minor stroke who are at high early risk of recurrent stroke and has limited potential to improve access to care after TIA and minor ischaemic stroke.

5.5 References

1. Chandratheva A, Lasserson DS, Geraghty OC, Rothwell PM. Population-based study of behaviour immediately after transient ischaemic attack and minor stroke in 1000 consecutive patients: lessons for public education. Stroke 2010;41:0-7
2. Pancioli AM, Broderick J, Kothari R, Brott T, Tuchfarber A, Miller R, et al. Public perception of stroke warning signs and knowledge of potential risk factors. JAMA 1998;279(16):1288-92.
3. Parahoo K, Thompson K, Cooper M, Stringer M, Ennis E, McCollam P. Stroke: awareness of the signs, symptoms and risk factors--a population-based survey. Cerebrovasc Dis 2003;16(2):134-40.
4. Reeves MJ, Hogan JG, Rafferty AP. Knowledge of stroke risk factors and warning signs among Michigan adults. Neurology 2002;59(10):1547-52.
5. Carroll C, Hobart J, Fox C, Teare L, Gibson J. Stroke in Devon: knowledge was good, but action was poor. J Neurol Neurosurg Psychiatry 2004;75(4):567-71.
6. Evenson KR, Rosamond WD, Morris DL. Prehospital and in-hospital delays in acute stroke care. Neuroepidemiology 2001;20(2):65-76.
7. Harraf F, Sharma AK, Brown MM, Lees KR, Vass RI, Kalra L. A multicentre observational study of presentation and early assessment of acute stroke. BMJ 2002;325(7354):17.
8. Lacy CR, Suh DC, Bueno M, Kostis JB. Delay in presentation and evaluation for acute stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (S.T.R.O.K.E.). Stroke 2001;32(1):63-9.
9. Salisbury HR, Banks BJ, Footitt DR, Winner SJ, Reynolds DJ. Delay in presentation of patients with acute stroke to hospital in Oxford. QJM 1998;91(9):635-40.
10. Smith MA, Doliszny KM, Shahar E, McGovern PG, Arnett DK, Luepker RV. Delayed hospital arrival for acute stroke: the Minnesota Stroke Survey. Ann Intern Med 1998;129(3):190-6.
11. Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians and ambulance staff using the face arm speech test. Stroke 2003;34:71-76
12. Nor AM, McAllister C, Louw SJ et al. Agreement between ambulance paramedic-and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. Stroke 2004;35:1355-9

13. Whitely WN, Wardlaw J, Dennis M, Sandercock PG. Clinical scores for the identification of stroke and transient ischaemic attack in the emergency department: a cross-sectional study. JNNP 2011; online doi:10.1136/jnnp2010.235010
14. http://www.nhs.uk/actfast. Accessed September 20th 2011.
15. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363(9425):1925-33.
16. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, 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). Lancet 2005;366(9499):1773-83.
17. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke 2004;35(9):2041-5.
18. The Ad Hoc Committee on the classification and outline of cerebrovascular disease II. Stroke 1975;6:566-616.
19. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL 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;24:35-41
20. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati prehospital stroke scale: reproducibility and validity. Ann Emerg Med. 1999; 33:373–378.
21. Kleindorfer D, Lindsell CJ, Moomaw CJ, Alwell K, Woo D, Flaherty ML, Adeoye O, Zakaria T, Broderick JP, Kissela BM Which stroke symptoms prompt a 911 call? A population-based study. Am J Emerg Med 2010;28 (5):605-12
22. Kleindorfer DO, Mille R, Moomaw CJ, Alwell K, Broderick JP, Khoury J et al. Designing a message for public education regarding stroke: does FAST capture enough stroke? Stroke 2007;38:2864-2868.
23. Bray JE, O'Connell B, Gilligan A, Livingston PM, Bladin C. Is FAST stroke smart? Int J Stroke 2010;5:440-446.

CHAPTER 6

Feasibility, safety and cost of outpatient management of TIA and acute minor ischaemic stroke: a population-based study

6.1 Introduction ……..126

6.2 Methods ……..126

6.2.1 Analysis ……..128

6.3 Results ……..129

6.4 Discussion ……..138

6.5 References ……..142

6.1 Introduction

Patients with TIA and minor stroke may be investigated and treated in the inpatient or outpatient clinic setting.[1,2] Since patients differ in terms of risk factors, co-morbidities, type of event and other demographic and clinical characteristics, it is important to select the most appropriate setting for the management of each patient in order to improve prognosis and limit costs. Secondary prevention delivered via rapid access outpatient clinics has been shown to be effective in patients with TIA, significantly reducing the risk of early recurrent stroke,[3,4] and is recommended in clinical guidelines.[5-13] However, for patients with minor stroke, whether outpatient secondary care is similarly safe is less clear. Prompt specialist assessment is recommended for those with non-disabling stroke at high early risk of recurrence but most guidelines do not specify in which setting this should be delivered,[6-11] some suggesting admitting all with minor stroke to hospital,[6,12,14] and others suggesting that outpatient assessment is an option.[5,13] I aimed to assess the clinical outcomes, early hospital admission rates, and hospital care costs in clinic-referred and hospital-referred minor stroke patients in a prospective, population based study of all incident and recurrent TIA and stroke in Oxfordshire, UK (Oxford Vascular Study).

6.2 Methods

The Oxford Vascular Study (OXVASC) is a prospective, population based study of all stroke and TIA in 91,105 individuals of all ages registered with 63 general practitioners in Oxfordshire, UK. The study methods have been described in chapter 1 and elsewhere.[15,16] Briefly, multiple overlapping methods of “hot” and “cold” pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke.[15,16] These include:

1) A daily (weekdays only), urgent open-access “TIA clinic” to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital, with alternative on-call review provision at weekends.

2) Daily searches of admissions to the stroke unit, medical, neurology and other relevant wards.

3) Daily searches of the local A&E and eye hospital attendance register.

4) Monthly computerised searches of GP diagnostic coding and hospital discharge codes.

5) Monthly searches of all cranial and carotid imaging studies performed in local hospitals.

6) Monthly reviews of all death certificates and coroners reports.

All patients were consented and seen by study physicians as soon as possible after their initial presentation. Baseline characteristics and time of first seeking medical attention were recorded in all patients. Assessments were made for severity of event using the National Institute of Health Stroke Scale (NIHSS)[17] and clinical features. Events were classified as minor stroke if there was a focal neurological deficit lasting more than 24 hours and an NIHSS score ≤3 at time of assessment by a study physician. Brain imaging (usually CT), carotid imaging and ECG were usually obtained on the same day or shortly thereafter. Trans-thoracic or trans-oesophageal echocardiography (when clinically indicated) were arranged during the following week. Patients with rehabilitation needs were referred for outpatient assessments when clinically indicated. All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA, stroke or other condition using standard definitions.[15] Aetiological classification of events was performed according to the TOAST classification once investigations were complete.[18] This sub-study includes all cases with events from the 1st April 2002 to 31st March 2007. Nested within OXVASC, the Early use of Existing Preventive Strategies for Stroke (EXPRESS) study evaluated the introduction of early assessment and treatment of patients in the daily TIA and minor stroke clinic.[4] The EXPRESS study intervention involved more urgent assessment and immediate treatment in

clinic from 1st October 2004- March 31st 2007.[4] Prior to this, treatment was initiated in primary care after clinic assessment. The treatment protocol for clinic patients has been described in chapter 1 and elsewhere.[4] In phase 2, all those who were considered to have had a TIA or stroke were given aspirin 300mg to take in the clinic. Those seen within 48 hours of the event or those seen within 7 days who were thought to be at particularly high risk were prescribed a loading dose of clopidogrel 300mg.[4] A CT brain scan was obtained during the clinic for patients with incomplete resolution of symptoms at the time of assessment to exclude intracerebral haemorrhage before giving aspirin, clopidogrel or anticoagulants.[4]

All patients were followed up face-to-face at 1 month, 6 month, 1 year and 5 years by a study nurse or physician. Recurrent symptoms, medications and any episodes requiring hospitalisation were recorded with reason for admission and length of hospital stay. All recurrent events requiring hospital admission would also be identified acutely by ongoing daily case-ascertainment within OXVASC. All patients with recurrent events were reassessed by a study physician and reviewed by PMR.

6.2.1 Analysis

I restricted analysis to patients with first TIA or stroke in the study period (index event) referred to secondary care. Cases presenting to non-OXVASC clinics (such as neurology or the eye hospital) were included as clinic treated cases. Those who had their event whilst out of the study area and were ascertained late after the event were excluded. Secondary prevention measures started after the index event were analysed, including prescription of anti-platelet, anticoagulant, lipid lowering and blood-pressure lowering medications and referral for carotid endarterectomy. As a measure of safety of the out-patient clinic, I analysed the risk of recurrent stroke and all hospitalisations up to 30 days after clinic assessment with reasons for admission including admission for recurrent stroke. Patients admitted directly from clinic due to worsening symptoms, recurrent stroke or need for

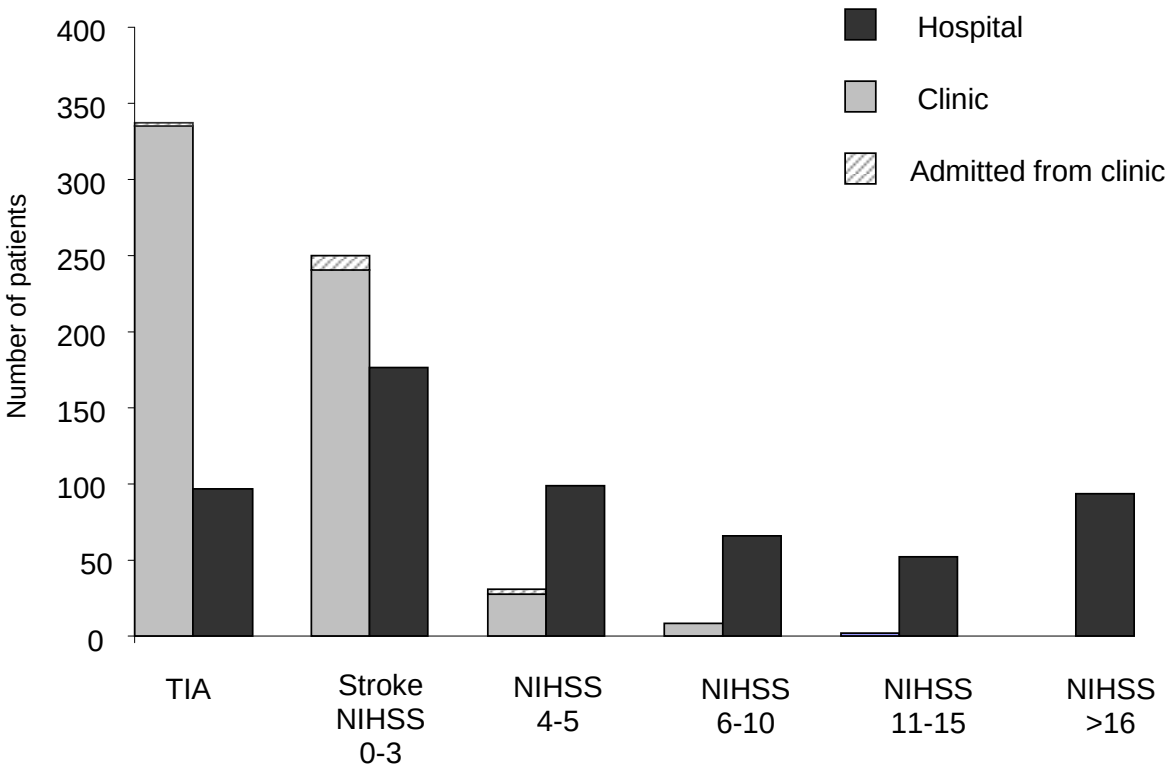
nursing care were analysed as clinic-referred cases since this was an appropriate use of the clinic. Patients who were admitted with a recurrent stroke before their clinic appointment were included as clinic-referred patients for the analysis. For those treated in hospital, readmission rates up to 30 days after discharge, reasons for re-admission and recurrent stroke rates were also analysed.

All admissions to hospital, day case assessments, and lengths of stay were recorded. Unit costs were obtained from national reference costs and calculated for each day spent in each specialty ward and each outpatient clinic appointment. Costs were standardised to 2008–09 prices by use of the UK National Health Service hospital and community health services inflation index to calculate the 30 day hospital care cost per patient. The daily TIA clinic cost was derived from UK National Institute for Health and Clinical Excellence guidelines on stroke and TIA management.[6] Although not directly comparable due to differences in measured and unmeasured characteristics, a regression analysis, with robust standard errors, was performed to assess whether clinic attendance was an independent predictor of reduced 30-day hospital care costs. Included as predictors were NIHSS score, history of AF, days to medical attention, and whether the patient was living alone. Due to the skewness in cost data, costs were logarithmically transformed. Predicted costs obtained from the regression were then retransformed using Duan's smearing estimator.

6.3 Results

Of 1293 patients with TIA and stroke who sought medical attention, 1213 (94%) were referred to secondary care (31 patients had their event on holiday and 49 were managed by their GP). The setting of secondary care delivery for each event type and event severity is shown in Figure 6.1.

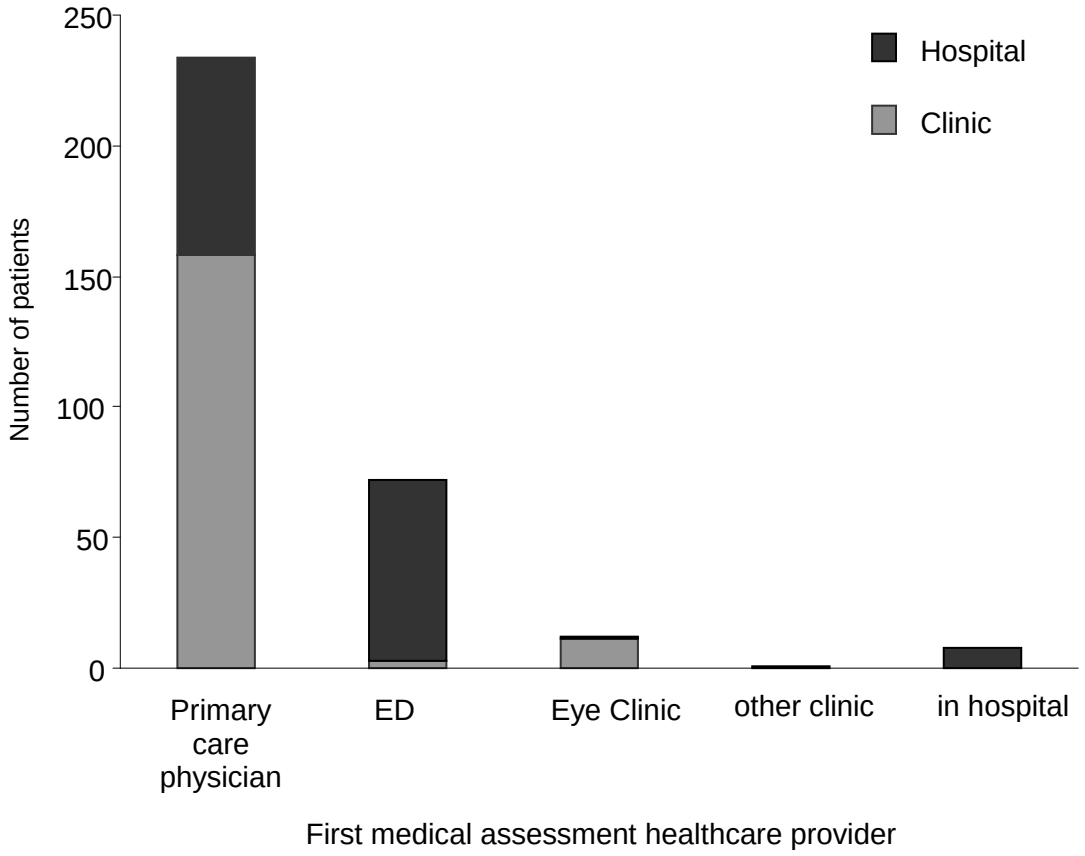
Figure 6.1. Distribution of patients referred to secondary care by event type, event severity and treatment provision setting, n=1213 (excludes 31 cases who had their event on holiday)



Of 1213 patients referred to secondary care, 434 patients had TIA, 411 had minor stroke (15 with primary intracerebral haemorrhage (PICH)), 326 had major stroke (46 PICH) and 42 had subarachnoid haemorrhage. Amongst patients with minor stroke, 61% (250) were referred to the outpatient clinic (including 14 to non-OXVASC clinics such as neurology or ophthalmology) and 39% (161) were referred directly or self-presented to hospital. The outpatient clinic also treated 78% of patients with TIA (337) and 13% (41) of patients with major stroke (NIHSS >3) (Figure 6.1).

Of those with minor stroke, 80% (327) sought medical attention within 24-hours of symptom onset. Of these, 72% (234) presented to their primary care physician and 22% (72) presented to the hospital emergency department (ED) (Figure 6.2).

Figure 6.2. First medical assessment provider of patients with minor stroke seeking medical attention within 24 hours and referred to secondary care, n=327



Of those seeking medical attention within 24-hours from the primary care physician, 68% (158) were referred to clinic and 32% (76) were referred to hospital. Premorbid mRS>2 and subsequent diagnosis of PICH were associated with hospital referral (p=0.005 and p=0.04 respectively). The median time from seeking medical attention to clinic attendance was 2 days (IQR 1-5), although this was reduced to 1 day (IQR 0-4) post-EXPRESS and 41 (16.4%) of patients were seen on the same day.

Of 250 clinic referred patients with minor stroke, 2 with minor ischaemic stroke (MIS) were admitted with a recurrent stroke before their appointment, both of whom were pre-EXPRESS. In addition, 1 patient with MIS was an in-patient at the time of clinic referral and 10 patients

(6 MIS, 4 PICH) were admitted directly from the clinic for further investigation or nursing care. The baseline characteristics of patients with minor stroke are shown in Table 6.1.

Those with minor stroke seen in the clinic were less likely to live alone (28% vs 38.5%, p=0.03), less likely to have prior AF (13.2% vs 23.6%, p=0.008), less likely to seek medical attention from their GP at the weekend (12.8% vs 29.2%, p<0.001), and had less severe events (median NIHSS 1 (IQR 0-2) vs NIHSS 2 (0-3, p<0.001) (Table 6.1). There was a higher proportion with cardioembolic aetiology amongst in-patients with MIS compared with those seen in the clinic (26% vs 13% in clinic cases, p=0.002). Undetermined and unknown aetiology were more common amongst clinic patients (p<0.01). The proportions of cases with large artery disease were similar in both treatment settings (10% vs 6.7%, p=0.28).

Table 6.1. Baseline characteristics of patients with minor stroke (NIHSS≤3) by treatment provision setting, n=411*.

	Stroke clinic n=250 (%)	Acute hospital n=161 (%)	p
Age (mean (SD))	72.7 (12.1)	74.8 (12.2)	0.08
Male	122 (48.8)	101 (62.7)	0.06
Living alone	70 (28.0)	62 (38.5)	**0.03**
Hypertension	149 (59.6)	96 (59.6)	1.0
Diabetes	27 (10.8)	18 (11.2)	1.0
Current smoking	39 (15.6)	22 (13.7)	0.67
Prior angina or myocardial infarction	45 (18.0)	41 (25.5)	0.08
Prior stroke	42 (16.8)	20 (12.4)	0.26
Prior TIA	30 (12.0)	11 (6.8)	0.09
Peripheral vascular disease	20 (8.0)	14 (8.7)	0.86
Atrial fibrillation	33 (13.2)	38 (23.6)	**0.008**
Prior antiplatelet	101 (40.4)	78 (48.4)	0.13
Prior statin	51 (20.4)	32 (19.9)	1.0
Prior anti-hypertensive	147 (58.8)	93 (57.8)	0.84
Premorbid mRS≥2	75 (30.2)	60 (37.3)	0.13
Days to seeking medical attention, median (IQR)	0 (0-2)	0 (0-0)	**<0.001**
Presented at the weekend	32 (12.8)	47 (29.2)	**<0.001**
NIHSS, median (IQR)	1 (0-2)	2 (0-3)	**<0.001**
TOAST subtype (MIS, n=396)			
Cardioembolic	33 (13.4)	39 (26.0)	**0.002**
Large artery	25 (10.2)	10 (6.7)	0.28
Small vessel	66 (26.8)	30 (20.0)	0.15
Undetermined	97 (39.4)	35 (23.3)	**0.001**
Unknown	14 (5.7)	27 (18.0)	**<0.001**
Multiple	4 (1.6)	3 (2.0)	1.0
Other	7 (2.8)	6 (4.0)	0.57

*includes 15 PICH, 4 referred to clinic, 11 referred to hospital

Of 237 patients with MIS discharged from clinic, 6.8% (16) required non-elective admission within 30 days (8 within 7 days) (Table 6.2). There was no difference in the 30-day admission rate in patients seen in the clinic compared with the 30-day readmission rate after discharge in hospital treated patients (16/237 vs 9/150, p=0.83). Most of those with MIS requiring readmission within 30 days from both treatment settings were those who presented within 24-hours of symptom onset, 88% (22/25). The 30-day recurrent stroke risk in patients with MIS was also similar between those discharged from clinic compared with those seen in hospital (3.8% (9/237) vs 5.3% (8/150), OR 0.70, 0.27-1.80, p=0.61). All results were similar when patients presenting at the weekend were excluded.

Of 161 patients with minor stroke seen in hospital, 96% sought medical attention within 24 hours compared with 69% of clinic referred patients (154/161 vs 173/250, p<0.001). The median length of hospital stay for in-patients with minor stroke presenting in 24 hours was 8 days (IQR 3-32) and for all patients was 9 (3-33) days.

In those presenting within 24 hours, the 30-day recurrent stroke risks after MIS in clinic and hospital referred patients were similar (5.2%, 9/172 vs 4.1% 6/145, OR 1.27, 0.46-3.54, p=0.79). The 30-day readmission rates were also similar (8.1%, 14/172 vs 5.5% 8/145, OR 1.5, 0.63-3.6, p=0.36). The mean (SD) 30-day hospital care cost per patient with MIS was £8323 (13,133) for those referred to hospital versus £743 (1794) for those referred to the outpatient clinic, representing a mean significant difference of £7567 (95% CI of the difference: 5866 - 9269; p<0.0001) per patient. After adjusting for NIHSS score, history of atrial fibrillation, days to medical presentation and living arrangements, the adjusted mean 30-day hospital care cost per patient with MIS was £5852 for those referred to hospital versus £973 for those referred to the outpatient clinic (p<0.0001). In those presenting within 24 hours, the mean (SD) 30-day hospital care cost per patient was £8327 (13,342) for those seen in hospital versus versus £807 (1765) for those seen in the outpatient clinic representing a mean significant difference of £7520 (95% CI of the difference: 5444 - 9596; p<0.0001) per patient.

Table 6.2. Reasons for non elective admission in patients with TIA and minor ischaemic stroke up to 7 and 30 days after discharge from treatment provision setting, n=810*

	Stroke clinic, n=563				Acute hospital, n=247			
	TIA, n=326		MIS, n=237		TIA, n=97		MIS, n=150	
	<7 days	8-30 days	<7 days	8-30 days	<7 days	8-30 days	<7 days	8-30 days
Recurrent stroke	2	1	4	2	3	0	0	2 (1 ICH, 1 ischaemic stroke)
Recurrent TIA	1	0	0	0	0	0	0	0
Rehabilitation	1	0	1	0	0	0	1	0
Sepsis	2	0	1	2	0	1	2	0
Fall	1	0	1	2	0	0	0	0
Bleeding	0	2 (GI bleed)	0	2 (1GI, 1GU bleed)	0	2 (GI bleed)	0	1(GI bleed)
Other	1 (angina)	1 (giant cell arteritis)	1 (angina)	0	0	0	0	3 (urinary retention, colitis, pulmonary oedema)
Total	8	4	8	8	3	3	3	6

*13 deaths at 30 days: 3 clinic referred (1TIA, 2 MIS), 10 hospital cases (3 TIA, 7 MIS).

Of the 8 recurrent strokes requiring admission after MIS within 30 days of discharge from both settings, 6 were ischaemic, 1 was a PICH and 1 was due to CNS vasculitis. The recurrent stroke risk remained similar in patients treated in the clinic compared with those managed in hospital at one year (11.5% (7.6-15.8) vs 12.4% (7.5-17.3), p=0.86) and five year follow–up (21.2% (15.5-26.9) vs 20.5 (14.2-26.8) p=0.84).

Regarding other causes of 30-day admission in clinic-referred patients with MIS, 3 were due to sepsis and 3 because of falls. Admission for nursing care was not common (1 patient). After TIA, the proportions of patients requiring readmission within 30 days of clinic discharge were similar (12/326, 4.0% vs 16/237, 6.8%, p=0.12). Of 28 patients requiring admission within 30-days after clinic discharge, 4 (2 TIA, 2 MIS) were due to bleeding (3 gastrointestinal, 1 gynaecological) (Table 6.2). In all cases, bleeding occurred later, at 8-30 days.

Of 97 patients with TIA seen in hospital, 6 (6.2%) were re-admitted within 30 days of discharge. Of 3 patients re-admitted within 7 days, the cause was a recurrent stroke in all cases. The 30 day admission rate in clinic patients with TIA was similar to the 30 day re-admission rate amongst patients seen in hospital (12/326 vs 6/97, p=0.27).

Amongst 387 patients with MIS discharged from secondary care, rates of secondary prevention implementation were high, though there were differences between patients seen in hospital and those seen in the clinic (Table 6.3). Patients treated in hospital were more likely to receive warfarin (12.7% vs 6.3%, p=0.04). Patients seen in clinic were more likely to receive lipid lowering therapy (p<0.001). Similar proportions of patients with symptomatic carotid stenosis ≥50% were referred for carotid endarterectomy in both settings (32%, 9/28 vs 20%, 2/10, p=0.69). At 1 year follow up, higher rates of statin use in clinic referred patients remained (84%, 190/225 vs 69%, 81/117, p=0.002).

Table 6.3. Secondary prevention measures at discharge and one year follow-up in patients with MIS seen in the clinic and hospital, n=387

	At discharge			One year follow-up[b]		
	Stroke clinic n=237 (%)	Acute hospital n=150 (%)	p	Stroke clinic n=225(%)	Acute hospital n=117 (%)	p
Antiplatelet	206 (86.9)	112 (74.7)	**0.003**	182 (80.9)	90 (76.9)	0.40
Warfarin	15 (6.3)	19 (12.7)	**0.04**	24 (10.7)	14 (12.0)	0.72
Lipid lowering	199 (84.0)	103 (68.7)	**<0.001**	190 (84.4)	81 (69.2)	**0.002**
At least 1 anti-hypertensive	183 (77.2)	115 (76.7)	0.90	183 (81.3)	90 (76.9)	0.39
2 or more antihypertensives	113 (47.7)	57 (38.0)	0.07	128 (56.9)	59 (50.4)	0.3
Symptomatic carotid stenosis ≥50%[a]	28 (11.8)	10 (6.7)	0.58			
Referred for carotid endarterectomy	9 (3.8)	2 (1.3)	0.22			

[a] 48 cases did not have carotid imaging (3 clinic cases, 45 hospital cases)

[b] 50 cases dead at 1 year follow-up (21 clinic cases, 29 hospital cases), data missing on 4 hospital cases

6.4 Discussion

Clinics offering urgent assessment and treatment after TIA have been shown to have good outcomes and to be cost-effective.[3,4,19] This study of the feasibility, safety and cost of management of patients with minor stroke in a specialised outpatient clinic showed that the 30-day recurrent stroke risk and unplanned admission rates were low, with similar outcomes to those after hospital treatment of minor stroke, recognizing, of course, that there were differences in clinical characteristics of patients referred to clinic versus admitted to hospital. However, after trying to control for these differences in a regression analysis, my results showed savings, of around £4800 per patient treated in clinic, with patients seen in hospital costing over 6 times more after adjusting for patient characteristics.

The outpatient clinic treated 40% of patients with stroke and 61% of those with minor stroke. I found 80% of patients with minor stroke sought medical attention within 24 hours, of which 72% first presented to their primary care physician. In a similar US survey, 88% of stroke patients presenting to family practices were evaluated on the day of symptom onset, but two thirds were hospitalised,[1] whereas two thirds were managed as outpatients in this study. I found similar delays to secondary care as in a Dutch study of management of TIA and stroke in which 71% of hospital-admitted patients arrived within 24 hours of onset compared to 17% of outpatients.[20] This study also found less use of secondary prevention measures amongst admitted patients.[20]

Potential advantages of hospitalisation after TIA include early access to thrombolysis to treat recurrent stroke,[21] but thrombolysis would generally not be indicated to treat recurrence after minor stroke due to the increased risk of intracerebral haemorrhage, although admission may provide early access to secondary prevention and rehabilitation. However, nearly all clinic

managed patients in this study received antiplatelet therapy and more than three quarters received statins, suggesting secondary prevention was good in the clinic setting.

The disadvantages of outpatient assessment may be related to delays in appointment times therefore missing the opportunity for early intervention, but recurrent stroke rates in this study were similar in both settings, and most recurrences after clinic assessment occurred in the pre-EXPRESS phase of the study where delays to clinic assessment were greater and there was a delay to subsequent initiation of secondary prevention in primary care.

The risk of recurrent stroke and other complications are highest during the first days after a minor stroke.[3,4,22-26] I found 4% of clinic referred patients with minor stroke were admitted directly after their appointment for further investigations or nursing care in hospital. In those additional patients subsequently admitted after clinic discharge, it is possible that initial hospitalisation could have reduced the likelihood of adverse outcomes such as falls. However, since up to 96% of patients hospitalised for stroke experience medical or neurological complications during their admission,[27] the benefit of outpatient care in avoiding hospitalisation related morbidity, such as hospital-acquired infection, also should be considered. I found the 30-day unplanned admission rate after clinic attendance after minor stroke was similar to that in patients with TIA discharged from the clinic.

This study did not assess patients' preferences for treatment, patients may prefer outpatient management if it is considered possible and safe. Patients should be informed which treatments are available and their preferences should be taken in account.[28] Such an approach may increase adherence to treatment and decrease dissatisfaction, two additional potential gains of outpatient treatment for medically stable patients.[28,29] On the other hand, it may be that hospitalisation reinforces the seriousness of the event and alleviates concerns about potential side effects of secondary prevention which may lead to better treatment adherence.[30,31] However, in this study, rates of secondary prevention at one year were as

high in clinic managed patients compared with hospital managed patients. Finally, the economic aspect of hospitalisation of TIA and minor stroke patients should also be considered. I showed that the cost of outpatient management of minor stroke was substantially lower than inpatient care.

The main strengths of the present study are its population-based design, rigorous ascertainment and follow-up. The possibility of selection and misclassification bias was minimised since all stroke patients presenting for medical attention in the study population were prospectively recruited, and outcomes were assessed by assessors blinded to the study hypotheses.[15,16] However, this study has also limitations. First, it was not a randomised comparison of different management strategies. I simply aimed to determine the outcomes in those patients that family doctors considered appropriate for referral for potential outpatient management. These patients tended to have less severe strokes and different aetiologies to those admitted directly to hospital, although there was considerable overlap between the groups, all had NIHSS<3, and 68% of patients with minor stroke in this population who sought medical attention from family practitioners within 24 hours of symptom onset were referred to the clinic. Second, differences in baseline characteristics in the clinic managed group may have influenced GPs decision to refer to the clinic rather than the hospital. However, whilst I have presented outcomes after clinic discharge, I did study events after referral and before clinic attendance and there were only 2 patients with recurrent stroke. Third, the median length of stay was long in this study, if this was shorter, for example, as in other countries, the cost savings may be less. Fourth, I did not assess patients' preferences, but it is common for patients to prefer to avoid hospital admission where possible. Fifth, I did not assess long-term disability. It may be that early access to rehabilitation in hospital reduces long-term disability which may offset the initial cost-savings of clinic care. However, this effect is unlikely to be substantial in patients with minor stroke.

In conclusion, this non-randomised study shows that rapid assessment and treatment of minor stroke can be achieved in the outpatient clinic and the complication rate of outpatient management is relatively low. A randomised comparison of either treatment setting would be justified.

6.5 References

1. Goldstein LB, Bian J, Samsa GP, Bonito AJ, Lux LJ, Matchar DB. New transient ischemic attack and stroke: outpatient management by primary care physicians. Arch Intern Med 2000;160:2941-6.
2. Roebers S, Wagner M, Ritter MA, Dornbach F, Wahle K, Heuschmann PU. Attitudes and current practice of primary care physicians in acute stroke management. Stroke 2007;38:1298-303.
3. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): Feasibility and effects. Lancet Neurol. 2007; 6: 953–960.
4. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN 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;370:1432-42.
5. Intercollegiate Stroke Working Party. National clinical guideline for stroke, 3rd edition. London: Royal College of Physicians, 2008.
6. National collaborating centre for chronic conditions. Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE clinical guideline 68, July 2008. http://guidance.nice.org.uk/CG68/NICEGuidance/pdf/English
7. Scottish Intercollegiate Guidelines Network. Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention: A national clinical guideline. 2008. www.sign.ac.uk
8. Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2011;42;227-276.
9. National Stroke Foundation (Australia): Melbourne. Clinical Guidelines for Acute Stroke Management. 2007. www.strokefoundation.com.au/acute-clinical-guidelines-for-Acute-stroke-management
10. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis, 2008. 25(5): 457-507.
11. Stroke foundation of New Zealand. New Zealand guideline for the assessment and management of people with recent transient ischaemic attack (TIA). 2008. www.stroke.org.nz

12. The Stroke Prevention and Educational Awareness Diffusion (SPREAD) Collaboration. The Italian Guidelines for stroke prevention. Neurol Sci 2006;21(1):5-12.
13. Canadian Stroke Network and the Heart and Stroke Foundation of Canada: Ottawa. Canadian Stroke Strategy: Canadian Best Practice Recommendations for Stroke Care: 2006.
www.canadianstrokestrategy.ca/eng/resourcestools/documents/StrokeStrategyManual.pdf
14. Schwamm LH, Pancioli A, Acker JE 3rd, Goldstein LB, Zorowitz RD, Shephard TJ, et al; American Stroke Association's Task Force on the Development of Stroke Systems. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. Stroke. 2005;36(3):690-703
15. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363(9425):1925-1933.
16. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE 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). Lancet 2005;366:1773-83.
17. Brott T, Adams HP Jr., Olinger CP, Marler JR, Barsan WG, Biller J et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864-70.
18. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL 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;24:35-41.
19. Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. Lancet Neurol 2009;8:235-43.
20. Scholte op Reimer WJ, Dippel DW, Franke CL, van Oostenbrugge RJ, de Jong G, Hoeks S, Simoons ML. Quality of hospital and outpatient care after stroke or transient ischemic attack: insights from a stroke survey in the Netherlands. Stroke. 2006 Jul;37(7):1844-9.
21. Nguyen-Huynh MN, Claiborne Johnston S. Is hospitalization after TIA cost-effective on the basis of treatment with tPA. Neurol 2005; 65:1799-1801.
22. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283-92.

23. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet 2005;366:29-36.
24. Rothwell PM, Buchan A, Johnston SC. Recent advances in management of transient ischaemic attacks and minor ischaemic strokes. Lancet Neurol 2006;5:323-31.
25. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328:326.
26. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901-6.
27. Ingeman A, Andersen G, Hundborg HH, Svendsen ML, Johnsen SP. Processes of care and medical complications in patients with stroke. Stroke. 2011 Jan;42(1):167-72.
28. Bowling A, Ebrahim S. Measuring patients' preferences for treatment and perceptions of risk. Qual Health Care 2001;10 Suppl 1:i2-i8.
29. Asplund K, Jonsson F, Eriksson M, Stegmayr B, Appelros P, Norrving B et al. Patient dissatisfaction with acute stroke care. Stroke 2009;40:3851-6.
30. Ovbiagele B, Saver JL, Fredieu A, Suzuki S, Selco S, Rajajee V et al. In-hospital initiation of secondary stroke prevention therapies yields high rates of adherence at follow-up. Stroke 2004;35(12):2879-83.
31. Touzé E, Coste J, Voicu M, Kansao J, Masmoudi R, Doumenc B et al. Importance of in-hospital initiation of therapies and therapeutic inertia in secondary stroke prevention: IMplementation of Prevention After a Cerebrovascular evenT (IMPACT) Study. Stroke 2008;39(6):1834-43.
32. Josephson SA, Sidney S, Pham TN, Bernstein AL, Johnston SC. Factors associated with the decision to hospitalize patients after transient ischemic attack before publication of prediction rules. Stroke 2008;39:411-3.

CHAPTER 7

Prognosis of TIA and minor stroke in the subacute phase

7.1 Introduction 146

7.2 Methods 146

7.2.1 Analysis 148

7.3 Results 148

7.4 Discussion 161

7.5 References 166

7.1 Introduction

The high early risk of stroke after TIA has been established in population based and hospital-based studies.[1-7] In a recent systematic review including 18 independent cohorts, which reported stroke risk in 10 126 TIA patients, the pooled stroke risk was 5.2% (95% CI 3.9-6.5) at seven days.[8] Furthermore, the very early stroke risk after TIA has been shown to be particularly high, with 42% of all strokes during the 30 days after a first TIA occurring within the first 24 hours.[9] Population based studies have shown the recurrence risk depends on the clinical characteristics, vascular territory and aetiology of the event.[10-14] In addition, urgent intervention after TIA has been shown to be highly effective in reducing the early recurrent stroke risk.[15-17] However, whilst much is known about prognosis and predictors of risk early after TIA, there is less published data on the risk after minor stroke, particularly in the medium and long-term.[18] Furthermore, whether there are differences between TIA and minor stroke in the time course of recurrent stroke risk is not known. Data on any differences in the timing of recurrent events could help to target secondary prevention. The aim of this study was to determine the time course of recurrent events after TIA and minor stroke in the sub-acute phase, that is beyond 7 days. I addressed this issue in a prospective population based study of all incident and recurrent TIA and stroke in Oxfordshire, UK (Oxford Vascular Study).

7.2 Methods

The Oxford Vascular Study (OXVASC) is a prospective, population based study of all stroke and TIA in approximately 91 000 individuals of all ages registered with 63 general practitioners in Oxfordshire, UK. The study methods have been described in Chapter 1 and elsewhere.[19,20] Briefly, multiple overlapping methods of “hot” and “cold” pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke.[19-21]

All patients were consented and seen by study physicians as soon as possible after their initial presentation. Baseline characteristics were recorded in all patients and assessments were made for severity of event (using National Institute of Health Stroke Scale, NIHSS[22]) and clinical features. Events were classified as minor stroke if there was a focal neurological deficit lasting greater than 24 hours and an NIHSS score ≤5 at time of assessment by a study physician. A cut off of NIHSS score ≤5 was chosen as this included the majority (96%) of patients with stroke seen in the outpatient setting.[15] Patients ascertained with a stroke but who had a preceding TIA that they had not brought to medical attention were included.

Event characteristics and risk factors were recorded and all patients underwent brain imaging, with CT or MRI as appropriate. All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA or stroke or other condition using standard definitions.[19,20] All patients with recurrent events were reassessed by a study physician and then case reviewed by PMR. Patients with stroke in whom it was impossible to obtain a definite history of preceding TIAs or stroke because they were aphasic, confused, or unconscious were excluded. Patients with primary intracerebral haemorrhage and those who presented as a stroke death were excluded. All patients received best medical treatment and secondary prevention according to current guidelines.

Patients were followed up face-to-face at 30 days, 6 months, 1 year and 5 years by a study nurse or physician. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. The timing of all recurrent events within 2 years of the first event was recorded. Aetiological classification of cerebrovascular events was performed according to the TOAST classification once investigations were complete. All recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within

OXVASC. This sub-study includes all cases with first ischaemic events from the 1st April 2002 to 31st March 2007.

7.2.1 Analysis

I restricted analysis to the risk of recurrent events after the first TIA or ischaemic stroke in the study period (index event). The risks of recurrent stroke within 2 years of TIA, minor ischaemic stroke (MIS) and major ischaemic stroke were censored for deaths and follow-up until 31st July 2010. Risks were analysed from the time of index event and from time of first seeking medical attention. A recurrent stroke was defined as a new persistent neurological symptom in a patient in whom the initial symptoms were stable or had already substantially or fully recovered. In patients who had multiple recurrent events, the end point was classified as the first recurrence following the index event. Kaplan-Meier survival analysis was used to calculate recurrence risks.

7.3 Results

Complete baseline data and complete face to face or telephone follow data up to 2 years were available on 1174 consecutive, first ischaemic cerebrovascular events within the study period from 1st April 2002 to 31st March 2007. Table 7.1 shows the clinical characteristics of all 1174 first events in the study period. The mean (range) age at first TIA was 72.6 (24-98) years and at first stroke 75.5 (37-96) years. 40% of cases (472/1174) were aged over 80 years. Male sex was more common in patients with MIS than in patients with TIA and major stroke ($p<0.001$). Increasing event severity was associated with age ($p<0.001$), hypertension ($p<0.0001$), peripheral vascular disease ($p=0.001$), atrial fibrillation ($p<0.0001$), previous stroke ($p=0.002$) and prior antiplatelet use ($p=0.006$).

Table 7.1. Baseline characteristics, vascular risk factors and premorbid medication of patients presenting with TIA or ischaemic stroke, n=1174

	TIA (n=491)	Minor ischaemic stroke (n=487)	Major ischaemic stroke (n=196)	p-value
Age (mean (SD))	72.6 (12.8)	74.2 (11.5)	78.7 (10.2)	**<0.001**
Male Sex	214 (43.6)	260 (53.4)	75 (38.3)	**<0.001**
Hypertension	258 (52.5)	287 (58.9)	138 (70.4)	**<0.0001**
Diabetes	67 (13.6)	54 (11.1)	22 (11.2)	0.442
Angina or myocardial infarction	99 (20.2)	108 (22.2)	47 (24.0)	0.507
Peripheral vascular disease	29 (5.9)	43 (8.8)	29 (14.8)	**0.001**
Previously diagnosed atrial fibrillation	80 (16.3)	79 (16.2)	68 (34.7)	**<0.0001**
Current Smoker	66 (13.4)	73 (15.0)	11 (5.6)	**0.002**
Previous TIA	91 (18.5)	52 (10.7)	21 (10.7)	**0.001**
Previous stroke	61 (12.4)	80 (16.4)	46 (23.5)	**0.002**
Prior antiplatelet	199 (40.5)	227 (46.6)	105 (53.6)	**0.006**
Prior statin	123 (25.1)	110 (22.6)	42 (21.4)	0.515
Prior antihypertensive	261 (53.2)	258 (53.0)	135 (68.9)	**<0.001**

There were 202 recurrent strokes within 2 years of first ischaemic events (Table 7.2). 83% (168/202) of these had brain imaging after the recurrent event. At 2 years the recurrent stroke risks after TIA and MIS were similar (19.3% (15.8-22.8) vs 18.3% (14.8-21.8), p=0.69, Figure 7.1).

Figure 7.1. Risk of recurrent stroke up to 2 years after TIA and MIS

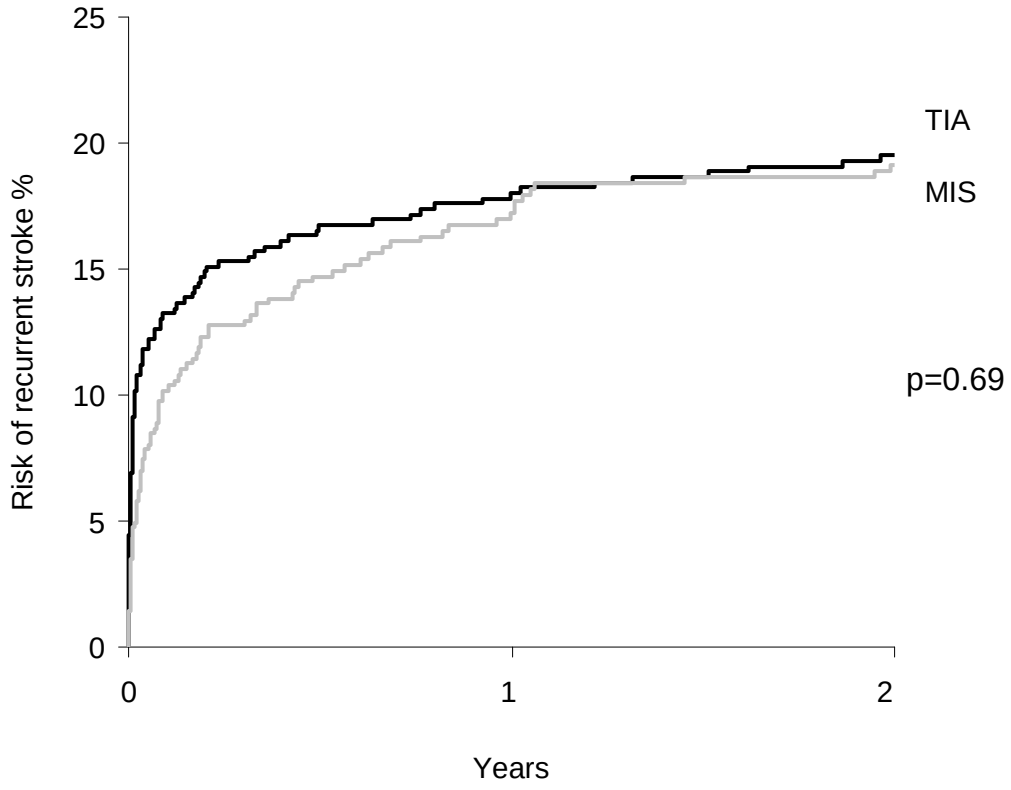
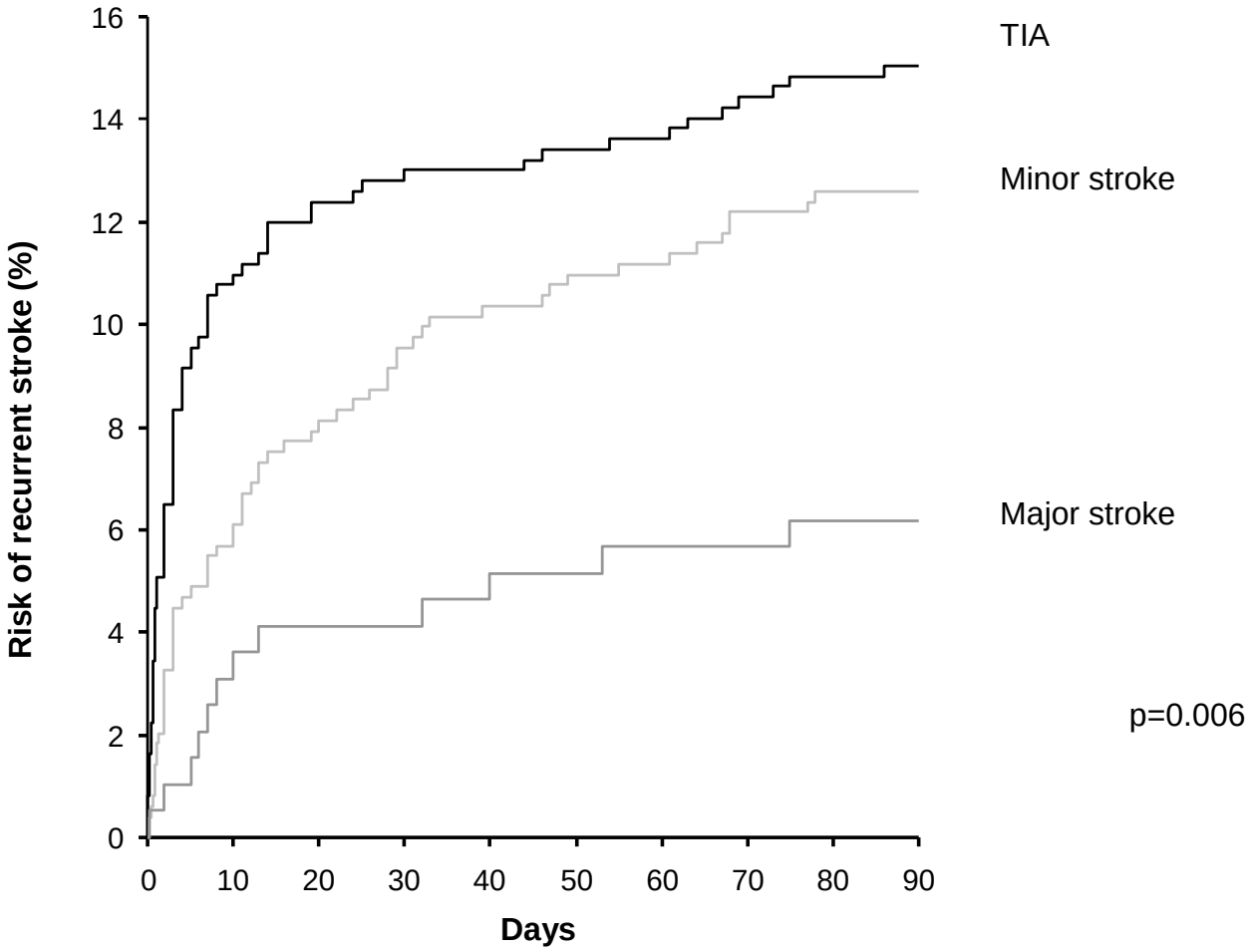


Table 7.2 shows the time course to recurrent stroke after each event type. Of the 202 cases of recurrent stroke at 2 years, most occurred within 7 days (82, 41%) and the majority (52, 62%) were preceded by a TIA. Of the 148 recurrent events within 90 days, 75 (51%) were preceded by a TIA, 61 (41%) by MIS and 12 (8%) by major ischaemic stroke. The 90-day stroke risk after TIA was 15.3% (95% CI 12.2-18.4), after MIS was 12.5% (9.5-15.4) and after major ischaemic stroke was 6.1% (2.8-9.4) (Figure 7.2).

Table 7.2: Recurrent strokes (% risk, 95% CI) up to 2 years after TIA and ischaemic stroke, n=1174

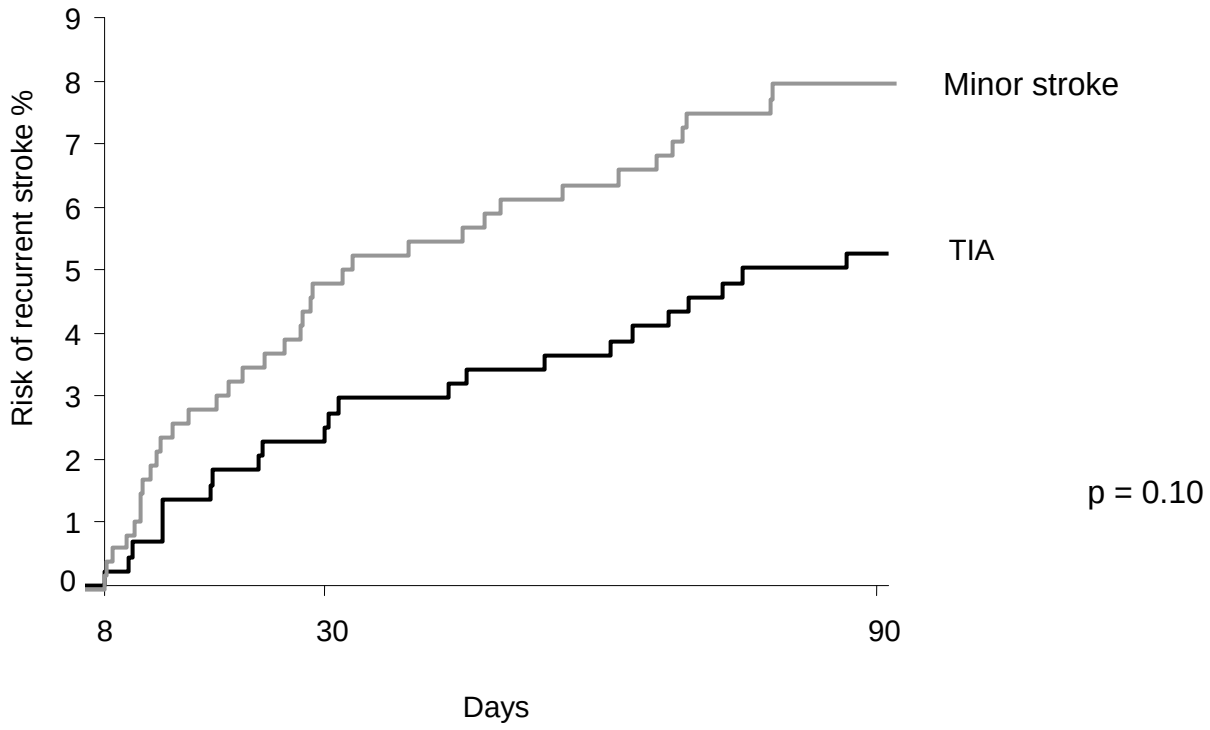
		7 days		30 days		90 days		1 year		2 years	
	Patients	Strokes	% risk	Strokes	% risk	Strokes	% risk	Strokes	% risk	Strokes	% risk
TIA	491	52	10.6 (7.9 - 13.3)	63	12.8 (9.9 - 15.7)	75	15.3 (12.2 - 18.4)	88	17.9 (14.6 - 21.2)	95	19.3 (15.8-22.8)
Minor stroke	487	25	5.1 (3.1 - 7.1)	47	9.7 (7.2 - 12.2)	61	12.5 (9.5 - 15.4)	81	16.5 (13.3 - 19.9)	89	18.3 (14.8-21.8)
Major stroke	196	5	2.6 (0.4 - 4.8)	8	4.1 (1.4 - 6.8)	12	6.1 (2.8 - 9.4)	16	8.2 (4.3 - 12.1)	18	9.2 (5.1 - 13.3)
All patients	1174	82	7.1 (5.5 - 8.7)	118	10.1 (8.3 - 11.9)	148	12.6 (10.6 - 14.6)	185	15.8 (13.6 - 18)	202	17.2 (15 - 19.4)

Figure 7.2. Risk of recurrent stroke up to 90 days after TIA, minor ischaemic stroke and major ischaemic stroke



By 2 years the numbers of recurrent events after TIA and MIS were similar (95 vs 89). However, the timing of recurrence varied according to initial event type. The majority (52/95, 55%) of recurrences after TIA occurred within 7 days. In contrast, many recurrent events after MIS occurred later, predominantly between 8-90 days (36/89, 40%). Up to 7 days, the stroke risk following TIA was double that after MIS (10.6%, 52/491 vs 5.1% 25/487, OR 2.19, 95% CI 1.30-3.70, p=0.002). However, between 8-90 days, the risk after MIS remained high, in contrast with the falling risk after TIA (7.8%, 36/460 vs 5.2%, 23/439, p=0.10, Figure 7.3).

Figure 7.3. Risk of recurrent stroke between 8-90 days of onset of TIA and minor ischaemic stroke



The high recurrent stroke risk after minor stroke persisted but was less pronounced beyond 90 days up to 1 year (4.7% 20/426 vs 3.1%, 13/416, p=0.29). Between one to two years after the index event, the stroke risk after both TIA and minor stroke was low (1.7%, 7/403 vs 2.0%, 8/406, p=0.81). MIS was defined as those with ischaemic stroke and NIHSS ≤5, recurrence risks remained similar when those with NIH>3 were excluded. For recurrences within the first year, the median time to recurrent stroke after event onset was 4 days (interquartile range 1-45) for TIA compared with 22 days (3-94) for minor stroke (p=0.002). The number of recurrences during the first year after major stroke was small (16/196, 8.2%), however the median time to recurrent event was similarly delayed when compared to TIA (22 days (6-98), p=0.04).

There were 35 patients with TIA (7.1%) and 11 patients with MIS (2.3%) who did not seek medical attention at the time of the event but presented only after a recurrent stroke. The recurrent stroke risks up to 2 years from first seeking medical attention after TIA and MIS are shown in Table 7.3. When cases that did not seek medical attention at the time of the first event were excluded, the risks of recurrence after TIA and MIS were similar up to 7 days (6.8% (4.4-902) vs 4.0%, 2.2-5.8), p=0.52, Figure 7.4). However, at 8 to 90 days from seeking medical attention, recurrent stroke risk was higher after MIS than after TIA (7.2%, 32/455 vs 2.6%, 11/425, p=0.02, Figure 7.5). The high recurrent stroke risk after MIS persisted beyond 90 days up to 1 year after first seeking medical attention (5.0% (20/401)) although the risk was not significantly higher than the risk after TIA (2.9% (12/411), p=0.12).

Table 7.3: Recurrent strokes (% risk, 95% CI) up to 2 years from time of seeking medical attention after TIA and minor ischaemic stroke (n=932, 46 cases did not seek medical attention at the time of their event but presented after recurrent stroke)

		7 days		30 days		90 days		1 year		2 years	
	Patients	Strokes	% risk	Strokes	% risk	Strokes	% risk	Strokes	% risk	Strokes	% risk
TIA	456	31	6.8 (4.4 - 9.2)	34	7.5 (5.1 - 9.9)	42	9.2 (6.5 - 11.9)	54	11.8 (8.9 - 14.7)	60	13.2 (10.1 - 16.3)
Minor stroke	476	18	4.0 (2.2-5.8)	37	7.8 (5.4 - 10.2)	50	10.7 (8.6-13.4)	70	14.7 (11.6 - 17.8)	78	17.2 (13.7-20.7)
All patients	932	49	5.3 (3.9 – 6.7)	71	7.6 (5.8 - 9.4)	92	10.0 (8.0 – 12.0)	124	13.6 (11.4 - 15.8)	138	15.3 (12.9 -17.7)

Figure 7.4. Risk of recurrent stroke within 90 days of first seeking medical attention after TIA and minor ischaemic stroke

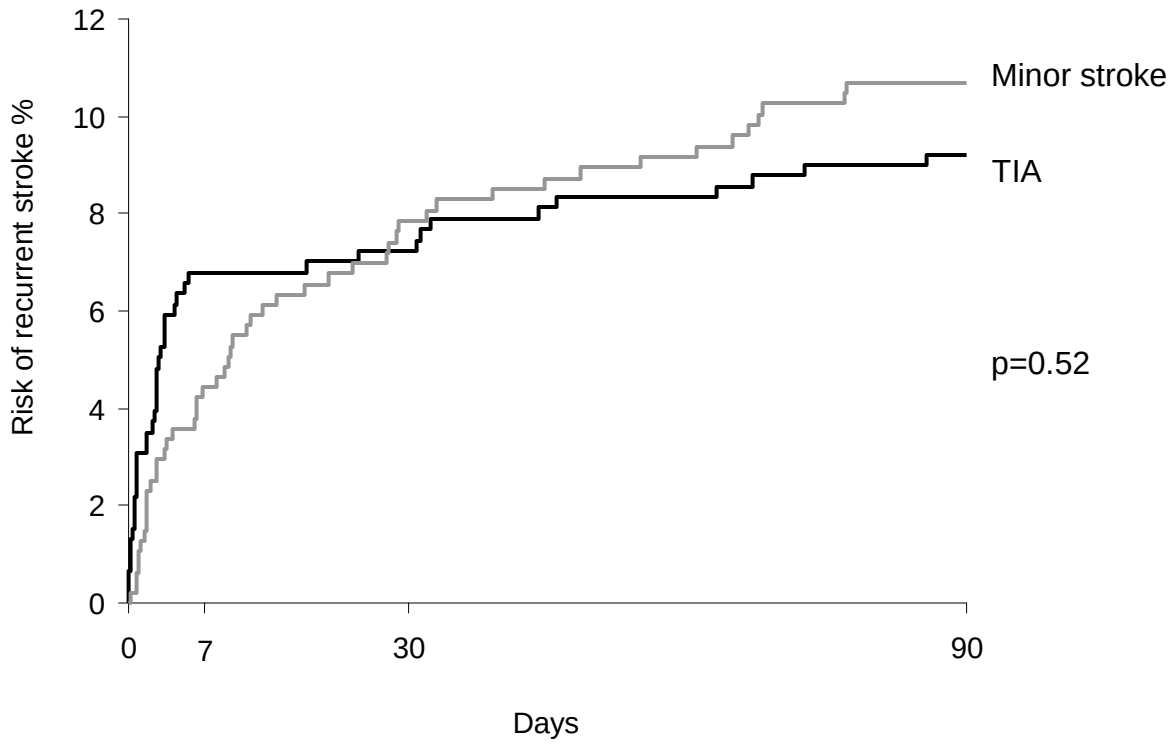
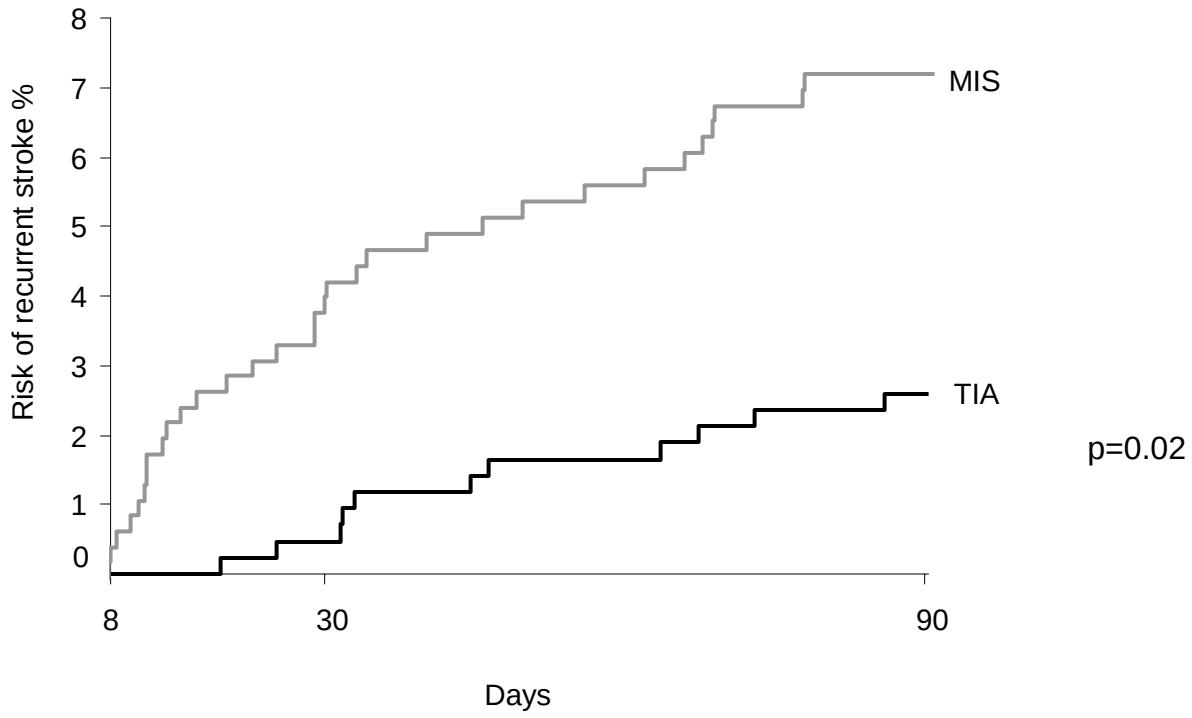


Figure 7.5. Risk of recurrent stroke between 8-90 days of fist seeking medical attention after TIA and minor ischaemic stroke



Of the 36 patients with MIS that had a recurrent stroke between 8-90 days, 4 did not present to medical attention at the time of the first event and presented only after the recurrent stroke. Of the remaining 32 cases, there were 21 seen in the pre-EXPRESS phase of the study and 11 were seen post-EXPRESS (8.9% vs 5.0%, p=0.15). The TOAST subtype of the first event was cardioembolic (CE) in 9 cases, small vessel in 6, large artery atherosclerosis (LAA) in 5, unknown or undetermined in 10 and other in 2 (1 vasculitis, 1 post coronary angiography). Of the 5 cases of LAA aetiology, 1 had a carotid endarterectomy after the recurrent stroke, 1 had an internal carotid artery occlusion, 2 were vertebrobasilar events and 1 had a 50% symptomatic carotid stenosis. Of the 9 cases of CE aetiology, only 2 were started on warfarin after the first event.

Table 7.4 shows the mortality risks up to 2 years stratified by event type. Mortality was highest after major stroke within the first seven days (24.5%, 95% CI 18.4-30.6). Time to death was related to initial event severity, with 89% (48/54) of all deaths within 7 days occurring after major stroke. Mortality risks after TIA and MIS were similar up to 7 days (0.4% vs 0.8%, p=0.45). However, between 8 to 90 days, mortality risk after MIS was 3 times the risk after TIA (6.2%, 30/483 vs 2.0%, 10/489, OR 3.17, 95% CI 1.55- 6.7, p=0.001). By 2 years, the mortality risk after MIS remained higher then the risk after TIA but was less pronounced (19.1% vs 12.2%, OR 1.70, 95% CI 1.19-2.41)

Table 7.4: Mortality (% risk) up to 2 years after TIA, minor stroke and major stroke

		7 days		30 days		90 days		1 year		2 years	
	Patients	Deaths	% risk	Deaths	% risk	Deaths	% risk	Deaths	% risk	Deaths	% risk
TIA	491	2	0.4 (0-1)	7	1.4 (0.4-2.4)	12	2.4 (1-3.8)	29	5.9 (3.7-8.1)	60	12.2 (9.3-15.1)
Minor stroke	487	4	0.8 (0-1.6)	17	3.5 (1.9-5.1)	34	7 (4.6-9.4)	71	14.6 (11.5-17.7)	93	19.1 (15.6-22.6)
Major stroke	196	48	24.5 (18.4-30.6)	80	40.8 (33.9-47.7)	96	49.0 (41.9-56.1)	117	59.7 (52.8-66.6)	124	63.3 (56.6-70)
All patients	1174	54	4.6 (3.4-5.8)	104	8.9 (7.3-10.5)	142	12.1 (10.1-14.1)	217	18.5 (16.3-20.7)	277	23.6 (21.3-26.0)

Secondary prevention measures were similar in patients with TIA and MIS at 1 month, although patients with TIA were more likely to be on an antiplatelet or anticoagulant (p=0.04) and patients with MIS had more aggressive blood pressure lowering, with 81% vs 73% taking one or more antihypertensive (p=0.01, Table 7.5). However by 1 year, there were no differences in secondary prevention measures in patients with TIA and MIS (Table 7.6.)

Table 7.5: Secondary prevention measures assessed at 1 month follow-up in patients with TIA and minor ischaemic stroke who presented to medical attention at the time of their event, n=824*

	TIA n=414 (%)	Minor stroke n=410 (%)	p
On an antiplatelet or anticoagulant [a]	400 (97.1)	381 (94.1)	**0.04**
On a statin	295 (71.3)	303 (73.9)	0.44
On one or more antihypertensive	302 (72.9)	332 (80.7)	**0.01**
On two or more antihypertensives[b]	159 (38.5)	178 (43.6)	0.14
Systolic blood pressure, mm Hg (mean, SD)[c]	136.8 (21.4)	139.7 (20.7)	0.07
Diastolic blood pressure, mm Hg (mean, SD)[c]	75.9 (9.8)	77.1 (11.2)	0.12

*Excludes 24 patients who died before 1 month follow-up, and data not available for 87 patients (36 TIA, 51 MIS).

[a] 7 cases missing (2 TIA, 5 MIS) [b] 3 cases missing (1 TIA, 2 MIS) [c] 102 cases missing (63 TIA, 39 MIS)

Table 7.6: Secondary prevention measures assessed at 1 year follow-up in all patients (n=663)*

	TIA n=324 (%)	Minor stroke n= 339 (%)	p
On an antiplatelet or anticoagulant	307 (94.8)	316 (93.2)	0.42
On a statin[a]	249 (77.1)	277 (81.7)	0.15
On one or more antihypertensive[a]	246 (76.2)	279 (82.3)	0.06
On two or more antihypertensives[b]	168 (52.0)	193 (57.1)	0.21
Systolic blood pressure, mm Hg (mean, SD)[c]	136 (20.3)	137 (19.2)	0.75
Diastolic blood pressure, mm Hg (mean, SD)[c]	75.6 (10.0)	76.9 (11.6)	0.12

* Excludes 100 patients who died before 1 year follow-up, and data not available for 215 patients (138 TIA, 77 MIS).

[a] one case missing [b] two cases missing (1 TIA, 1 MIS) [c] 48 cases missing (23 TIA, 25 MIS)

7.4 Discussion

In this study, the recurrent stroke risks after TIA and MIS remained similar up to 2 years, however the time course to recurrent events differed. Recurrent stroke after MIS occurred later than after TIA. For recurrences in the first year, the median time to recurrence after MIS was 22 days compared with 4 days after TIA.

The 90 day recurrent event rates in this study are similar to those in a hospital based cohort of TIA and minor stroke which found the risk after TIA to be 19% and after minor stroke to be 14.7%.[24] The one year recurrent stroke rate of 16% after all events in this study is higher than that found in a US study of medicare beneficiaries hospitalised for recurrent stroke, which found one year recurrence risk to be 13%.[25] Although recurrence risks in hospital based studies tends to be lower as elderly patients managed in the community and those with milder events are not included.

I found the 2-year risk of recurrent stroke after TIA and MIS in this study to be 19%, this is higher than in other population based studies. In the Oxford Community Stroke project (OCSP), the 2 year recurrent stroke risk after TIA and MIS was 13%, however OCSP excluded patients who did not present to medical attention at the time of TIA and MIS.[26] The 2 year recurrent stroke risk in this study is also higher than in the South London Stroke Registry cohort, which found 2-year risk after ischaemic stroke to be 10%, however this could be because recurrent strokes within the same vascular territory within the first 21 days of the event were excluded from their study.[27]

Clinical factors (age, BP, duration of event and diabetes), vascular territory, aetiology and appearances on brain imaging have been associated with recurrence risk after TIA.[13,28] Several clinical prediction scores have been developed and validated for identifying those at high risk of stroke or death within 1-10 years after TIA or stroke. The Essen Stroke Risk Score, Stroke Prognostic Instrument score, Life Long after Cerebral Ischaemia score and the score by Hankey et al, all show that the medium and long-term risks are more dependent on underlying vascular risk factors than characteristics of the event itself which is more predictive of early risk.[29,30] Similar factors may affect the timing to recurrent event. Compared with patients with TIA, those with MIS in this study were more likely to be male and hypertensive and less likely to have had a prior TIA, however other baseline risk factors were similar in the 2 groups. Other reasons could account for the difference in timing to recurrent events. First, differences in patient delays to presentation after TIA and minor stroke. A longer delay to seeking medical attention after the presenting event may delay access to secondary prevention which could result earlier recurrent events. However, in OXVASC, similar proportions of TIA and minor stroke patients (70%) sought medical attention within 24 hours of the event (chapter 2).[31] Second, I defined MIS as those with ischaemic stroke and NIHSS ≤5. It may be that those with NIHSS 0-3 have a different prognosis compared with those with NIHSS 4-5, however risks remained similar when those with NIH>3

were excluded. Third, different treatment settings for TIA and minor stroke could lead to differing access to secondary prevention. If patients with TIA were generally seen in the outpatient setting with secondary prevention being started after the clinic appointment by their GP and patients with minor stroke were seen as inpatients, then a higher earlier recurrence rate after TIA may be expected. However, in this study around half of all patients with minor stroke were seen in the urgent outpatient setting and therefore had similar access to preventative treatments to patients with TIA. It may be that compliance with secondary prevention differs depending on the treatment setting, the higher rate of recurrence 8-90 days after MIS may coincide with hospital discharge and possibly patient discontinuation of secondary prevention. Although, I have previously shown that secondary prevention measures were similar at one month follow-up in patients with minor stroke seen in either the outpatient or in-patient setting (chapter 6). Therefore it is unlikely that treatment setting has affected the time to recurrence. Cases in this study included patients who received the intervention of the EXPRESS clinic in which secondary prevention was initiated at the time of clinic assessment. Although the proportion of patients with recurrent stroke at 8-90 days was higher amongst those seen pre-EXPRESS, there was no significant difference in 8-90 day recurrence risk when compared to those seen in the post-EXPRESS phase. Fourth, the intensity of secondary prevention may have varied between the TIA and minor stroke cases causing a difference in the timing of recurrent events. At one month there were more patients with TIA on aspirin and anticoagulants however, at one year follow-up, the rates of use of aspirin, anticoagulants, statins and anti-hypertensive medication were similar amongst TIA and MIS patients. Furthermore, regular face-to-face or telephone follow-up ensured high rates of compliance. EXPRESS and SOS-TIA showed the early recurrent stroke risk after TIA and minor stroke can be reduced by urgent use of best available medical treatment.[15,16] The comparatively delayed recurrence after minor stroke in my study highlights the need for better secondary prevention in the subacute phase after minor stroke. It may be that the effect of early initiation of aspirin, statins and antihypertensive is maximal in the first 7 days, but in the

subacute 8-90 day period, other risk factors may need to be addressed. I found the most common aetiology of recurrent stroke in the subacute phase to be cardioembolic and warfarin use was low in this group. Underuse of warfarin in primary and secondary prevention of stroke has been previously reported and may be one of the factors contributing to later risk of recurrence after MIS.[32,33] It may be that concerns regarding haemorrhagic transformation after stroke delays warfarin use in the acute and subacute phase after stroke compared with after TIA. It is also possible that there may be inadequacies in the standards for investigation of TIA and stroke, with misclassification of aetiology and failure to address treatable pathologies, such as paroxysmal AF which may be resulting in a high subacute risk of recurrent stroke. Another possibility is that current standards for diagnosis and treatment of hypertension during early follow-up may be inadequate resulting in misclassification of severity and under-treatment, this will be explored in the next chapter.

Mortality in the subacute phase and at 2 years was also higher in patients with MIS compared with patients with TIA. A similar finding was reported in OCSP and 2 year mortality risks were also similar.[26] The 1 year mortality rate of 18.5% in my study is similar to that of a hospital-based stroke cohort which found a rate of 21.5%.[34]

This study had some potential limitations. First, the risk of stroke in the acute phase may not be completely precise because an unknown proportion of patients with TIA and stroke will never seek medical attention. Second, I may have underestimated the risk after TIA and MIS as some patients with a major stroke with preceding events may not have been identified if it was impossible to obtain a history of events because they were aphasic, confused or unconscious. Third, this study included patients recruited into the EXPRESS study,[15] Phase 2 of which involved more urgent investigation and treatment, which will have reduced the absolute risk of events and possibly influenced the timing of recurrent events. A recent Californian hospital-

based cohort study of patients with ischaemic stroke in 2004-2006 has shown the one-year risk of recurrent stroke to be much lower, at 4.8%.[34] This low one year risk likely reflects improvements secondary prevention.[34]

In summary, timing to recurrent events varies according to event type. Recurrent stroke occurs early after TIA and is delayed after minor stroke. There is an unmet need for more effective prevention of recurrence in the subacute phase after minor ischaemic stroke.

7.5 References

1. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284(22):2901-6.
2. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369(9558):283-92
3. Giles MF, Rothwell PM. Substantial underestimation of the need for outpatient services for TIA and minor stroke. Age Ageing 2007; 36(6):676-80.
4. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005; 36(4):720-3.
5. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004;62(11):2015-20.
6. Lisabeth LD, Ireland JK, Risser JM, Brown DL, Smith MA, Garcia NM, Morgenstern LB. Stroke risk after transient ischemic attack in a population-based setting. Stroke 2004;35(8):1842-6.
7. Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. Stroke 2003; 34(8):e138-40.
8. Giles MF, Rothwell PM. Risk of stroke early after transient ischemic attack: a systematic review and meta-analysis. Lancet Neurol. 2007; 6(12):1063-1072.
9. Chandratheva A, Mehta Z, Geraghty OC, Marquardt L, Rothwell PM. Population-based study of risk and predictors of stroke in the first few hours after a TIA. Neurology 2009;72:1941-1947
10. Chandratheva A, Geraghty OC, Luengo-Fernandez R, Rothwell PM. The $ABCD^2$ score predicts severity rather than risk of early recurrent events after TIA. Stroke. 2010;41(5):851-6
11. Johnston SC, Sidney S, Bernstein A, Gress D. A comparison of risk factors for recurrent TIA and stroke in patients diagnosed with TIA. Neurology 2003;60:280-285
12. Flossmann E, Rothwell PM. Prognosis of vertebrobasilar transient ischaemic attacks and minor ischaemic stroke. Brain 2003;126:1940-1954
13. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischaemic stroke in population-based incidence studies. Neurology 2004; 62:569-573.

14. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, Mehta Z. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lance*t* 2005; 366(9479):29-36.
15. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lance*t.* 2007; 370(9596):1432-1442.
16. Lavallee PC, Meseguer E, Abboud H, et al. A transient ischemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol*.* 2007;6(11):953-960.
17. Calvet D, Lamy C, Touze E, Oppenheim C, Meder JF, Mas JL. Management and outcome of patients with transient ischemic attack admitted to a stroke unit. Cerebrovasc Dis. 2007;24(1):80-85.
18. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004; 328(7435):326.
19. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet*.* 2004;363(9425):1925-1933.
20. Rothwell PM, Coull AJ, Silver LE, 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). Lancet*.* 2005;366(9499):1773-1783.
21. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke. 2004;35(9):2041-2045.
22. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864-70.
23. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL 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;24:35-41.
24. Ois A, Gomis M, Rodriguez-Campello A, Cuadrado-Godia E, Jimenez-Conde J, Pont-Sunyer C, et al. Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. Stroke 2008;39(6):1717-21
25. Allen NB, Holford TR, Bracken MB, Goldstein L, Howard G, Wang Y, Lichtman JH. Trends in one-year recurrent ischaemic stroke among the elderly in the USA: 1994-2002. Cerebrovasc Dis 2010;30:525-532

26. Dennis MS, Bamford JM, Sandercock PAG, Warlow CP. A comparison of risk factors and prognosis for transient ischaemic attacks and minor ischaemic strokes: the Oxford Community stroke project. Stroke 1990; 20:1494-1499.
27. Mohan KM, Crichton SL, Grieve AP, Rudd AP, Wolfe CDE, Heuschmann PU. Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register. J Neurol Neurosurg Psychiatry 2009;80(9): 1012-8.
28. Petty GW, Brown RD Jr, Whisnant JP et al. Ischaemic stroke subtypes. A population based study of functional outcome, survival and recurrence. Stroke 2000;31:1062-1068.
29. Weimar C, Benemann J, Michalski D, Muller M et al on behalf of the German Stroke study collaboration. Prediction of recurrent stroke and vascular death in patients with transient ischaemic attack or nondisabling stroke: A prospective comparison of validated prognostic scores. Stroke 2010;41:487-493.
30. Pendlebury ST, Rothwell PM. Risk of recurrent stroke, other vascular events and dementia after transient ischaemic attack and stroke. Cerebrovasc Dis. 2009; 27 Suppl 3:1-11.
31. Chandratheva A, Lasserson DS, Geraghty OC, Rothwell PM. Population-based study of behaviour immediately after transient ischaemic attack and minor stroke in 1000 consecutive patients. Stroke 2010;41: 1108-14
32. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010; 123(7): 638-45 e4.
33. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. Stroke. 2009; 40(1): 235-40.
34. Navi B, Kamel H, Sidney S, Klingman J, Nguyen-Huynh MN, Johnston SC. Validation of the Stroke Prognostic instrument-II in a large, modern, community-based cohort of ischaemic stroke survivors. Stroke 2011; epub http://www.ncbi.nlm.nih.gov/pubmed/21960582. Accessed Ocrober 23rd 2011.

CHAPTER 8

Treating blood pressure to target levels in patients with TIA and non-disabling stroke: Feasibility, acceptability and blood pressure control with intensive Bluetooth home BP-monitoring

8.1 Introduction 170

8.2 Methods 171

8.2.1 Patients included in the study 171

8.2.2 Assessment and management of hypertension in the clinic .. 172

8.2.3 Patient training in home BP monitoring 172

8.3 Results 175

8.4 Discussion 184

8.5 References 189

8.1 Introduction

Hypertension is by far the most important modifiable risk factor for stroke.[1,2] Specifically, systolic blood pressure (BP) is associated with increased risk and isolated systolic hypertension is particularly important in elderly people.[1,3] Most patients have raised BP immediately after acute stroke.[4] BP lowering in the subacute phase and in the longer-term after TIA and stroke has been shown to reduce the risk of recurrent stroke, myocardial infarction and all vascular events[5-7] and is recommended in clinical guidelines.[8] However BP control in routine clinical practice is often poor.[9,10]

There may be several reasons for this, including under-treatment with anti-hypertensives due to "clinical inertia" (tendency of physicians to accept higher BP thresholds than stated in guidelines); underestimation of hypertension due to single rather than multiple measurements; "masked hypertension" (patients with normal office but pathological home BP readings), and patient non-adherence.[11] Since achieving BP control based on outpatient clinic readings is difficult, alternative methods are needed. Home BP monitoring (HBPM) has the potential to overcome some of these shortcomings: the greater number of measurements reveals masked hypertension, abolishes the "white-coat-effect", and helps to detect patients with high BP variability, a strong predictor of stroke, independent of mean systolic BP (SBP).[12-15] Furthermore, HBPM is a stronger predictor of cardiovascular risk than office BP measurements[16-18] and randomised controlled trials (RCTs) have consistently shown that HBPM improves BP control compared with office BP measurements.[19,20] Therefore replacement of office BP measurement with physician-independent methods such as ambulatory BP monitoring (ABPM) and home BP self-measurements is recommended in European and American guidelines.[21,22] However, HBPM has not previously been assessed in patients with TIA and minor stroke, who are mostly old and very-old patients with neurological and cognitive impairment. I therefore aimed to assess the feasibility and acceptability of treating BP to target levels in patients after TIA or minor stroke in

the Oxford Vascular Study (OXVASC) using HBPM. To enable constant monitoring with the ability of instantaneous intervention, Bluetooth-equipped BP telemonitors were used with immediate automatic transmission of measurements to the central stroke unit.

8.2 Methods

8.2.1 Patients included in the study

Patients were participants of OXVASC, a prospective, population-based study of all vascular events occurring within a population of approximately 91 100 individuals. The methods have been described in chapter 1 and elsewhere. [23,24] I studied consecutive patients directly referred from GPs to the OXVASC clinic with a TIA or minor stroke from 1st June 2008 to 31st May 2010. Patients who self-presented to the emergency department (ED) and were subsequently referred to the OXVASC clinic were also included. Patients who were admitted because of a stroke after presenting to their GP or to the ED, patients with recurrent TIAs already within OXVASC, patients who refused to participate and those unable to measure their own BP at home (e.g. because of dementia) were excluded.

All patients were consented and assessed by study neurologists as soon as possible after their initial presentation. Baseline characteristics, demographic data, vascular risk factors, and symptomatology were recorded in all patients. Pre-morbid BP readings were collected by study nurses reviewing life-long patient records held in primary care. Stroke severity was assessed using the National Institute of Health Stroke Scale Score (NIHSS).[25] Brain imaging, carotid ultrasound imaging and ECG were performed the same day (all patients), transthoracic or trans-oesophageal echocardiography (when clinically indicated) were arranged during the following week. All patients received best medical treatment and secondary prevention according to current guidelines.

8.2.2 Assessment and management of hypertension in the clinic

BP in the outpatient clinic was measured twice with an interval of at least three minutes using an automated BP monitor (AD UA-767). BP lowering therapy was started or continued in all patients with a history of hypertension or in patients with BP readings above 130/80 mmHg. In patients with BP> 130/80 who were not already on anti-hypertensives, perindopril 4mg with or without indapamide 1.25mg od or an alternative was started. In those with BP> 130/80 who were already taking anti-hypertensives, existing medication was increased or an additional drug was added (usually a diuretic, calcium channel blocker or angiotensin-II receptor blocker).

8.2.3 Patient training in home BP monitoring

During the clinic appointment, immediately after assessment, all patients were asked to monitor their BP at home with a Bluetooth-equipped BP monitor (UA-767PlusBT). Patients willing to participate were instructed how to measure their BP and how to use the mobile phone (t+ Medical, Abingdon, UK). Appropriately sized BP cuffs were fitted. Patients were asked to measure their BP in the contralateral arm to their dominant hand unless there was a 20 mmHg inter-arm difference in BP. In these cases, BP was measured in the arm with the higher readings. Competency taking readings, without the help of the instructor, was assessed and further practiced during the clinic appointment if required. If the patient was unable to measure their BP a family member or constant carer was instructed where possible. The use of the mobile phone and charger were explained. The phone was specifically designed by t+Medical so that, other than plugging the charger into the socket at home, the patient did not need to handle the phone.

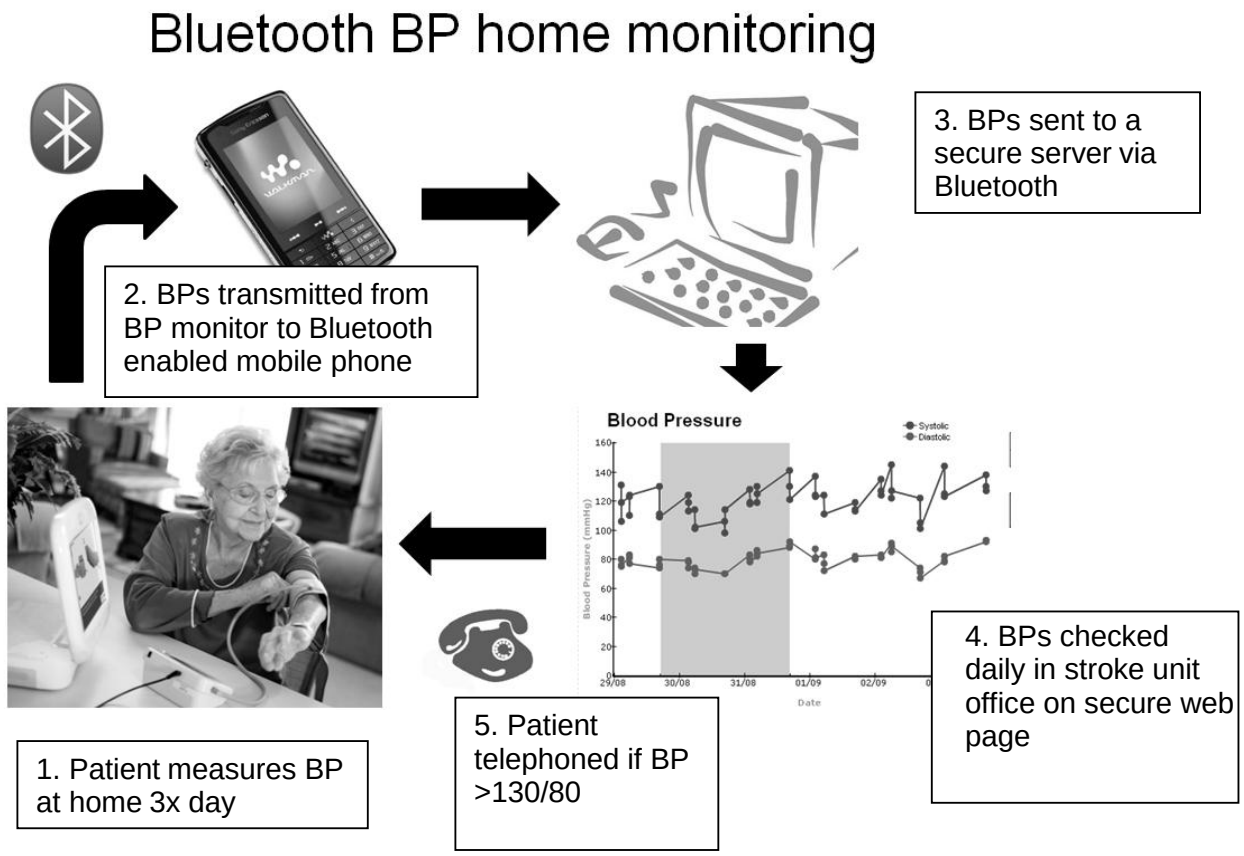
Patients were asked to measure their BP at home, sitting after a few minutes rest, three times a day: after wakening; at mid-morning (i.e. 10am) and before going to bed. At each sitting, patients were asked to take three BP readings waiting 3 minutes between each measurement. Patients

were asked to contact the stroke unit if they experienced problems with the equipment or had any adverse effects from medication and were given an instruction sheet containing written support and our phone number (Appendix XI.i). Bluetooth BP measurements were transmitted automatically in real time to the stroke unit where they were checked via secure web page in the morning of every working day by myself or another a clinical research fellow and once weekly by the senior neurologist (PMR) (Figure 8.1). If no readings were obtained from the previous day, patients were contacted to check if they had measured their BP and if the equipment was working. Any technical problems with the equipment could usually be managed by telephone (Appendix XI.ii). If BP was consistently above guidelines (>130/80 mmHg in ≥50% readings) antihypertensive therapy was intensified, either by starting perindopril with or without indapamide, increasing existing medication or adding in an additional drug. Patients with stenosis of the intra- or extracranial vessels were treated less aggressively. GPs were informed of changes to medication, and changes made by GPs were also recorded. In cases where BP could not be controlled despite increased medication or if there was clinical suspicion of secondary causes of hypertension, patients were referred to hypertension specialists for further investigations. If BP was controlled after one month of Bluetooth HBPM, patients were asked to return their equipment at their one month follow-up appointment. Otherwise they were asked to continue monitoring until BP was controlled. All patients who stopped Bluetooth monitor were asked to check their BP once weekly with a conventional home BP monitor (UA-767) and write down the readings on a pre-designed form (Appendix XI.iii). If the SBP of the third measurement of the weekly readings was above 160 mmHg or if the SBP of the third measurement was persistently above 140 mmHg, patients were asked to contact the stroke unit.

All patients were followed-up by study nurses in clinic one and three months after their event. Six month follow-up was performed at patients' homes. All patients were asked whether they had fallen since their last assessment. Disability was measured with the modified Rankin Scale

(mRS).[26] If office BP readings at one and three months were above guidelines, treatment was increased as per the treatment protocol above. At one month all patients received an anonymised questionnaire regarding their experience with Bluetooth HBPM (Appendix XI.iv). Patients were asked to answer 7 questions on HBPM and to rate their overall satisfaction on a scale ranging from 0 (poor) to 100 (excellent). Cognitive impairment was assessed during clinic appointments using the Mini-Mental State Examination (MMSE) at one month and the Montreal Cognitive Assessment (MoCA) at six months (Appendix XI.v).

Figure 8.1 Schematic diagram of process of home blood-pressure monitoring



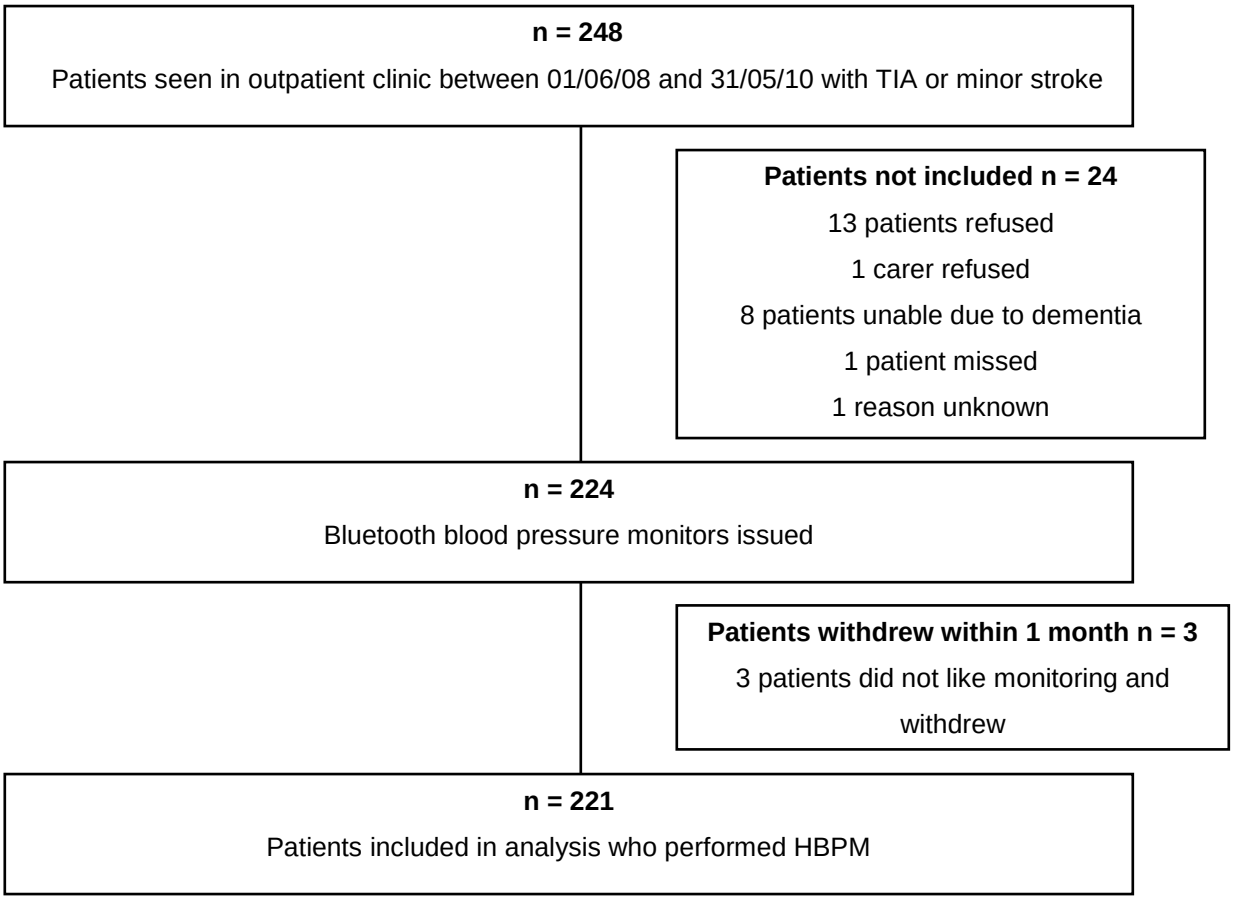
Upper limits of normal office and home BP were defined according to the American Heart Association.[27] Masked hypertension was defined as office BP <140/90 mmHg and mean BP of

all home readings ≥135/85 mmHg. White coat hypertension was defined as office BP ≥140/90 mmHg and mean BP of all home readings <135/85 mmHg.

8.3 Results

There were 248 patients with TIA or minor stroke referred to the OXVASC outpatient clinic between 1st of June 2008 and 31st of May 2010 who fulfilled the inclusion criteria. Thirteen patients and one carer (5.6%) refused to measure BP at home, 2 patients (1%) missed inclusion into the study and 8 patients (3.4%) were unable to measure their BP at home because of cognitive impairment (Figure 8.2).

Figure 8.2. Flowchart of patients included in the study



224 patients received a Bluetooth equipped BP monitor, of which 3 patients (1.2%) withdrew

within one month. Therefore 221 patients monitored their BP at home for at least one month. Baseline characteristics and cognitive status at follow-up are shown in Table 8.1.

Table 8.1. Baseline clinical characteristics of all 248 patients with a TIA or non-disabling stroke

		n (%)
Age (mean (SD))		70.0 (13)
Age ≥80		72 (29)
Male Sex		118 (48)
Hypertension		132 (53)
Diabetes		34 (14)
Previous angina		36 (14)
Previous myocardial infarction		14 (6)
Peripheral vascular disease		8 (3)
Previously diagnosed atrial fibrillation		33 (13)
Current smoker		38 (15)
Previous TIA		43 (17)
Previous stroke		13 (5)
Prior antiplatelet		100 (40)
Prior statin		61(25)
Event type	Incident	192 (77)
	Recurrent	56 (23)
TIA		148 (60)
Stroke		100 (40)
Cognitive function, median (range)		
MMSE at 1 month		27 (4-30)
MOCA at 6 month		23 (6-30)
Disability	mRS≥2	38 (15)

Mean age of the study population was 70 years (SD 13) and 29% of patients were older than 80 years. 60% of patients presented with a TIA and 40% with a minor stroke. An example of the graph of the BP readings viewed each day from a patient is shown in Appendix Xi.vi. The mean office and home BP readings from the first three and seven days from all patients are shown in Table 8.2.

Table 8.2. Office BP readings and home blood measurements, n=221

Office BP		**Bluetooth home BP measurements**			
		First three days		**First week**	
	n (%)	Mean <135/85	Mean ≥135/85	Mean <135/85	Mean ≥135/85
BP <140/90	67 (30.3)	40 (59.7)	27 (40.3)	47 (70.1)	20 (29.9)
BP ≥140/90	154 (69.7)	55 (35.7)	99 (64.3)	66 (42.9)	88 (57.1)

40% of patients with normal office BP measurements had a mean BP ≥135/85 mmHg during the first three days of HBPM, whereas 35.7% with high BP readings in office had normal measurements at home. Mean BP at assessment was 151/83 mmHg and dropped to 127/72 mmHg at the 6-month follow-up visit (Table 8.3).

Table 8.3. BP in patients before and after TIA and minor stroke participating in HBPM, n=221

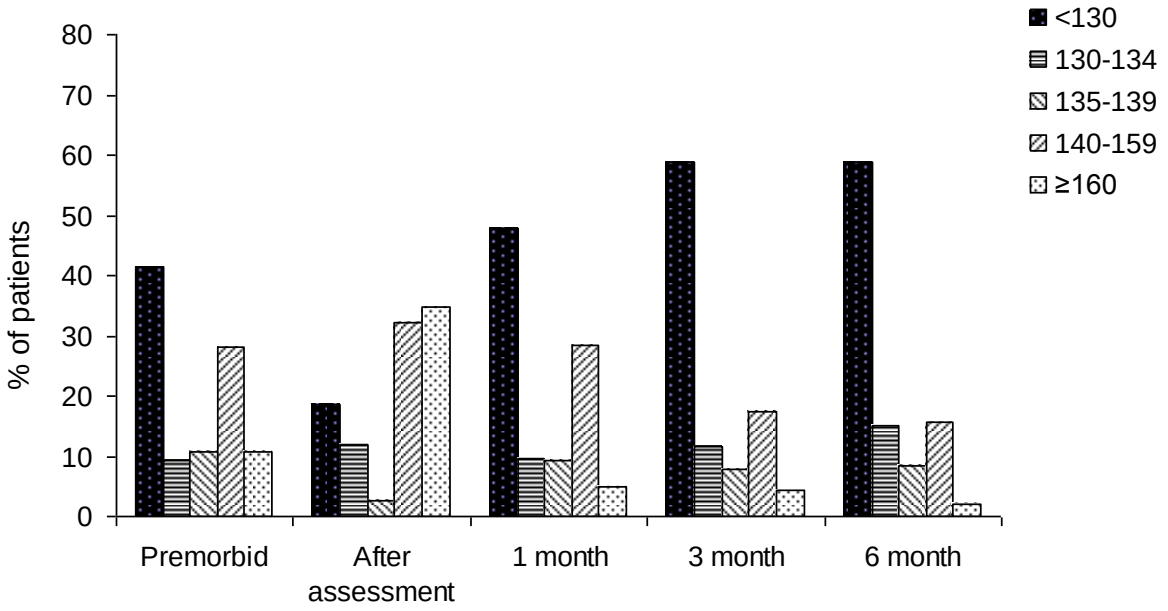
	Pre morbid	At assessment	At 1 month[a]	At 3 months[b]	At 6 months[c]
Mean SBP (SD)	136 (16.7)	151 (24.3)	132 (17.1)	127 (17.1)	127 (13.9)
Mean DBP (SD)	77 (10.3)	83 (13.2)	74 (9.8)	72 (10.8)	72 (9.6)
Number of patients	196	221	218	207	206

a. 3 cases missing (1 died,2 withdrew)
b. 14 cases missing (2 died, 2 declined, 4 withdrew, 4 did not attend, 2 telephone follow-up)
c. 15 cases missing (4 died, 4 declined or did not attend, 5 withdrew, 2 telephone follow-up)

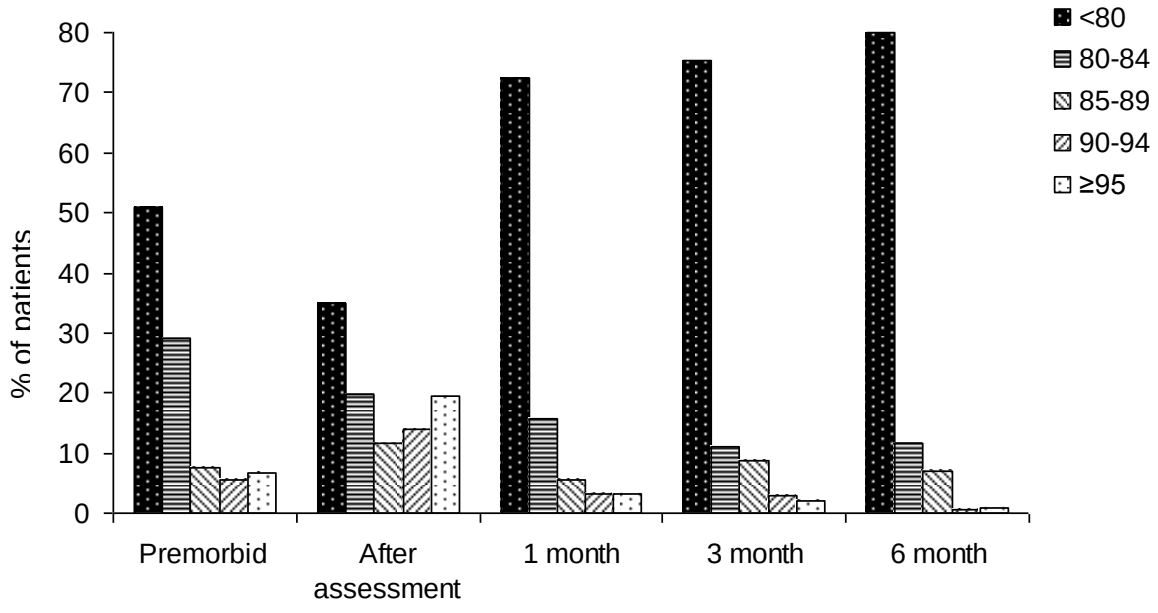
The proportion of patients with severe hypertension (BP≥160/95 mmHg) dropped from 39% at baseline assessment to 3% at 6 months and the number of patients with well controlled BP (<130/80 mmHg) increased from 14% to over 50% (Figure 8.3).

Figure 8.3. BP control before and after the event in patients participating in HBPM

a) Systolic blood pressure

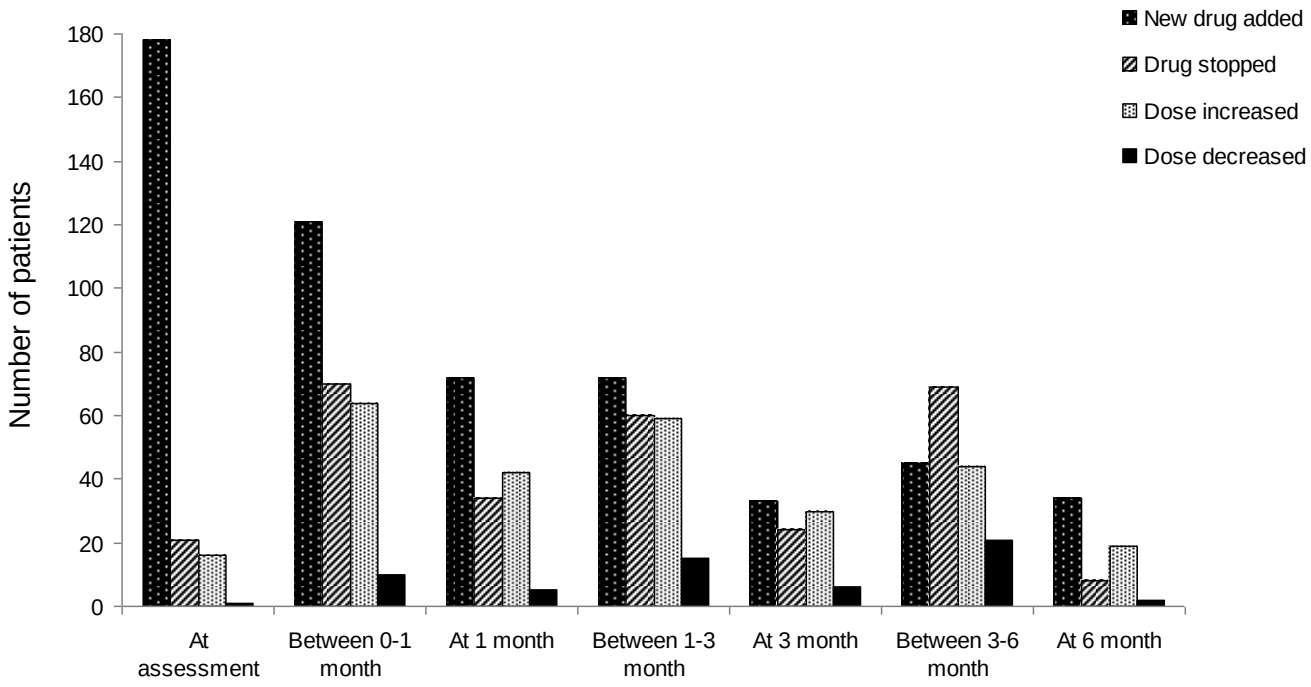


b) Diastolic blood pressure



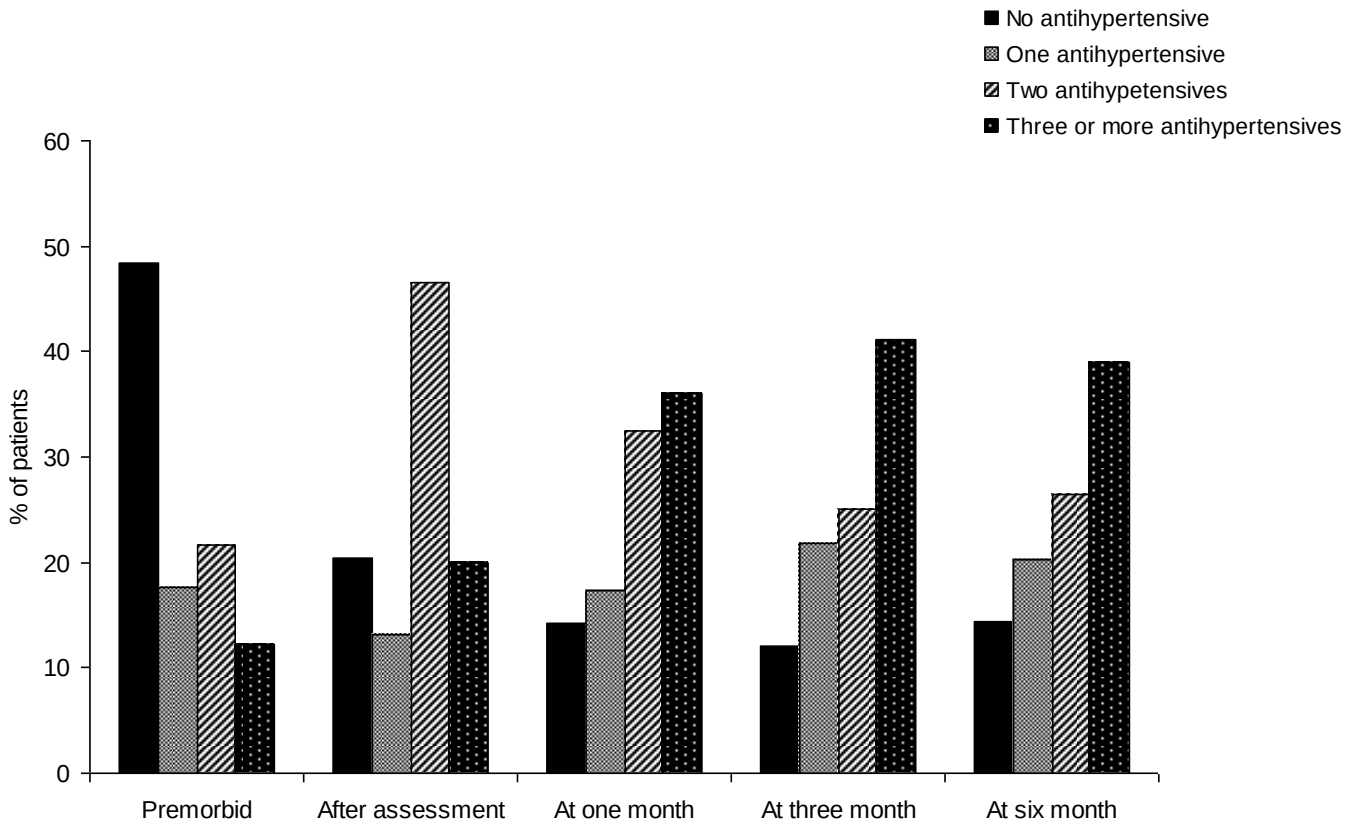
Monitoring resulted in 1175 changes in BP lowering medication: antihypertensive therapy was started 555 times, increased in 274 and decreased in 60 cases and had to be stopped 286 times. The number of interventions at baseline and during follow-up is shown in Figure 8.4.

Figure 8.4. Number of interventions in patients participating in HBPM



Before their event, 48% of patients were not taking anti-hypertensives (Figure 8.5). This number decreased to 14% at six months and 39% of patients were on three or more antihypertensives.

Figure 8.5. Percentage of patients on blood pressure lowering drugs



There were 191 (86%) who responded to the patient satisfaction questionnaire. Patient satisfaction (0=poor to 100=excellent) with HBPM was high (mean score = 87.1, SD 18.6), with 91% approving of intensive monitoring and 89% being reassured by the automated surveillance. 89% appreciated having a direct phone number to discuss BP readings and treatment (Figure 8.6a). Some patients felt that home BP measuring was uncomfortable (14%), too time consuming (13%), made them anxious (15%) and was difficult to remember (17%) (Figure 8.6b).

Figure 8.6a. Patients opinion on blood pressure self-measurement with Bluetooth system (n=191)

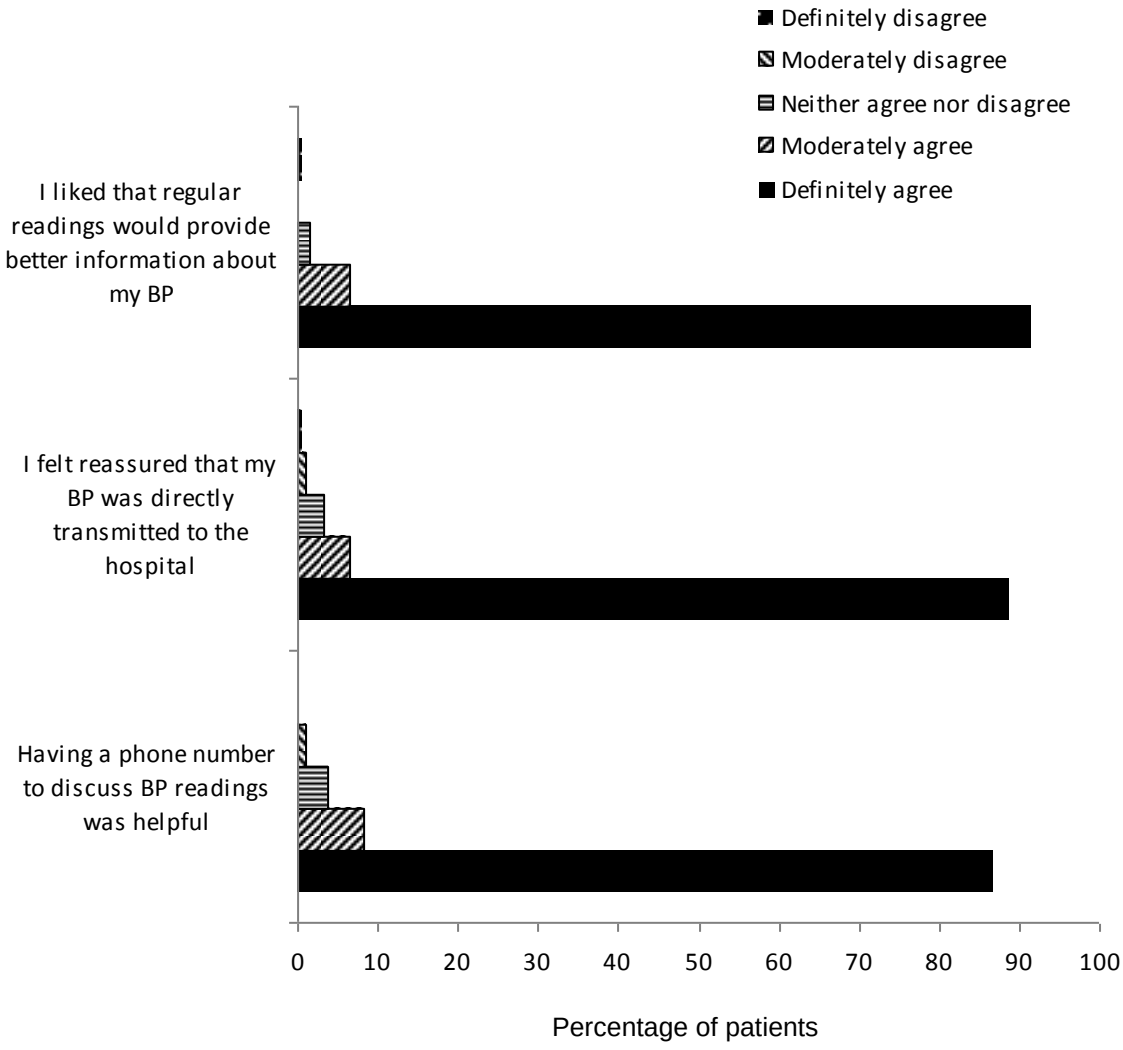
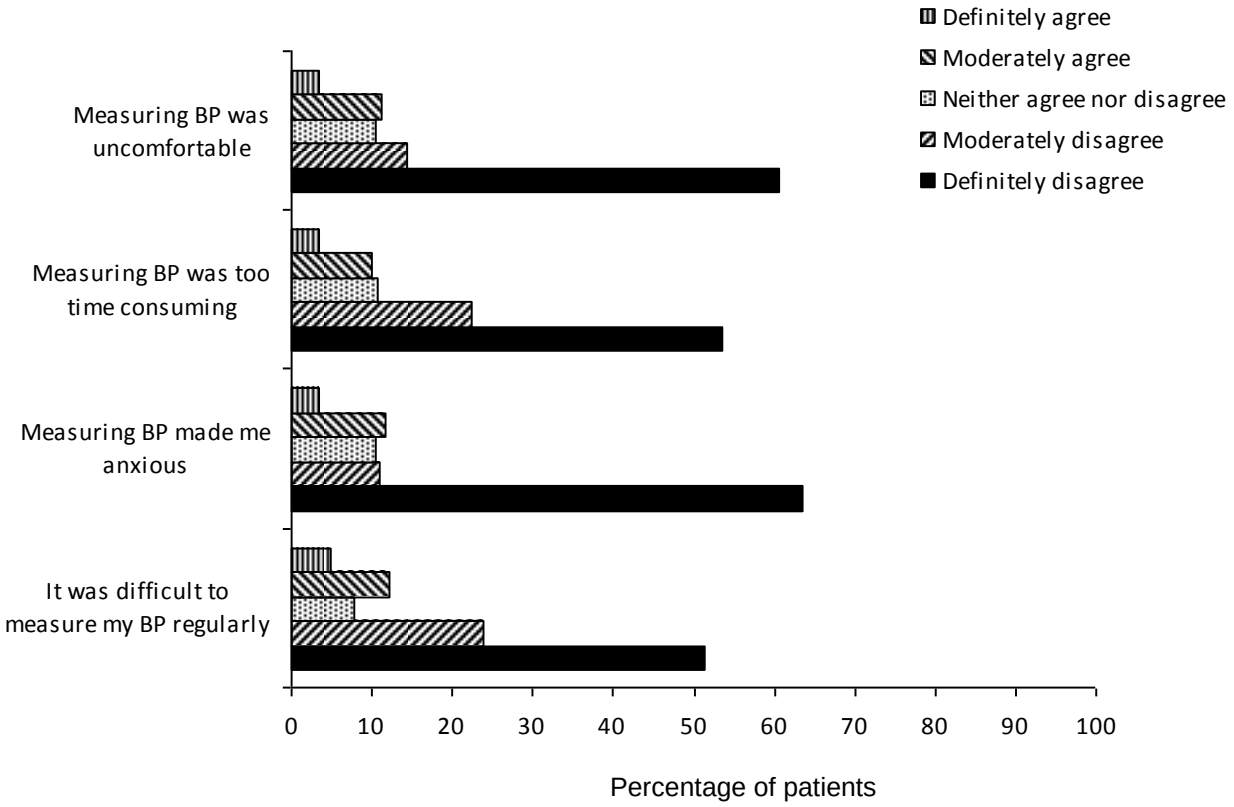


Figure 8.6b. Patients opinion on blood pressure self-measurement with Bluetooth system (n=191)



During the study period there were 110 (50%) patients who reported adverse events presumed to be due to antihypertensive medications and 59 (27%) reported more than one side effect (Table 8.4). There were 63 (29%) patients who reported a fall during the 6-month follow-up period. However, the number of patients with serious injury from their fall was low (2 patients, 0.9%). One patient required admission after a fall and one patient sustained a wrist fracture but did not require admission. There were 33 patients (15.1%) who reported ankle swelling, all of these cases were taking amlodipine.

Table 8.4. Adverse events in those participating in Bluetooth home BP monitoring, n=219*

Adverse event	Number of patients (%)
Dizziness/ pre syncope	51 (23.3)
Ankle swelling	33 (15.1)
Metabolic disturbance (hypokalaemia/hyponatraemia)	26 (11.9)
ACE inhibitor related cough	11 (5.0)
GI disturbance	9 (4.1)
Rash	8 (3.7)
Fatigue	6 (2.7)
Headache	4 (1.8)
Impotence	2 (0.9)
Depression	2 (0.9)
Myalgia	4 (1.8)
Palpitations/ chest pain	4 (1.8)
Falls	63 (28.8)
Mechanical	34
Unclear cause	23
Postural hypotension	4
Causing fracture or requiring admission	2

*Data unavailable for 2 patients

8.4 Discussion

This study on treating blood pressure to target with BP home telemonitoring in patients with acute TIA or minor stroke has three main findings. First, Bluetooth HBPM is feasible in most patients with TIA and minor stroke, irrespective of age and disability. Second, HBPM detects high levels of masked hypertension and informs titration of medication in most of patients. Third, HBPM is associated with good BP control at six months.

During the past decade, there has been a growing interest in HBPM as small, easily and reliably operated automatic devices have become available. HBPM is now advocated by European and American guidelines.[8,10] Although HBPM has already been performed in the elderly,[28,29] studies on feasibility in patients after TIA and minor stroke, mostly old and very-old patients with neurological and cognitive impairment, are lacking. In this study, 90% of patients with acute TIA and minor stroke were able to monitor their BP at home. The mean age in this population was 70 years with 29% above 80 years. The patients in this study had mild disability (mean NIHSS on admission: 0.5, mRS >0 at 1 month: 66%) and cognitive impairment (mean MMSE at 1-month 27 and MOCA at 6-month 23). However, only 8 of 248 patients (3.2%) were unable to measure their BP at home because of dementia and 19 patients (7.7%) refused monitoring or withdrew within one month. The readiness to participate and the high rate of compliance with continued monitoring may have been due to the ease of use of Bluetooth equipped BP monitors. In contrast to other monitors, these devices transmit BP readings automatically via mobile phone to the stroke unit. Patients do not have to document the readings and do not need technical knowledge to use a computer or a mobile phone, which for many elderly patients can be an obstacle to participation in studies using modern communication technology.[30]

Patients and clinicians can be falsely reassured by normal office BP measurements. Masked

hypertension, which can only be detected by home BP measurement, is associated with an increased risk of vascular events similar to the risk of sustained hypertension.[31-32] Rates of masked hypertension in the general population are estimated at 10%,[33] however rates in the elderly have been reported from 42% to more than 50%.[34,35] In this study, masked hypertension during the first 3 days of measurement was 40% and then dropped to 30% during the first week, which may be partly related to the natural decline of the hypertensive response in patients after TIA and minor stroke during the first few days after the event,[36] but may also be due to interventions with antihypertensives. Masked hypertension is also one of the possible manifestations of increased BP variability, a novel strong predictor of stroke, independent of mean SBP.[13-15] Blood pressure not only varies over months, weeks and days, but also within minutes. Variability in BP in patients after TIA and minor stroke is significantly higher than in the general population.[37] Multiple measurements assessed with HBPM help to detect patients with an increased BP variability, often elderly patients with impaired baroreceptor function and increased vessel stiffness.

HBPM with immediate transfer of data has advantages over conventional BP self-measurements without telemonitoring, since the constant feedback on BP control gives the potential to intervene immediately if necessary. In this study, monitoring lead to 1175 changes in BP lowering medication in 221 patients. The number of patients with three or more antihypertensives increased from 12% before the event to 39% at 6 months, and only 14% of patients were on no antihypertensives at 6 months. Clinicians starting antihypertensive therapy are often concerned about hypotension and the risk of falls. HBPM helps to detect hypotensive episodes and can therefore reassure patients and clinicians. RCTs and meta-analysis on HBPM have shown BP control is better when measured at home than in office.[38-39] In this study mean BP at assessment dropped from 151/83 mmHg to 127/72 mmHg at the 6-month follow-up visit. More importantly, the proportion of patients with severe hypertension (BP≥160/95 mmHg)

dropped from 39% at baseline assessment to 3% at 6 months and the number of patients with well controlled BP (<130/80 mmHg) increased from 14% to over 50%. Treating patients to target BP seems therefore possible, even in elderly patients with cerebrovascular disease.

Patient satisfaction with HBPM was high, 91% approving of intensive monitoring and 89% being reassured by the automated surveillance. There are concerns that BP self-monitoring worries patients and increases anxiety, which in turn influences BP behaviour. However in this study only a minority of patients reported anxiety. The availability of direct phone contact with the central stroke unit providing the option of discussing BP readings might have contributed to the high acceptability of HBPM.

There is increasing evidence from surveys that patients are willing to become more involved in managing their own care.[40] HBPM is one way to increase patient involvement. A comparison of acceptability and preferences for different methods of BP measuring in primary care showed that BP home self-monitoring performed significantly better than ABPM or office measurements by physicians and nurses.[41] The constant feedback on BP control also has the potential to increase adherence with antihypertensive therapy.

In my study, half of patients reported adverse events considered by the patient and assessing clinician to be related to anti-hypertensive medication. 29% of patients reported a fall during 6 months of follow up, although a clear history of postural hypotension could be obtained in only 6% of these cases and most of the falls were felt to be mechanical. Furthermore, only 2 patients required hospital treatment because of their fall. The rate of falls among patients with stroke ranges from 25-44%.[42] A prospective, population-based study from New Zealand, reported 37% of 1104 interviewed patients had at least 1 fall within 6 months after stroke.[43] Therefore, the proportion of patients with falls in my study does not exceed the proportion reported in other

studies. Ankle swelling occurred in 15% of patients, all of whom were taking amlodipine. Peripheral oedema, particularly of the lower limbs, has been reported to occur in up to 35% of patients receiving dihydropyridine calcium channel blockers for hypertension in clinical trials and is a common reason for treatment discontinuation. In recent studies, the addition of valsartan to amlodipine has been shown to reduce ankle oedema and this could be an approach considered for use in this study.[44]

This study has some limitations. First, although I have assessed the feasibility of home HBPM and used the results to treat to target BP levels, the gold-standard method of hypertension assessment is ambulatory BP monitoring (ABPM). All patients in this study were offered 24 hour ABPM at 1 month and the analysis of these results in comparison with the clinic and HBPM data is an area of ongoing work. The advantage of HBPM, is that medium and long-term BP variability can be assessed whereas 24 hour ABPM assesses only short-term, diurnal BP variability. The effect of BP variability on recurrent stroke risk within OXVASC is an area of on-going study. Second, although 91% of patients approved of HBPM, these results are based on the 86% of patients who responded to the patient satisfaction questionnaire. The non-responders may have different attitudes toward HBPM and may have been less inclined to answer the questionnaire. Third, although the proportion of patients who reported falls in this study is comparable with the proportions found at 6 months post stroke in other studies, data on the frequency of falls in those in the OXVASC population who did not participate in this blood pressure study would be useful to establish whether there is an excess of falls over that expected, associated with this method of BP control. This data could be obtained from hospital event statistics and is an area of future work. Fourth, it may be that the results from this study are not generalisable to the wider TIA and minor stroke population, however it has previously been shown that after TIA and minor stroke BP follow-up by telephone alone is not an effective method of BP management,[43] therefore an alternative strategy, such as with HBPM, is required.

In this study, a proof of concept is presented; validation in other studies is needed. Fifth, in this study I have only presented outcomes up to 6-months, ongoing work is needed to see if the benefits of this approach persist. Sixth, cost-effectiveness of HBPM not been assessed in this study but could be topic for further work.

In conclusion, this study shows that HBPM is feasible in the majority of patients after TIA and minor stroke with high acceptability and with good BP control during follow-up. Whether intense HBPM with Bluetooth technology also reduces recurrent stroke risk after TIA and minor stroke in the subacute and long-term phase is currently being addressed in a large prospective population-based sequential comparison within OXVASC.

8.5 References

1. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies
2. Law MR, Morris JK, Wald NJ. 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:b1665
3. Blood Pressure Lowering Treatment Trialists' Collaboration. Turnbull F, Neal B, Ninomiya T et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomized trials. BMJ 2008: 336:1121-23
4. Wallace JD, Levy LL. Blood pressure after stroke. JAMA 1981;246:2177-80
5. 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; 358:1033-41.
6. Schrader J, Luders S, Kulschewski A, Berger J, Treib J et al. The ACCESS study: evaluation of Acute Candesartan Cilexitil Therapy in Stroke Survivors. Stroke 2003:34:1699-703.
7. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin converting-enzyme inhibitor, ramipril, on death from cardiovascular causes, myocardial infarction and stroke in high-risk patients. N Engl J Med 2000; 342: 145–53
8. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, et al. Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25:1105-87.
9. Degli Eposti L, Valpiani G. Pharmacoeconomic burden of undertreating hypertension. Pharmacoeconomics. 2004;22:907-928.
10. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. and the National High BP Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection and Evaluation, and Treatment of High BP. Hypertension 2005; 42: 12061252.
11. Cuffe RL, Howard SC, Algra A, Warlow CP, Rothwell PM. Medium-term variability of blood pressure and potential underdiagnosis of hypertension in patients with previous transient ischemic attack or minor stroke. Stroke. 2006;37:2776-2783.
12. Rothwell PM. Limitations of the usual blood pressure hypothesis and the importance of

variability, instability and episodic hypertension. Lancet. 2010;375:938-48.

13. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010;375;895-905
14. Rothwell PM, Howard SC, Dolan E, et al. Effects of beta-blockers and calcium channel blockers on within-individual variability in blood and risk of stroke. Lancet Neurology. 2010;9:469-80.
15. Webb AJS, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive drug class on inter-individual variation in blood pressure: a systematic review and meta-analysis. Lancet. 2010;375:906-15.
16. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, et al. Cardiovascular prognosis of “masked hypertension” detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA. 2004;291:1342-1349.
17. Niiranen TJ, Hänninen MR, Johansson J, Reunanen A, Jula AM. Home-measured blood pressure is a stronger predictor of cardiovascular risk than office blood pressure. The Finn-Home study. Hypertension. 2010;55:1346-1351.
18. Asayama K, Ohkubo T, Kikuya M, Metoki H, Hoshi H, Hashimoto J, et al. Prediction of stroke by self-measurement of blood pressure at home versus casual screening blood pressure measurements in relation to the Joint National Committee 7 classification: the Ohasama study. Stroke. 2004;35:2356-2361.
19. Green BB, Cook AJ, Ralston JD, Fishman PA, Catz SL, Carlson J, et al. Effectiveness of home blood pressure monitoring, web communication, and pharmacist care on hypertension control. A randomized controlled trial. JAMA. 2008;299:2857-2867.
20. Agarwal R, Bills JE, Hecht TJW, Light RP. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control. A systematic review and meta-analysis. Hypertension. 2011;57:29-38.
21. Parati G, Stergiou GS, Asmar R, Bilo G, de Leeuw P, Imai Y, et al.; ESH Working Group on Blood Pressure Monitoring. 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. J Hypertens. 2008.26:1505-26.
22. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: executive summary. A joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. Hypertension. 2008;52:1–9
23. Rothwell PM, Coull AJ, Silver LE, 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). Lancet. 2005;66:1773-83.

24. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;33:1925-33.
25. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20:846–870.
26. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, von Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604-607.
27. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurements in humans and experimental animals: Part 1: blood pressure in humans: a statement for professionals from the subcommittee of professional and public education of the American heart association council on high blood pressure research. Circulation. 2005;111:697-716.
28. Friedman RH, Kazis LE, Jetta A, Smith MB, Stollerman J, Torgenson J, Carey K. A telecommunications system for monitoring and counselling patients with hypertension. Impact of medication adherence and blood pressure control. Am J Hypertens. 1996;9:285-92.
29. Broege PA, James GD, Pickering TG. Management of hypertension in the elderly using home blood pressures. Blood Press Monit. 2001;6:139-44
30. Green BB, Anderson ML, Ralston JD, Catz S, Fishman PA, Cook AJ. Patient ability and willingness to participate in a web-based intervention to improve hypertension control. J Med Internet Res. 2001;13:e1.
31. Mancia G, Bombelli M, Facchetti R, et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. Hypertension. 2009;54:226–32.
32. Pickering TG, Eguchi K, Kario K. Masked hypertension: a review. Hypertens Res. 2007;30:479–88.
33. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation. 2005;111:1777–1783.
34. Bobrie G, Genès N, Vaur L, Clerson P, Vaisse B, Mallion JM, Chatellier G. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? Arch Intern Med. 2001;161:2205–2211.
35. Oikawa T, Obara T, Ohkubo T, Kikuya M, Asayama K, Metoki H, et al. J-HOME Study Group. Characteristics of resistant hypertension determined by self-measured blood

pressure at home and office blood pressure measurements: the J-HOME study. J Hypertens. 2006;24:1737–1743.

36. Tikhonoff V, Zhang H, Richart T, Staessen JA. Blood pressure as a prognostic factor after acute stroke. Lancet Neurol 2009;8:938-48
37. Howard SC, Rothwell PM. Regression dilution of systolic and diastolic blood pressure in patients with established cerebrovascular disease. J Clin Epidemiol. 2003;56 :1084-1091
38. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. Lancet. 2010;376:163-72
39. Cappuccio FP, Kerry SM, Forbes L, Donald A. Blood pressure control by home monitoring: meta-analysis of randomised trials. BMJ. 2004;329:145.
40. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program in patients with chronic disease. Eff Clin Pract. 2001;4:256-262.
41. Little P, Barnett J, Barnsley L, Marjoram J, Fitzgerald-Barron A, Mant D. Comparison of acceptability of and preferences for different methods of BP measuring in primary care. BMJ.2002;325:258-259.
42. Divani AA, Vazquez G, Barrett AM, Asadollahi M, Luft A. Risk factors associated with injury attributable to falling among elderly population with history of stroke. Stroke 2009;40:3286-3292
43. Adie K, James MA. Does telephone follow-up improve blood pressure after minor stroke or TIA. Age and Ageing 2010;39:598-603.
44. Fogari R, Malamani G, Corradi L, Mugellini A, Preti P, Zoppi A, Derosa G. Effect of Valsartan or Olmesartan addition to amlodipine on ankle edema in hypertensive patients. Adv Ther 2010;27:48-55.

CHAPTER 9

Long term outcomes after TIA and stroke

9.1 Introduction 194

9.2 Methods 195

9.2.1 Analysis 197

9.3 Results 197

9.4 Discussion 215

9.5 References 218

9.1 Introduction

Approximately 20% of all ischaemic strokes are recurrent strokes and they cause greater disability, financial burden and mortality than first strokes.[1-3] Population based studies have shown that risk after TIA and stroke is highest within the first year, around 12-14%, and then slowly decreases with time but remains elevated for up to 15 years. [4-8] Advances in secondary prevention and more widespread use of evidence-based practices such as early use of antiplatelets, statins, anticoagulation in patients with atrial fibrillation, blood-pressure lowering and revascularization in those with symptomatic carotid stenosis have reduced early recurrent stroke risk.[9,10] However, there is less published data on their effects on later outcomes. In chapter 7, the high recurrent stroke risk after minor ischaemic stroke (MIS) in the sub-acute phase despite high levels of secondary prevention use was discussed. The recent improvements in secondary prevention measures may also reduce cardiac risk as well as stroke risk. A meta-analysis has shown the risk of MI after TIA or stroke to be approximately 2% per year, however, whether there has been any reduction in risk in light of improvements in secondary prevention is not known.[11,12]

There is considerable variation in long-term recurrence risks and mortality risk after TIA and stroke in published studies, with annual stroke risks of 2.2-7% and 5 year mortality risks ranging from 41-72%.[8] This variation may be caused by different definitions of stroke recurrence, differences in acute and preventative management, and different methodology, (i.e. hospital based, population-based or clinical trial populations). Data on later outcomes after TIA and stroke in the modern era could help to target secondary prevention. The aims of this study were to determine the time course of recurrent stroke risk, cardiac risk and mortality after TIA and ischaemic stroke beyond the acute phase and determine whether the quality of secondary prevention is a factor determining late recurrence. I addressed these issues in a prospective

population based study of all incident and recurrent TIA and stroke in Oxfordshire, UK (Oxford Vascular Study), from 1st April 2002 to 31st March 2010 with follow-up until 31st July 2010.

9.2 Methods

The study methods and setting of the Oxford Vascular Study (OXVASC) have been described in chapter 1 and elsewhere.[13,14] Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke. [13-15] All patients were consented and seen by study physicians as soon as possible after their initial presentation. Baseline characteristics were recorded in all patients and assessments were made for severity of event (using National Institute of Health Stroke Scale, NIHSS[16]) and clinical features. Events were classified as minor stroke if there was a focal neurological deficit lasting greater than 24 hours and an NIHSS score ≤5 at time of assessment by a study physician. A cut off of NIHSS score ≤5 was chosen as this included the majority (96%) of patients with stroke seen in the outpatient setting.[9] Patients ascertained with a stroke but who had a preceding TIA that they had not brought to medical attention were included. Event characteristics and risk factors were recorded and all patients underwent brain imaging, with CT or MRI as appropriate. All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA or stroke or other condition using standard definitions.[13,14] All patients with recurrent events were reassessed by a study physician and then case reviewed by PMR. Patients with stroke in whom it was impossible to obtain a definite history of preceding TIA or stroke because they were aphasic, confused, or unconscious were excluded. Patients with primary intracerebral haemorrhage and those who presented as a stroke death were excluded. All patients received best medical treatment and secondary prevention according to current guidelines.

Patients were followed up face-to-face at 1 month, 6 months, 1 year and 5 years by a study nurse or physician. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. The timing of all recurrent strokes and cardiac events (including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and sudden cardiac deaths up to 8 years after the first event was recorded. All recurrent strokes and cardiac events that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. Aetiological classification of cerebrovascular events was performed according to the TOAST classification once investigations were complete. All deaths during follow-up were recorded with cause of death.[17] The cause of death was determined from death certificates, coroners reports, patient medical notes and coding from the Office for National Statistics National Health Service Central Register and then categorised into

- fatal stroke, in patients who died as a direct result or complication of stroke within 6 months of the event,
- myocardial infarction or sudden cardiac death,
- non-vascular death,
- peripheral vascular disease death, in patients who died due to an acute peripheral vascular event such as an abdominal aortic aneurysm rupture or a complication of limb ischaemia.

9.2.1 Analysis

I restricted analysis to the risk of recurrent events after the first TIA or ischaemic stroke in the study period (index event). The risks of recurrent ischaemic stroke, cardiac events and deaths within 8 years of TIA and ischaemic stroke were censored for deaths and follow-up until 31st July 2010. Recurrent stroke risks were analysed from the time of index event and from time of first seeking medical attention. A recurrent stroke was defined as a new and persistent neurological symptom in a patient in whom the initial symptoms were stable or had already substantially or fully recovered. In patients who had multiple recurrent cerebrovascular events the end point was classified as the first recurrence following the index event. Kaplan-Meier survival analysis was used to calculate recurrence risks.

9.3 Results

Of 2035 consecutive, first cerebrovascular events within the study period from 1st April 2002 to 31st March 2010, there were 1928 patients with ischaemic events, 100 with primary intracerebral haemorrhage and 7 acute stroke deaths of uncertain cause. Complete baseline data were available on all patients and face to face or telephone follow-up data were available on 1811 (94%) first ischaemic events (106 refused participation in the follow-up study and 11 moved out of area and were not available for follow up), however death certificates and Hospital Episode Statistics (HES) were available for all patients. The mean time to death or final follow-up for all cases was 3.13 years (SD 2.4). The mean (range) age at first TIA was 71.8 (24-99) years and at first stroke 75.2 (26-99) years (Table 9.1). 39.6% of cases (763/1928) were aged over 80 years. Patients with minor ischaemic stroke (MIS) were more likely to be male ($p<0.01$). Increasing event severity was associated with age ($p<0.0001$), atrial fibrillation ($p<0.0001$), hypertension ($p=0.002$), peripheral vascular disease ($p=0.007$), previous stroke ($p=0.001$), previous anti-platelet ($p=0.001$) and anti-hypertensive ($p=0.02$) use.

Table 9.1. Baseline characteristics, vascular risk factors and premorbid medication of patients presenting with TIA or ischaemic stroke, n=1928

	TIA (n=832)	Minor stroke (n=779)	Major stroke (n=317)	p-value
Age (mean (SD))	71.8 (13.4)	73.5 (12.7)	79.5 (10.8)	**<0.0001**
Male Sex	381 (45.8)	395 (50.7)	130 (41.0)	**0.009**
Hypertension	438 (52.6)	445 (57.1)	203 (64.0)	**0.002**
Diabetes	100 (12.0)	98 (12.6)	32 (10.1)	0.523
Angina or myocardial infarction	153 (18.4)	157 (20.2)	70 (22.1)	0.340
Peripheral vascular disease	40 (4.8)	60 (7.7)	30 (9.5)	**0.007**
Previously diagnosed atrial fibrillation	129 (15.5)	131 (16.8)	93 (29.3)	**<0.0001**
Current Smoker	102 (12.3)	108 (13.9)	38 (12.0)	0.569
Previous TIA	106 (12.7)	57 (7.3)	26 (8.2)	**0.001**
Previous stroke	77 (9.3)	106 (13.6)	53 (16.7)	**0.001**
Prior antiplatelet	292 (35.1)	319 (40.9)	149 (47.0)	**0.001**
Prior statin	190 (22.8)	174 (22.4)	69 (21.8)	0.925
Prior antihypertensive	450 (54.1)	442 (56.7)	200 (63.1)	**0.022**

There were 328 recurrent strokes within 8 years of follow-up (Table 9.2). Of 328 cases of recurrent stroke at 8 years, 114 occurred within 7 days (35%), the majority of these (74, 65%) following a TIA. Of 197 recurrent events within 90 days, 107 (54%) were preceded by a TIA, 73 (37%) by MIS and 17 (9%) by major ischaemic stroke. The 90-day stroke risks from event onset were 12.9% (95% CI 10.5-15.3) after TIA, 9.5% (7.3-11.7) after MIS and 7.3% (4.0-10.6) after major ischaemic stroke.

Table 9.2: Recurrent strokes (% risk, 95% CI) up to 8 years after TIA and ischaemic stroke from event onset and time of seeking medical attention

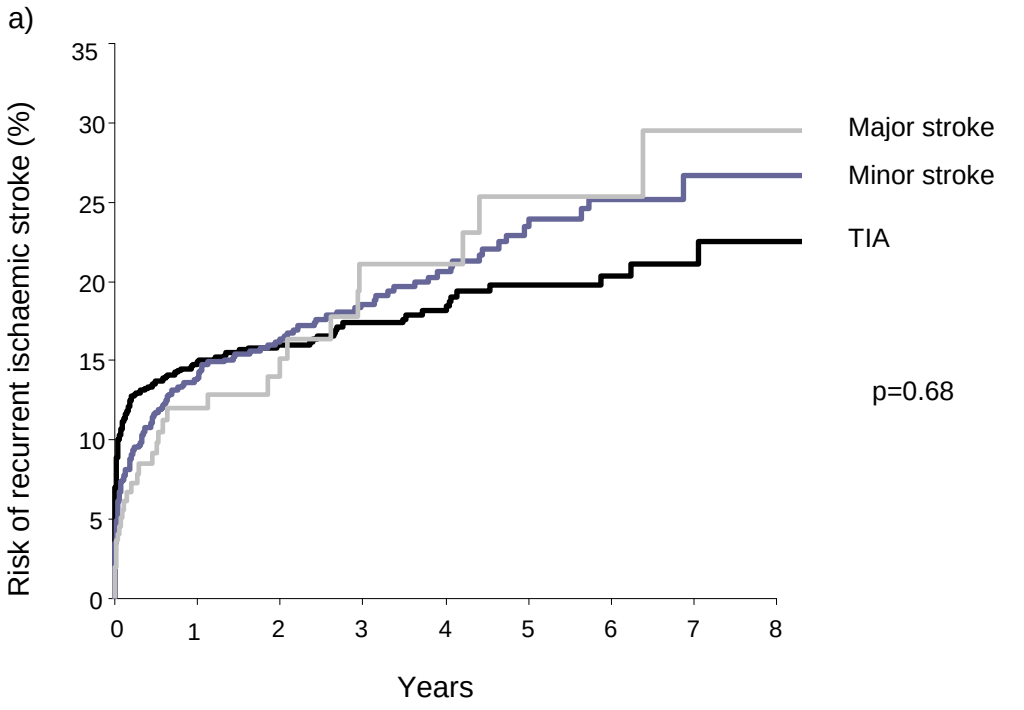
		7 days		90 days		1 year		5 years		8 years	
	Patients	Strokes	% risk	Strokes	% risk	Strokes	% risk	Strokes	% risk	Strokes	% risk
All TIA	832	74	8.9 (6.9 - 10.9)	107	12.9 (10.5 - 15.3)	123	14.9 (12.5 - 17.3)	145	19.7 (16.6 – 22.8)	148	22.5 (18.0 - 27)
TIA seeking medical attention	778	40	5.1 (3.5 – 6.7)	56	7.2 (5.4 -9.0)	69	9.0 (7.0 – 11.0)	91	14.1 (11.2 – 17.0)	94	17.1 (12.6 – 21.6)
Minor stroke	779	33	4.2 (2.8 - 5.6)	73	9.5 (7.3 - 11.7)	104	13.9 (11.4 – 16.4)	142	23.4 (19.7 – 27.1)	146	26.6 (21.7 – 31.5)
Minor stroke seeking medical attention	764	28	3.7 (2.3 – 5.1)	59	7.8 (5.8 – 9.8)	90	12.4 (10.0 – 14.8)	128	22.4 (18.5 – 26.3)	131	25.2 (20.1 – 30.3)
Major stroke	317	7	2.4 (0.6 - 4.2)	17	7.3 (4.0 – 10.6)	24	12.0 (7.3 – 16.7)	33	25.3 (15.9 – 34.7)	34	29.5 (17.7 – 41.3)
Major stroke seeking medical attention	314	5	1.7 (0.1 – 3.3)	14	6.1 (3.0 – 9.2)	21	10.9 (6.4 – 15.4)	30	24.4 (15.0 – 33.8)	31	28.6 (16.6 – 40.6)
All patients	1928	114	6.0 (5.0 – 7.0)	197	10.7 (9.3 - 12.1)	251	14.0 (12.4 – 15.6)	320	21.7 (19.3 – 24.1)	328	24.6 (21.5 – 27.7)
All seeking medical attention	1856	73	4.0 (3.0 – 5.0)	129	7.3 (6.1 – 8.5)	180	10.5 (9.1 – 11.9)	249	18.5 (16.1 – 20.9)	256	21.5 (18.4 – 24.6)

At one year, the recurrent stroke risk after any ischaemic events was 14.0% (12.4-15.6). The one year recurrence risks were similar between event types, being 14.9% (10.5-17.3) after TIA, 13.9% (11.4-16.4) after MIS and 12.0% (7.3-16.7) after major ischaemic stroke (p=0.21).

By 8 years from event onset, recurrent stroke risks after TIA, minor and major stroke remained similar (22.5% vs 26.6% vs 29.5%, p=0.68, Figure 9.1a). However, the timing of recurrence risk varied according to initial event type and time of seeking medical attention. Up to 7 days after event onset, stroke risk following TIA was double that after minor stroke (8.9%, 74/832 vs 4.2% 33/779, OR 2.21, 95% CI 1.41-3.44, p<0.001). 72 patients (54 TIA, 15 minor and 3 major strokes) did not seek medical attention at the time of their event but sought medical attention after the recurrent event. When cases that did not seek medical attention at the time of the first event were excluded, the risks of recurrence after TIA and minor stroke were similar up to 7 days (5.1%, 40/778 vs 3.7%, 28/764, p=0.17, Figure 9.1b), however, between 8-90 days the risk after minor stroke remained higher, (4.2%, 31/736 vs 2.2%, 16/738, OR 1.94, 1.06-3.55, p=0.04, Figure 9.1b). The higher recurrent stroke risk after minor stroke persisted beyond 90 days up to 8 years from seeking medical attention (18.8% (13.7-23.9) vs 10.7% (6.2-15.2), p<0.0001, Figures 9.2 and 9.3).

The median time to recurrent stroke within the first year after event onset was 4 days for TIA vs 23 days for minor stroke (p<0.001). After major stroke the median time to recurrent event was similarly delayed when compared to TIA (25 days vs 4 days, Table 9.3).

Figure 9.1. Risk of recurrent stroke up to 8 years after TIA, minor ischaemic stroke and major ischaemic stroke: a) from event onset and b) from time of seeking medical attention



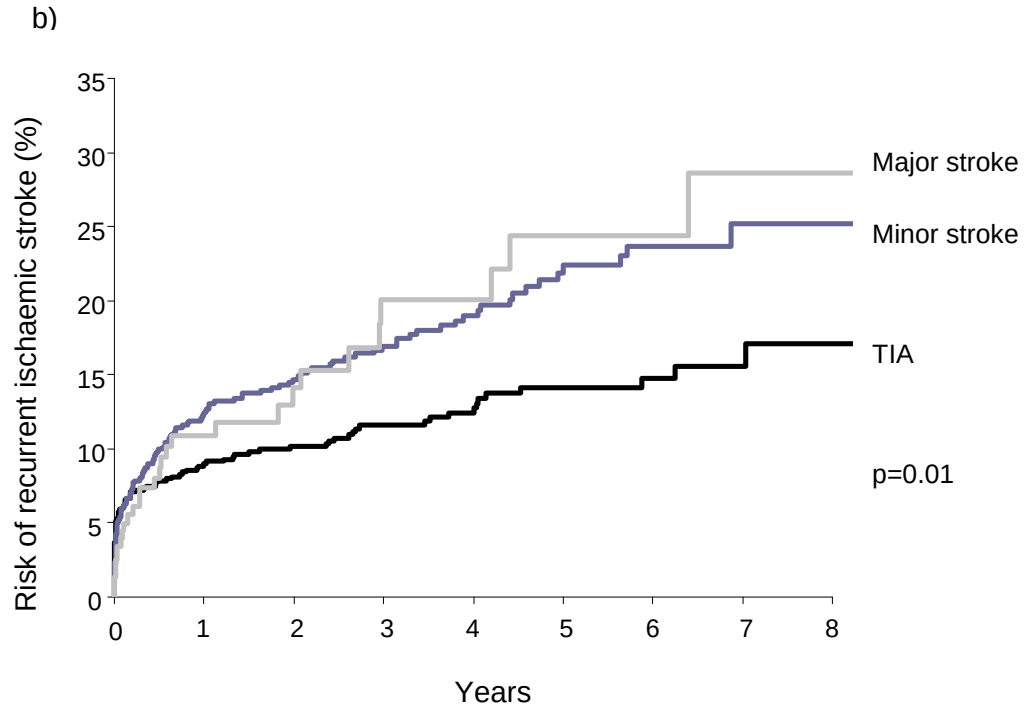


Figure 9.2. Post 90 day risk of recurrent stroke up to 8 years from time of first seeking medical attention after TIA or ischaemic stroke, (n=1856). 72 cases (54 TIA, 15 MIS and 3 major stroke) did not seek medical attention at the time of their event but presented after the recurrent stroke.

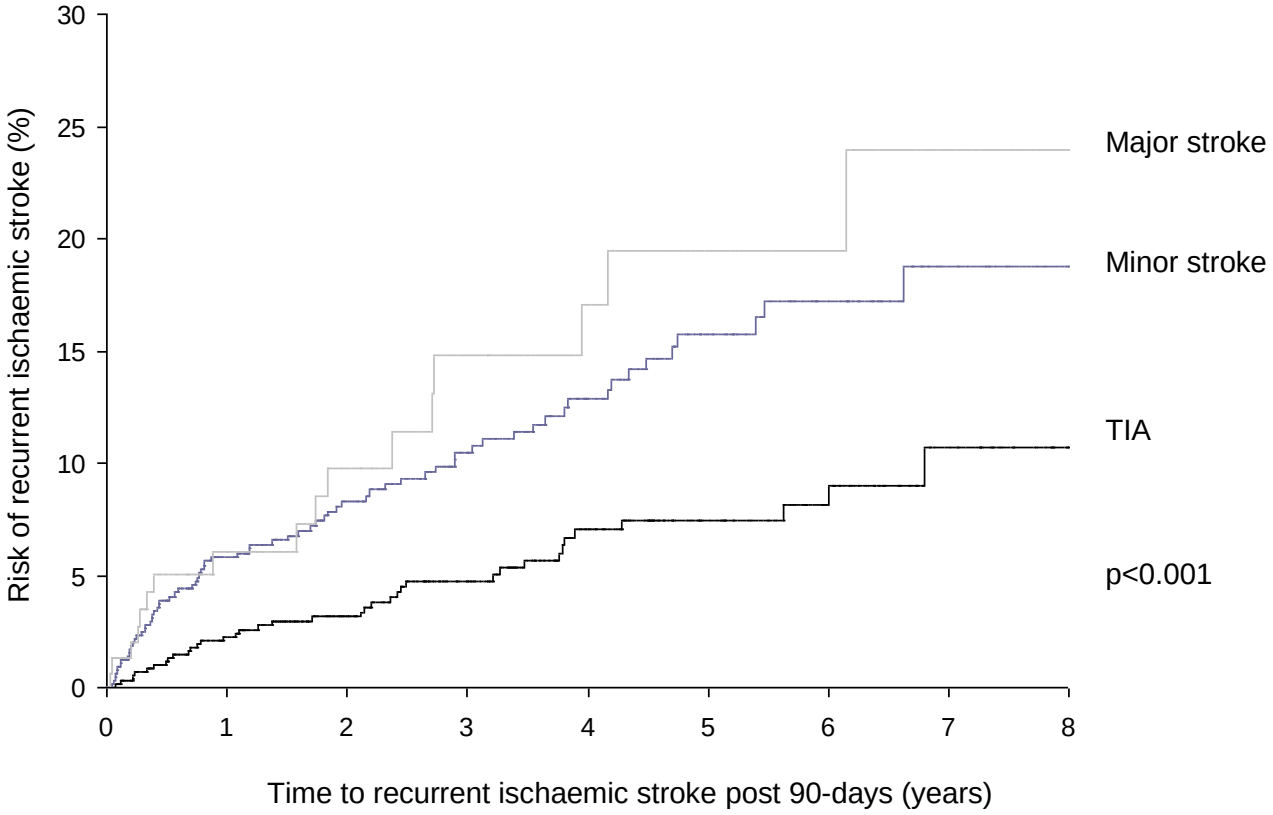


Figure 9.3. Risk of recurrent stroke up to 8 years post 90 days from time of first seeking medical attention after TIA or MIS, (n=1542).

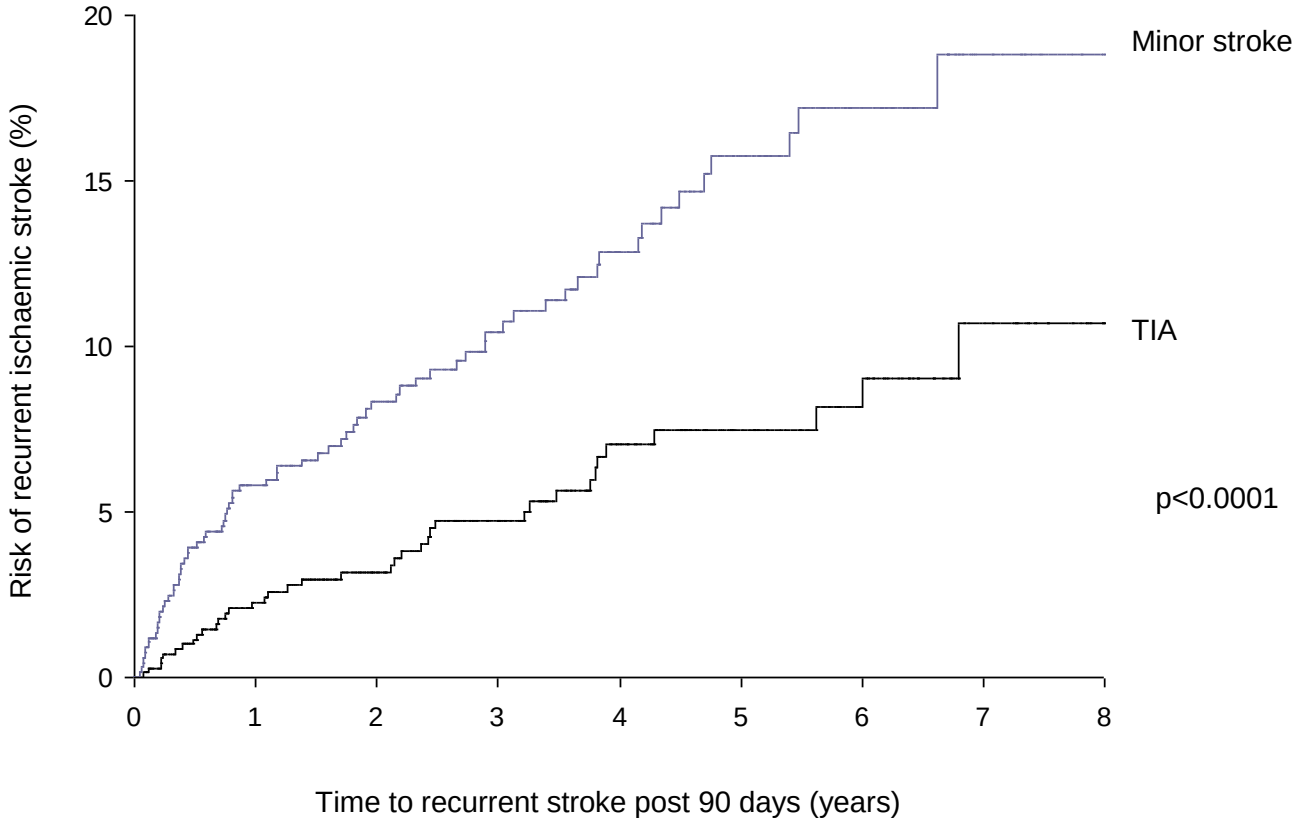


Table 9.3. Median time to recurrent event within the first year from event onset (n=1928) and time of seeking medical attention (n=1856, 72 cases did not seek medical attention at the time of the event but presented after a recurrent stroke).

	From event onset		From time of seeking medical attention	
	Recurrent strokes	Days to recurrence (median, IQR)	Recurrent strokes	Days to recurrence (median, IQR)
TIA, n=832	123	3.9 (1.0-36.3)	69	3.8 (0.9-55.5)
Minor stroke, n=779	104	22.8 (3.0-121.9)	90	29.4 (4.6-156.3)
Major stroke, n=317	24	25.0 (3.8-104.5)	21	32.4 (6.5-134.7)

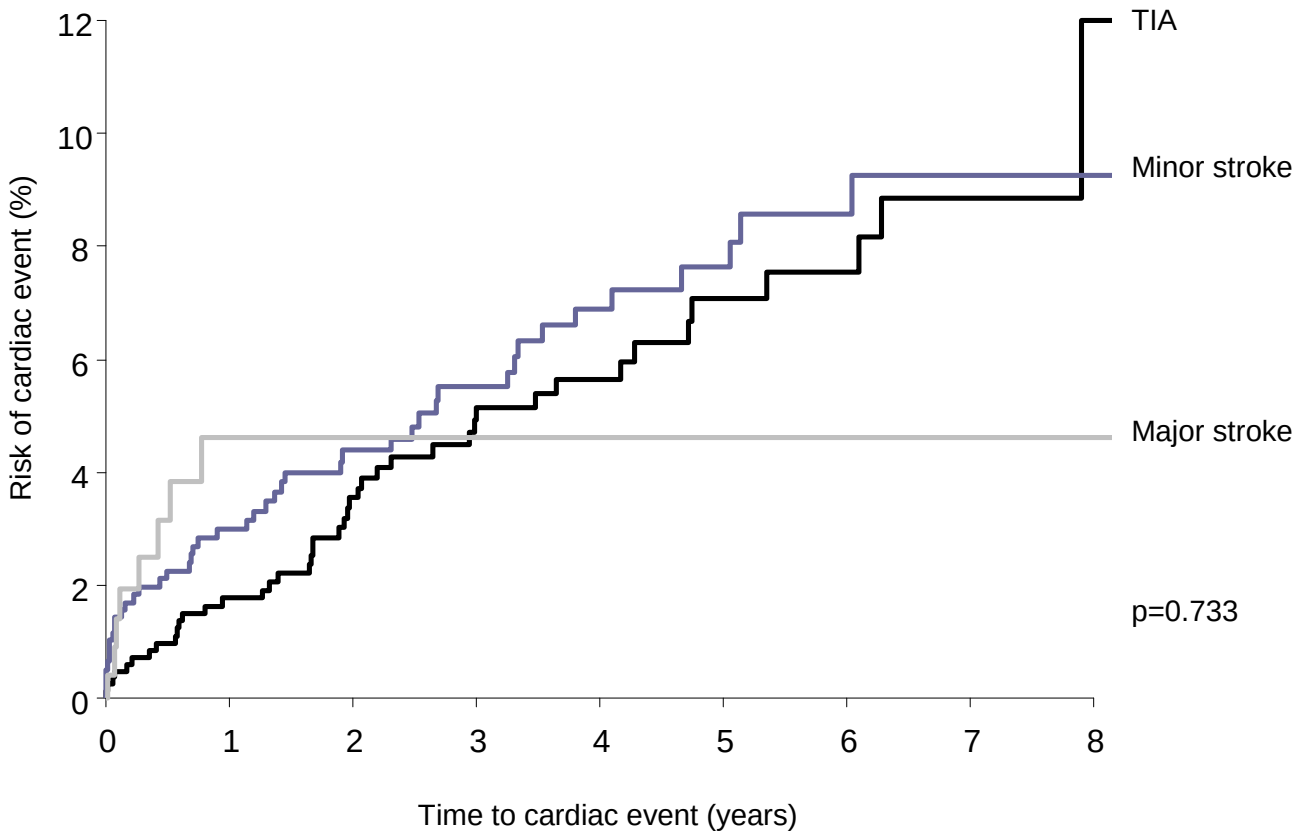
Table 9.4 shows the cardiac risks up to 8 years after TIA and ischaemic stroke. When all cardiac events (STEMI, NSTEMI and sudden cardiac death) were combined, the 8 year risk of a cardiac outcome was half the risk of a recurrent stroke (10.4% (6.7-14.1) vs 24.6% (21.5-27.7)). The cardiac risk after TIA was just as high as the risk after minor stroke (12% (5.3-18.7) vs 9.3 (6.4-12.2), p=0.73, Figure 9.4), with most of the risk accounted for by NSTEMI. After all event types, the 8 year risks of STEMI and sudden cardiac death were low (1.5% and 2.1% respectively). The risk of a cardiac event after major stroke was limited to the first year (Figure 9.4).

Table 9.4: Risk of cardiac events (% risk, 95% CI) with median time to event up to 8 years after TIA and ischaemic stroke, n=1928

	Patients	NSTEMI	8 year % risk	STEMI	8 year % risk	SCD	8 year % risk	All cardiac events	8 year % risk	Median time to cardiac event (days)
TIA	832	25	8.2 (1.5 – 14.9)	7	1.7 (0.1 – 3.3)	11	2.3 (0.9 – 3.7)	43	12 (5.3 – 18.7)	691
Minor stroke	779	30	6.3 (3.8 – 8.8)	8	1.4 (0.4 – 2.4)	7	1.7 (0.3 – 3.1)	45	9.3 (6.4 – 12.2)	418
Major stroke	317	2	1.5 (0 – 3.5)	1	0.4 (0 – 1.2)	5	2.8 (0.4 – 5.2)	8	4.6 (1.5 – 7.7)	691
All patients	1928	57	7.0 (3.3 – 10.7)	16	1.5 (0.5– 2.5)	23	2.1 (1.1 – 3.1)	96	10.4 (6.7 – 14.1)	478

SCD= sudden cardiac death
NSTEMI= non ST elevation MI
STEMI= ST elevation MI

Figure 9.4. Risk of cardiac event (NSTEMI, STEMI and sudden cardiac death) up to 8 years after TIA or ischaemic stroke



There were 667 deaths during the study period, the 8 year mortality risk after all events was 50.1% (46.2-54.0, Table 9.5). Mortality was highest after major stroke within the first 90 days (46.9%, 41.4-52.4). Time to death was related to initial event severity, with 87% (68/78) of all deaths within 7 days occurring after major stroke. Mortality risks after TIA and minor stroke were similar up to 7 days (0.5% vs 0.8%, p=0.54), however, between 8 to 90 days, mortality risk after minor stroke was 3 times the risk after TIA (5.8% vs 1.8%, OR 3.36, 95% CI 1.87- 6.0, p<0.001). By 8 years, the mortality risk after minor stroke remained higher than the risk after TIA but the difference was less pronounced (48.5% vs 37.8%, p<0.001, Figure 9.5). The 8 year risk of fatal stroke was six times the risk of fatal MI or sudden cardiac death (13.3 % vs 2.2%, Figure 9.6). Beyond 2 years, the risk of non-vascular death remained high and continued to rise, whilst risk of fatal stroke fell. The risk of death due to peripheral vascular disease remained low throughout the study period.

Figure 9.5. Mortality (% risk) up to 8 years after TIA and ischaemic stroke, n=1928.

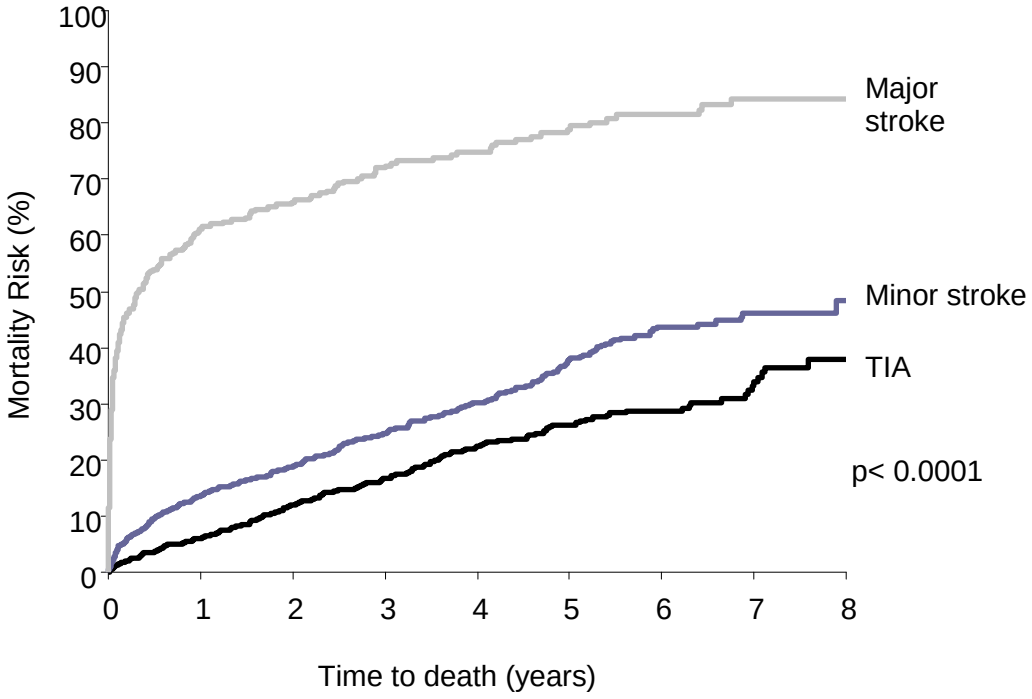
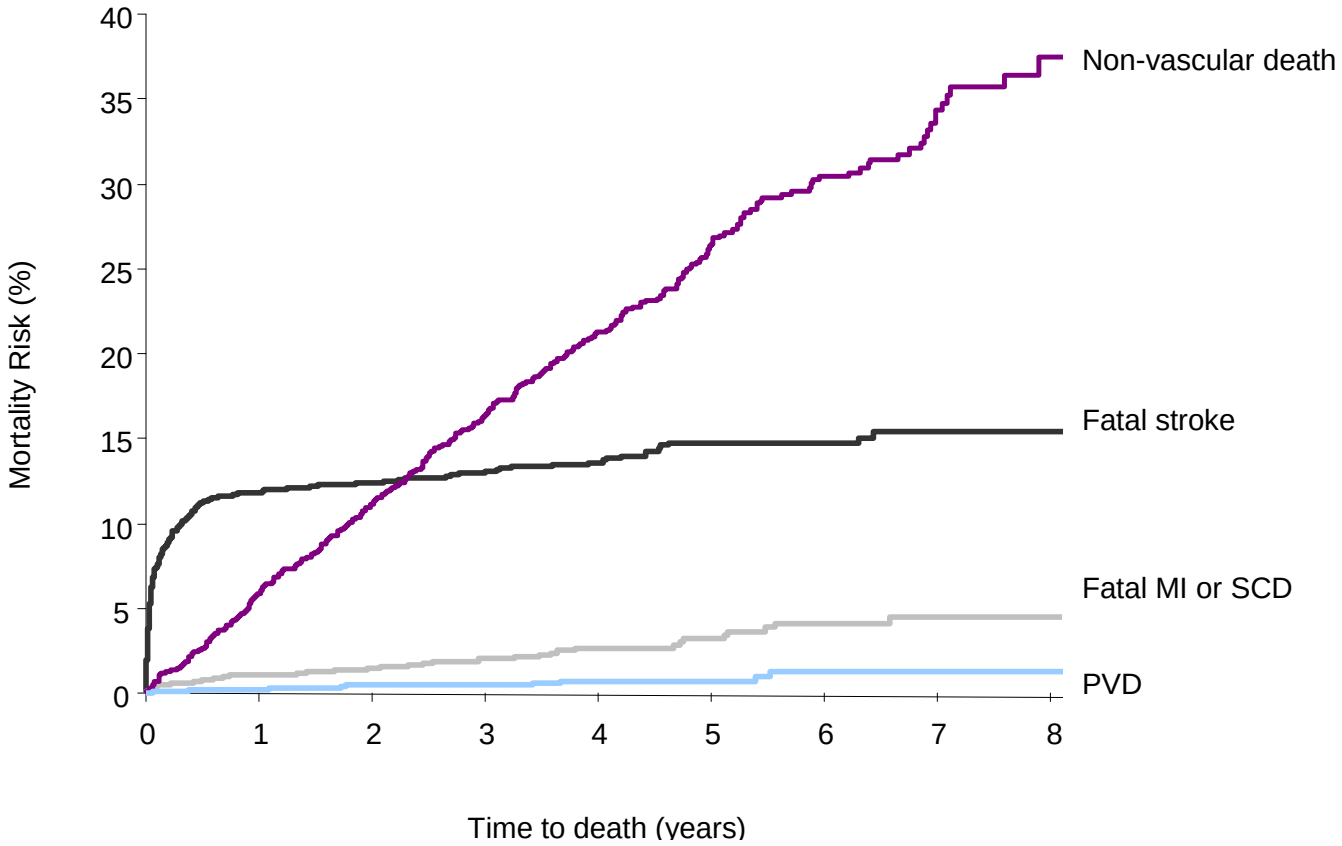


Table 9.5: Mortality (% risk, 95% CI) up to 8 years after TIA and ischaemic stroke, n=1928.

		7 days		90 days		1 year		5 years		8 years	
	Patients	Deaths	% risk	Deaths	% risk	Deaths	% risk	Deaths	% risk	Deaths	% risk
TIA	832	4	0.5 (0.1 – 0.9)	19	2.3 (1.3 – 3.3)	49	6.0 (4.4 - 7.6)	160	26.3 (22.6 - 30)	179	37.8 (31.7 – 43.9)
Minor stroke	779	6	0.8 (0.2 - 1.4)	51	9.7 (7.5 – 11.9)	105	13.7 (11.3 – 16.1)	227	37.8 (33.7 – 41.9)	249	48.5 (42.0 – 55.0)
Major stroke	317	68	21.4 (16.9 -25.9.)	149	46.9 (41.4 – 52.4)	192	60.8 (55.3 – 66.3)	232	78.7 (73.6– 83.8)	239	84.3 (79.0 – 89.6)
All patients	1928	78	4.0 (3.2 – 4.8)	219	11.4 (10 - 12.8)	346	18.1 (16.3 – 19.9)	619	39.8 (37.3 – 42.3)	667	50.1 (46.2 – 54.0)

Figure 9.6. Mortality (% risk) by cause of death up to 8 years after TIA and ischaemic stroke, n=1928.



Secondary prevention measures and blood pressures were similar in patients with TIA and minor stroke at 1 month, although patients with TIA were more likely to be taking an antiplatelet or anticoagulant (p=0.02, Table 9.6). However, by 1 year, there were no differences in secondary prevention measures between patients with TIA and minor stroke. Patients with major stroke were less likely than patients with TIA and minor stroke to be on an antiplatelet or anticoagulant at 1 month (86% vs 93%, p=0.001) and less likely to be taking 2 or more antihypertensives at 1 year (39% vs 51%, p=0.03) although there was no difference in blood pressure when compared to patients with TIA and minor stroke.

The recurrent stroke risks pre and post 90-days from seeking medical attention are shown in Table 9.7. Following minor stroke, the risk of recurrent stroke post 90-days was more than double the pre-90 day risk (18.8% vs 7.7%, p=0.05). The aetiology of recurrent strokes pre and post 90-days were also different. Table 9.8 shows the aetiology of all first and recurrent ischaemic events seeking medical attention. There were 2 patients with recurrent stroke of unknown aetiology whose first event was classified as cardioembolic aetiology. The recurrent strokes in these 2 cases were classified as unknown because investigation after the second event was incomplete. Both cases did not have vascular imaging performed after the second event which occurred more than 6 months after the first event. Recurrent events within 90-days were generally of the same aetiology as the initial event. However, beyond 90-days, there were a higher proportion of recurrent events of different aetiology to the initial event (Table 9.9). Of 127 recurrent strokes post 90-days, aetiology could be determined in 55% (70/127). Of these, 77% (54/70) were of cardioembolic aetiology, despite constituting only 22.5% (418/1856) of all first events.

Table 9.6: Secondary prevention measures assessed at 1 month and 1 year follow-up in all patients (n = 1769 at 1 month, n=1474 at 1 year)*

		TIA n (%)	Minor stroke n (%)	Major stroke n (%)	p
On an antiplatelet or anticoagulant	at 1 month[a]	773 (94.0)	676 (91.0)	160 (85.6)	**0.001**
	at 1 year[b]	644 (90.8)	551 (88.9)	93 (85.3)	0.15
On a statin	at 1 month[a]	595 (72.4)	543 (73.1)	129 (69.0)	0.53
	at 1 year[b]	539 (76.0)	481 (77.6)	86 (78.9)	0.71
On one or more antihypertensive	at 1 month[a]	587 (71.5)	557 (75.0)	126 (67.7)	0.09
	at 1 year[b]	514 (72.7)	476 (76.9)	79 (72.5)	0.19
On two or more antihypertensives	at 1 month[a]	587 (71.5)	557 (75.0)	126 (67.7)	0.09
	at 1 year[b]	343 (48.5)	325 (52.6)	43 (39.4)	**0.03**
Systolic blood pressure, mm Hg (mean, SD)					
	at 1 month[c]	136.2 (21.2)	137.8 (22.6)	133.3 (20.8)	**0.05**
	at 1 year[d]	135.5 (20.6)	135.9 (20.8)	134.7 (22.6)	0.83
Diastolic blood pressure, mm Hg (mean, SD)[b]					
	at 1 month[c]	75.5 (10.6)	76.6 (11.3)	74.2 (11.8)	**0.02**
	at 1 year[d]	75.1 (10.3)	75.8 (10.8)	76.0 (12.0)	0.46

* 159 patients died before 1 month follow-up, 346 patients died before 1 year follow-up and 108 patients had not reached 1 year post event

[a] 17 cases missing (7 minor stroke, 10 major stroke), [b] 36 cases missing (16 TIA, 13 MIS, 7 major stroke), [c] 241 cases missing (116 TIA, 96 minor stroke, 30 major stroke), [d] 119 cases missing (47 TIA, 54 MIS, 17 major stroke)

Table 9.7. Risk of recurrent ischaemic stroke pre and post 90-days up to 8 years from time of seeking medical attention after TIA and ischaemic stroke n=1856

Event type	Pre 90-days recurrent strokes	% risk	Post 90-days recurrent strokes	% risk	p
TIA, n= 778	56	7.2 (5.4 -9.0)	38	10.7 (6.2-15.2)	0.14
Minor stroke, n= 764	59	7.7 (5.7 – 9.7)	72	18.8 (13.7-23.9)	**0.05**
Major stroke, n= 314	14	6.5 (3.2 – 9.8)	17	23.9 (11.4-36.4)	**0.02**

Table 9.8. TOAST classification of all recurrent events by first event seeking medical attention, n=1856.

		TOAST of recurrent stroke							
N (%)	TOAST of first event	CE	LAA	SVD	UND	UNK	Multiple	Other	Total
418 (22.5)	CE	74	0	0	1	2	0	1	78 (30.5)
205 (11.0)	LAA	3	23	0	1	0	0	1	28 (10.9)
240 (12.9)	SVD	6	1	27	7	1	1	0	43 (16.8)
656 (35.3)	UND	7	3	4	52	8	0	1	75 (29.3)
242 (13.0)	UNK	2	0	0	2	17	0	0	21 (8.2)
39 (2.1)	Multiple	1	0	0	0	0	5	0	6 (2.3)
56 (3.0)	Other	1	0	0	0	1	0	3	5 (2.0)
1856 (100)	Total	94 (36.7)	27 (10.5)	31 (12.1)	63 (24.6)	29 (11.3)	6 (2.3)	6 (2.3)	256 (100)

Table 9.9. Difference in TOAST classification of recurrent stroke from TOAST classification of first event from time of seeking medical attention.

TOAST subtype of recurrent stroke	Patients	Pre 90-day strokes	Post 90-day strokes
		Recurrent stroke TOAST different to first event % (n/total)	Recurrent stroke TOAST different to first event % (n/total)
CE	94	5 (2/40)	33.3 (18/54)
LAA	27	5.3 (1/19)	37.5 (3/8)
SVD	31	4.3 (1/23)	37.5 (3/8)
UND	63	7.1 (2/28)	25.7 (9/35)
UNK	29	16.7 (2/12)	58.8 (10/17)
Multiple	6	0 (0/4)	50 (1/2)
Other	6	33.3 (1/3)	66.7 (2/3)
Total patients	256	7.0 (9/129)	36.2 (46/127)

9.4 Discussion

In this study, the recurrent stroke risks after TIA and minor stroke remained similar up to 90-days, however after 90-days, recurrence risk after minor stroke remained high and was greater than the risk after TIA. By 8 years, the post-90 day recurrent stroke risk after minor stroke reached 19%. The aetiology of post-90 day recurrent strokes was different to the aetiology of early recurrences: the proportion of cardioembolic recurrent strokes was higher post-90 days. Mortality was related to severity of initial event; the one year mortality risk after major stroke was 61% and in the subacute phase, the mortality after minor stroke was three times higher than after TIA. The risk of cardiac events was similar amongst all ischaemic event types and was half the risk of recurrent stroke at 8 years.

The possible reasons for delayed recurrent stroke after minor stroke despite high levels of secondary prevention were discussed in chapter 7. The high delayed recurrence risk after minor stroke in this study highlights the need for better secondary prevention in the subacute and late phase after minor stroke.

Given the higher proportion of cardioembolic recurrent strokes post-90 days, the high later risk may be secondary to undetected cardioembolism at the time of assessment after TIA and minor stroke. Although it has previously been shown that it is possible to reduce the high early risk of stroke by early initiation of secondary prevention after TIA and minor stroke,[9-10] I have shown there is a high later stroke risk after minor stroke which has not been reduced by current secondary prevention methods. Since the long-term cardiac risk is low, it may be that another, non-atheromatous mechanism is responsible for later recurrent stroke which is not being addressed by current secondary prevention. The high number of cardioembolic recurrent strokes identified post 90-days in this study which occurred after events of a different aetiology suggests

cardioembolism as a potential risk factor with current sub-optimal detection and management. It remains, that in spite of the known increased stroke risk associated with atrial fibrillation and the benefit of oral anticoagulation in reducing stroke risk, AF patients are not on adequate treatment.[18,19] This can result from a variety of reasons such as patients preferences, reduced awareness of stroke risk among physicians and difficulties detecting AF. The ongoing focus in the development of non invasive and invasive devices with longer term monitoring should lead to improved detection of occult atrial fibrillation thereby reducing this risk further.[20,21]

The potential benefits of long term secondary prevention in reduction of non fatal vascular deaths looks promising. Daily aspirin reduced the incidence of colorectal cancers and more importantly, deaths due to several common cancers.[22,23] The role of aspirin and its reduction in the risks of infection by inhibition of thromboxane dependent platelet activation continues to be explored.[24]

The cumulative risk of long term stroke in the South London Registry (up to 25% at 10 years) and up to 30% in 5 years in OCSP highlight the substantial risk of long term stroke recurrences.[25,26] Although, differing rates of risk may be explained by different definitions of stroke recurrence, a comparison between this data on stroke recurrence would be helpful in defining prognosis for TIA and stroke patients and highlighting the long term commitment needed to control risk factors to protect patients from further recurrence. Further studies are needed to determine long-term disability after recurrent stroke as an outcome measure and whether increased use of secondary prevention has any effect in reducing disability related to stroke recurrences.

This study had some potential limitations. First, the risk of stroke in the acute phase may not be completely precise because an unknown proportion of patients with TIA and minor stroke will

never seek medical attention. Second, I may have underestimated the risk of TIA and minor stroke as some patients with a major stroke with preceding events may not have been identified if it was impossible to obtain a history of events because they were aphasic, confused or unconscious. Third, this study included patients recruited into the EXPRESS study,[9] Phase 2 of which involved more urgent investigation and treatment, which will have reduced the absolute risk of events and possibly influenced the timing of recurrent events. Stroke prevention efforts increased over the period of the study due to EXPRESS which may have reduced the number of recurrent events in the early phase but have not prevented events in the late phase. Fourth, although face-to-face follow-up data up to 5 years was available for patients ascertained at the start of the study in 2002, data was not available for patients ascertained more recently as they have not reached 5 year follow-up yet. In light of improved secondary prevention efforts in the modern era, patients ascertained more recently may have even better outcomes, this could be a topic for future study. Fifth, the intensity of secondary prevention may have varied between the TIA and minor stroke cases causing a difference in the timing of recurrent events. However in OXVASC, the rates of prescription of aspirin, statin and anti-hypertensive medication after presentation to medical attention were similar in TIA and minor stroke. Furthermore, regular face-to-face or telephone follow-up ensured high rates of compliance. Poor compliance and prescribing is common after TIA and stroke therefore it is usually difficult to know how effective secondary prevention actually is. [27]

In summary, timing to recurrent events varies according to event type. Recurrent stroke occurs early after TIA and is delayed after minor stroke. In the long term, the risk of recurrent stroke is double the risk of a cardiac event. There is a major unmet need for more effective prevention of recurrent stroke in the late phase after minor ischaemic stroke.

9.5 References

1. Navi B, Kamel H, Sidney S, Klingman J, Nguyen-Huynh MN, Johnston SC. Validation of the Stroke Prognostic Instrument-II in a large, modern, community-based cohort of ischaemic stroke survivors. Stroke 2011; epub http://www.ncbi.nlm.nih.gov/pubmed/21960582. Accessed Ocrober 23rd 2011
2. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. Neurology 1997; 48:891-895.
3. Tallelli P and Greenwod RJ. Recurrent stroke: where do we stand with the secondary prevention of noncardioembolic strokes. Therapeutic Adv Cardiovascular Dis 2008:1-19
4. Petty GW, Brown RD Jr, Whisnant JP et al. Survival and recurrence after first cerebral infarction: a population-based study in Rochetser, Minnesota, 1975 through 1989. Neurology. 1998; 50:208-216.
5. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S et al. Long-term risk of first recurrent stroke in the Perth Community stroke study. Stroke 1998;29:2491-2500.
6. Burn J, Dennis M, Bamford J, Sandercock P et al. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke. 1994;25:333-337.
7. Clark TG, Murphy MFG, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in “low risk” patients with a non-recent transient ischaemic attack. JNNP 2003;74:577-580.
8. Hankey GJ. Long-term outcome after ischaemic stroke/ transient ischaemic attack. Cerebrovasc Dis 2003;16(suppl 1):14-19
9. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007; 370(9596):1432-1442.
10. Lavallee PC, Meseguer E, Abboud H, et al. A transient ischemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6(11):953-960
11. Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke. 2005 Dec; 36(12):2748-55.
12. Pendlebury ST, Rothwell PM. Risk of recurrent stroke, other vascular events and dementia after transient ischaemic attack and stroke. Cerebrovasc Dis. 2009; 27 Suppl 3:1-11.

13. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004; 363(9425):1925-1933.
14. Rothwell PM, Coull AJ, Silver LE, 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). Lancet. 2005; 366(9499):1773-1783.
15. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke. 2004; 35(9):2041-2045
16. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989; 20(7):864-70.
17. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL 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;24:35-41
18. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010; 123(7): 638-45 e4.
19. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. Stroke. 2009; 40(1): 235-40.
20. Liao J, Khali Z, Scallan C, Morillo C, O'Donnell M. Non invasive cardiac monitoring for detecting Paroxysmal Atrial fibrillation or flutter after acute ischaemic stroke: A systematic review. Stroke 2007;38;2935-40
21. Eitel C, Husser D, Hindricks G. Performance of an implantable atrial fibrillation detection device: Europace 2011;480-5
22. Flossmann E, Rothwell PM, on behalf of the British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long term risk of colorectal cancer: consistent evidence from randomized and observational studies. Lancet 2007; 369: 1603-13
23. Rothwell PM, Fowkes F, Belch J, Ogawa H, Warlow C, Meade T. Effect of daily aspirin on long term risk of death due to cancer: analysis of individual data from randomized trials. Lancet 2011;377:31-41
24. Halushka PV, Wise WC, Cook JA. Protective effects of aspirin in endotoxic shock. J Pharmacol Exp Ther. 1981 Aug; 218(2):464-9

25. Dennis, M. S., J. M. Bamford, et al. A comparison of risk factors and prognosis for transient ischemic attacks and minor ischemic strokes. The Oxfordshire Community Stroke Project. Stroke 1989;20(11): 1494-9.
26. Mohan, K. M., S. L. Crichton, et al. Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register. J Neurol Neurosurg Psychiatry 2009;80(9): 1012-8.
27. Ma R, Wang C, Zhao X, Xu M, Lv Y, Wei M, Cai Y, Zhang Z, Wang L, Zhang W, et al. A survey on compliance with secondary stroke prevention guidelines and follow up for the inpatients with atherosclerotic cerebral infarction/transient ischemic attack. Neurol Res. 2008;30(4):383-8.

CHAPTER 10

Change in late recurrent stroke, fatal stroke and fatal cardiac event risk after TIA and stroke in Oxfordshire from 1981- 2010

10.1 Introduction 222

10.2 Methods 223

10.2.1 Definition of recurrent stroke in OCSP and OXVASC 224

10.2.2 Definition of fatal recurrent stroke and cardiac deaths 225

10.2.3 Analysis 225

10.3 Results 226

10.4 Discussion 238

10.5 References 242

10.1 Introduction

The incidence of stroke has fallen in developed countries, such as the UK, France, Italy, Australia and Hong-Kong since the 1980s, likely due to reductions in pre-morbid vascular risk factors and improvements in use of primary preventative treatments such as aspirin, lipid-lowering agents and anti-hypertensive medications.[1-5] A systematic review of randomised control trials of medical therapy in secondary prevention showed that the risk of recurrent stroke has also fallen.[6] Whilst there were increases in pre-morbid diabetes and hypertension, blood pressure at entry into studies was less, there was less smoking, less carotid stenosis, lower cholesterol levels and higher pre-morbid anti-platelet and anti-hypertensive use.[6] A nationwide US study of 2.5 million Medicare beneficiaries aged over 65 found a 5% decrease in 1-year recurrent stroke risk between 1994 and 2002.[7] Urgent intervention has been shown to be highly effective in reducing the early recurrent stroke risk after TIA and minor stroke.[8-10] However, less is known about the effect on long-term outcomes and population-based studies of time trends of long-term outcomes in the modern era are limited.

Studies from the 1970's and 1980's demonstrated a high risk of cardiac death after TIA and stroke, 35% at 3.7 years after TIA in the Oxford Community Stroke project (OCSP).[11,12] A meta-analysis of 39 studies from 1980-2005 has shown the risk of MI after TIA or stroke remains high at approximately 2% per year,[13] however, whether there has been any reduction in risk in light of improvements in secondary prevention is not known.[13,14] The aim of this study was to determine time trends in outcomes after TIA and ischaemic stroke beyond the acute phase, that is beyond 90-days up to 5 years from event onset. I addressed this issue using data from patients in the Oxford Vascular Study (OXVASC) in comparison with patients from the OCSP cohort, a similarly high quality population-based incidence study of stroke and TIA performed in a similarly defined population in the 1980's.[15]

10.2 Methods

This study was nested within OXVASC, the study methods have been described in chapter 1 and elsewhere.[16,17] Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke.[16,17] I compared outcomes of patients with incident TIA and ischaemic stroke within OXVASC with data from patients in OCSP. The OXVASC population ascertains patients from 9 of the same GP practices included in OCSP. The study methods of OCSP have been described elsewhere.[15] The geographical area and racial mix (94% white) of the OXVASC and OCSP study population has changed little in the past 25 years, but the proportion of the population aged 75 or over has increased by about a third.[1] OXVASC included all practices that had participated in OCSP apart from two practices, which no longer refer patients to Oxford hospitals. In view of the high rate (93%) of imaging and autopsy in OXVASC, strokes of unknown type were coded as ischaemic for this analysis. In OCSP, strokes that did not have brain imaging or autopsy were classified as haemorrhages only if clinical scoring systems indicated a high degree of certainty.[15] The definitions of incident TIA[18] and ischaemic stroke used in OXVASC were the same as in OCSP. Cases with a previous history of stroke were excluded but a history of previous transient ischaemic attacks was allowed.

To ensure a similar methodology to OCSP, patients ascertained in OXVASC with a stroke but who had a preceding TIA that they had not brought to medical attention were included as incident stroke cases. Event characteristics were recorded and all patients underwent brain imaging, with CT or MRI as appropriate. All OXVASC cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA or stroke or other condition using standard definitions.[16,17] All patients with recurrent events were reassessed by a study physician and then case reviewed by PMR. Patients in whom it was impossible to obtain a definite history of TIA or stroke because they were aphasic, confused, or unconscious were excluded. Patients with

primary intracerebral haemorrhage, those who presented as a stroke death and those with possible events (where an alternative aetiology to a vascular event was likely) were excluded. All patients received best medical treatment and secondary prevention according to current guidelines. Patients in OXVASC were followed up face-to-face at 1 month, 6 months, 1 year and 5 years by a study nurse or physician. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. The timing of all recurrent strokes, fatal MI or sudden cardiac deaths up to 5 years after the first event was recorded. All recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. In OCSP, patients were followed up face-to-face by research nurses at 1, 6 and 12 months then annually from stroke onset.[11,15] This study includes all cases with first ischaemic events in OXVASC from 1st April 2002 to 31st March 2010 with follow-up until 31st July 2010 and all incident TIA and ischaemic stroke cases from OCSP from 1981-1986 censored to death or final follow-up.[15-16]

10.2.1 Definition of recurrent stroke in OCSP and OXVASC

A recurrent stroke in OCSP was defined as any new neurological deficit or an exacerbation of a previous deficit that could not be ascribed to toxic drug effects or intercurrent illness occurring more than 21 days after the preceding stroke.[19] The definition of recurrent stroke used in OXVASC has been reported elsewhere[20,21] and required a sudden new symptomatic neurological deterioration on a background of stability or improvement after the presenting event. Gradual or stuttering progression after an initial event was not coded as a recurrent stroke. Strokes that occurred within 24 hours of an initial TIA or minor stroke were included. If recurrence occurred before complete symptomatic resolution of the initial event, the initial event was coded as a stroke. All potential recurrent strokes were classified as definite, probable or not stroke by the assessing clinician. Probable recurrent strokes were mainly sudden deteriorations

after a major acute stroke for which a clinical diagnosis of recurrent stroke had been made by the patient's physicians but for which imaging evidence was equivocal or imaging was unavailable.

10.2.2 Definition of fatal recurrent stroke and cardiac deaths

In both cohorts, the cause of death was determined from death certificates, coroners reports, GP records, hospital notes and, for OXVASC cases, coding from the Office for National Statistics National Health Service Central Register. The definitions of fatal recurrent stroke and cardiac death were the same in both cohorts (Appendix XII). Fatal recurrent stroke was defined as death as a direct result or complication of a recurrent stroke. Cardiac deaths were those due to definite or probable MI or sudden cardiac death, deaths due to heart failure or chronic ischaemic heart disease were not included. Sudden deaths were regarded as cardiovascular unless an alternative explanation was found at autopsy.

10.2.3 Analysis

I restricted analysis to the risk of recurrent events after the first TIA or ischaemic stroke in the study period (index event). In OXVASC, the risks of recurrent ischaemic stroke, death, fatal MI and sudden cardiac death within 5 years of index event were censored for death and follow-up until 31st July 2010. Recurrent stroke risks were analysed from the time of index event. In patients who had multiple recurrent cerebrovascular events the end point was classified as the first recurrence following the index event. Kaplan-Meier survival analysis was used to calculate recurrence risks then compared with outcomes in OCSP from individual patient data.

10.3 Results

Of 2034 consecutive patients with cerebrovascular events in the OXVASC study period, 1382 were incident ischaemic events (486 TIA, 896 stroke) compared with 626 incident ischaemic events during OCSP (152 TIA, 474 stroke). The baseline characteristics of all patients with TIA are shown in Table 10.1 and those of all patients with stroke are shown in Table 10.2.

Table 10.1. Baseline characteristics, vascular risk factors and premorbid medication in patients with incident TIA

	OCSP 1981-1986 n=152	OXVASC 2002-2010 n=486	p-value
Age (mean (SD))	69.0 (12.7)	72.5 (13.0)	**0.004**
Male Sex	87 (57.2)	222 (45.7)	**0.015**
Hypertension	53 (34.9)	255 (52.5)	**<0.001**
Diabetes	8 (5.3)	67 (13.8)	**0.004**
Angina or myocardial infarction	38 (25.0)	91 (18.7)	0.11
Peripheral vascular disease	27 (17.8)	27 (5.6)	**<0.001**
Previously diagnosed atrial fibrillation	22 (14.5)	76 (15.6)	0.80
Current Smoker	42 (27.6)	61 (12.6)	**<0.001**
Prior antiplatelet/anticoagulant	9 (5.9)	162 (33.3)	**<0.001**
Prior statin	0 (0)	105 (21.6)	**<0.001**
Prior antihypertensive	53 (34.9)	271 (55.8)	**<0.001**

Patients were older in OXVASC compared with OCSP (mean age 74.0 vs 71.8, p=0.0004). There were more patients aged over 80 in OXVASC than in OCSP (175, 40.1% vs 554, 28.0%, p<0.0001). Mean age at first TIA was 72.5 in OXVASC vs 69.0 in OCSP (p=0.004) and mean age at first stroke was 74.8 vs 72.7 (p=0.004).

Table 10.2. Baseline characteristics, vascular risk factors and premorbid medication in patients with incident stroke

	OCSP 1981-1986 n=474	OXVASC 2002-2010 n=896	p-value
Age (mean (SD))	72.7 (12.8)	74.8 (12.6)	**0.004**
Male Sex	240 (50.6)	433 (48.3)	0.43
Hypertension	209 (44.1)	516 (57.6)	**<0.001**
Diabetes	54 (11.4)	111 (12.4)	0.66
Angina or myocardial infarction	86 (18.1)	177 (19.8)	0.52
Peripheral vascular disease	58 (12.2)	66 (7.4)	**0.004**
Previously diagnosed atrial fibrillation	54 (11.4)	190 (21.2)	**<0.001**
Current Smoker	105 (22.2)	140 (15.6)	**0.003**
Previous TIA	65 (13.7)	75 (8.4)	**0.003**
Prior antiplatelet/anticoagulant	26 (5.5)	343 (38.3)	**<0.001**
Prior statin	0 (0)	192 (21.4)	**<0.001**
Prior antihypertensive	110 (23.2)	538 (60)	**<0.001**

Overall, there were more males in OCSP (327/626, 52.2% vs 655/1382, 47.4%, p=0.05), there were more female patients with TIA in OXVASC (264/486, 54.3% vs 65/152, 42.8%, p=0.02). Since OCSP, there have been reductions in the proportions of current smokers (p<0.01) and of those with peripheral vascular disease (p<0.01). There have been increases in the levels of premorbid use of antiplatelets/anticoagulants (p<0.001), lipid lowering (p<0.001) and antihypertensive medications (p<0.001). In patients with TIA, there has been an increase in premorbid diabetes (p=0.004). In patients with stroke, there has been an increase in patients with premorbid atrial fibrillation (p<0.001).

Table 10.3 shows the post-90 day stroke risks after TIA and stroke in both cohorts. Post 90-days up to 5 years after TIA, there were 24 recurrent strokes in OCSP and 27 in OXVASC.

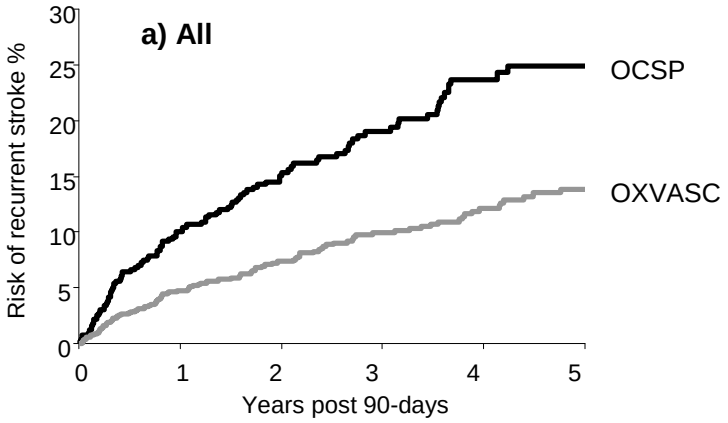
Table 10.3: Recurrent strokes (% risk, 95% CI) post 90 days up to 5 years after TIA and stroke in OCSP and OXVASC

	1981-1986			2002-2010			
	Patients	Strokes	% risk	Patients	Strokes	% risk	p
TIA	143	24	22.6 (14.2-31.0)	432	27	10.0 (6.1-13.9)	0.003
Stroke	366	74	25.3 (20.0-30.6)	699	74	15.7 (12.2-19.2)	<0.0001
All events	509	98	24.9 (20.2-29.6)	1131	101	13.5 (10.8-16.2)	<0.0001

The post 90-day stroke risk after TIA has fallen from 22.6% (14.2-31) in OCSP to 10% (6.1-13.9) in OXVASC, p=0.003 (Figure 10.1b). Adjusting for age and sex, the post 90-day recurrent stroke risk after TIA has fallen by 62% since OCSP (HR 0.38, 0.22-0.67, p<0.001). Figure 10.2 shows the post 90-day recurrent stroke risks after TIA at different age bands. The fall in risk was greatest for those under 75 years.

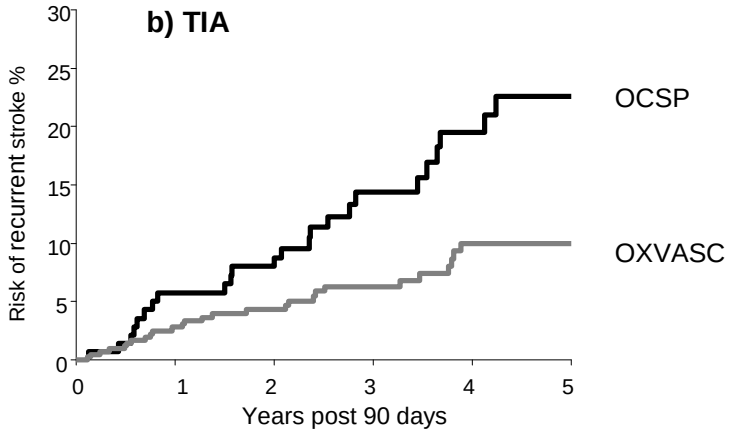
After ischaemic stroke in OXVASC, there were 74 recurrent strokes post 90 days up to 5 years. The post 90-day recurrent stroke risk was higher after stroke than after TIA in OXVASC (15.7%, 12.2-19.2) vs 10% (6.1-13.9) p=0.01, Table 10.3). The post 90-day recurrence risk after stroke has fallen from 25.3% (20.0-30.6) in OCSP to 15.7% (12.2-19.2) in OXVASC, p=0.00007 (Figure 10.1c). Since OCSP, the post 90-day age and sex adjusted recurrent stroke risk after stroke has fallen by 49% (HR 0.51, 0.37-0.70, p<0.001). Figure 10.3 shows the recurrent stroke risks up to 5 years after stroke by age-band. The fall in risk was greatest for those under 75 years.

Figure 10.1. Post 90-day risk of recurrent stroke up to 5 years in OCSP and OXVASC. (HR=Hazard ratio, Adj HR= Hazard ratio adjusted for age and sex)



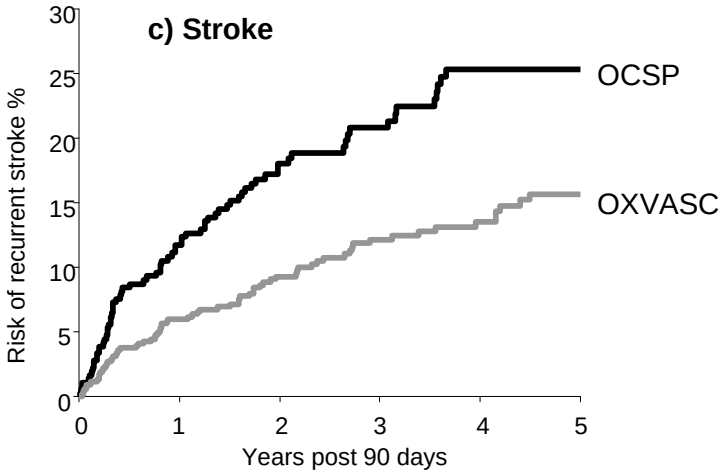
HR 0.48 (0.36-0.64)
Adj HR 0.45 (0.34-0.60)

p<0.0001



HR 0.44 (0.26-0.77)
Adj HR 0.38 (0.22-0.67)

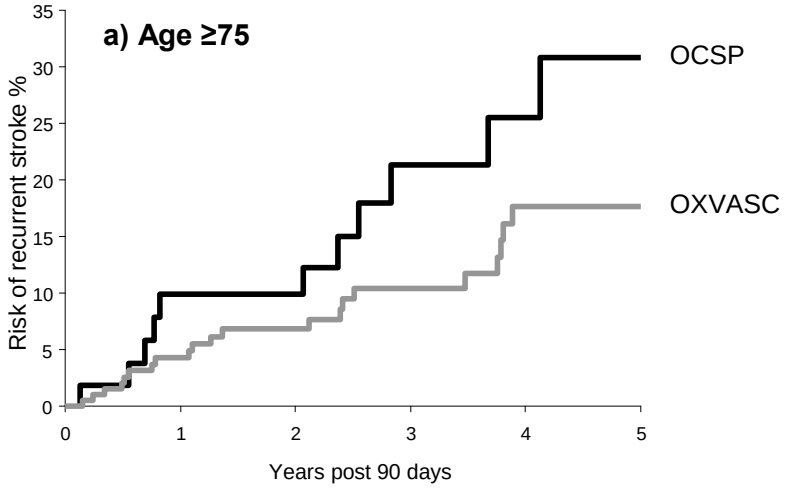
p=0.003



HR 0.53 (0.38-0.73)
Adj HR 0.51 (0.37-0.70)

p<0.0001

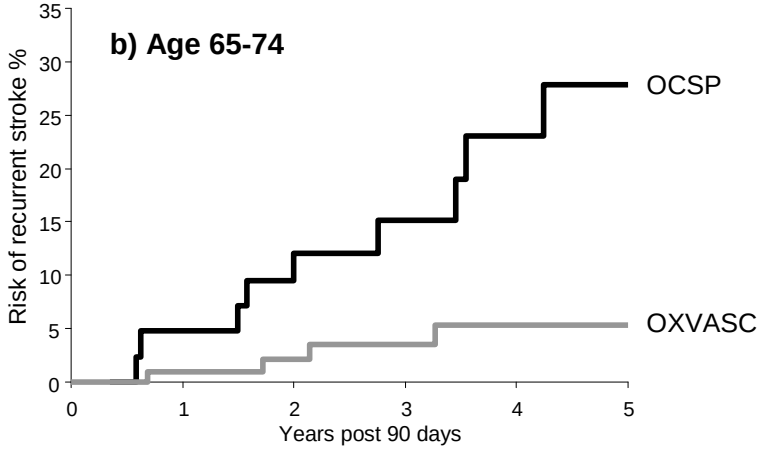
Figure 10.2 Post 90-day risk of recurrent stroke up to 5 years after TIA in OCSP and OXVASC by age. (Adj HR= Hazard ratio adjusted for age and sex)



HR 0.55 (0.26-1.14)

Adj HR 0.53 (0.26-1.11)

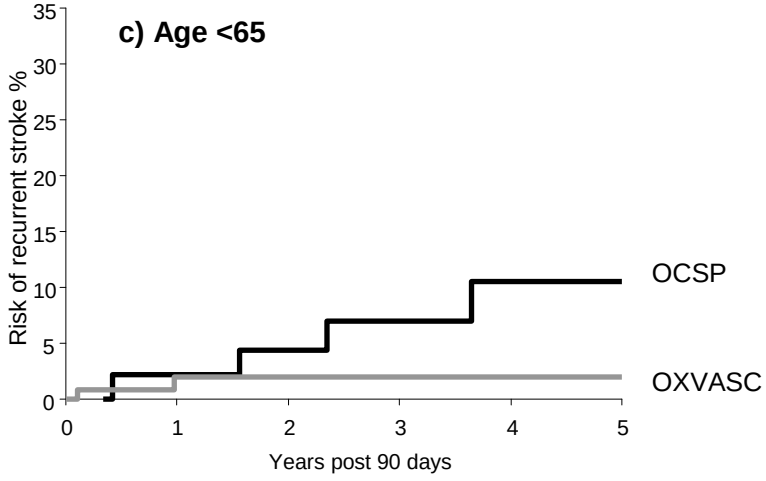
p=0.1



HR 0.20 (0.06-0.63)

Adj HR 0.22 (0.07-0.74)

p=0.002

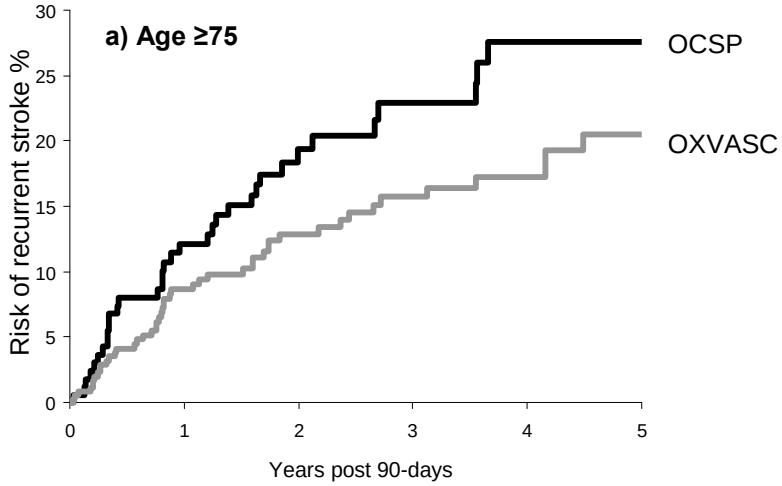


HR 0.25 (0.05-1.38)

Adj HR 0.28 (0.05-1.54)

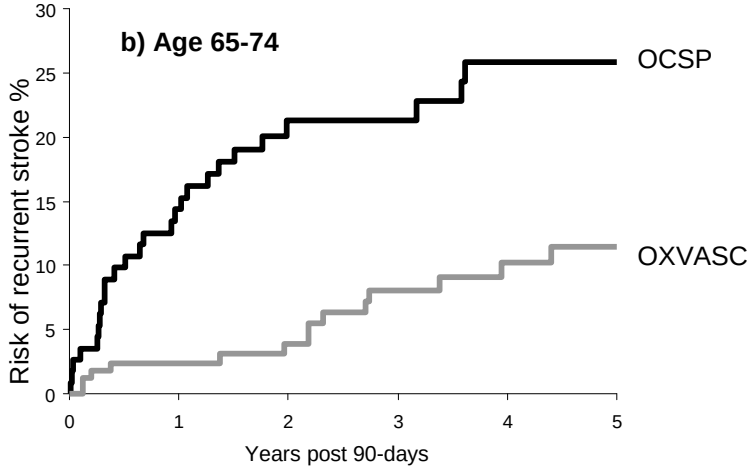
p=0.09

Figure 10.3 Post 90-day risk of recurrent stroke up to 5 years after stroke in OCSP and OXVASC by age.



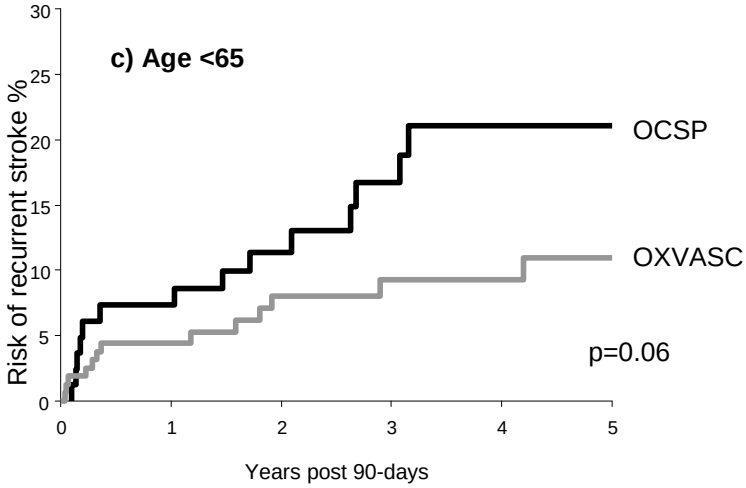
HR 0.66 (0.42-1.02)
Adj HR 0.66 (0.43-1.03)

p=0.06



HR 0.32 (0.17-0.62)
Adj HR 0.31 (0.16-0.60)

p=0.0003



HR 0.50 (0.23-1.06)
Adj HR 0.50 (0.23-1.05)

p=0.06

After TIA, mortality risks at 5 years were similar in OCSP and OXVASC (30.8% (21.8-39.8) vs 27.8% (22.7-32.9), p=0.98, Table 10.4). The risks remained similar after adjusting for age and sex (HR 0.76, 0.52-1.10, p=0.15). After stroke, 5 year mortality since OCSP has fallen by 31% (adjusted HR 0.69, 0.59-0.82, p<0.001). The fall in mortality after stroke was greatest for those under 75 years (Figure 10.4b and c). After stroke, mortality was highest within the first 90 days and the 90-day risks were similar in both cohorts (17.3%, 14.0-20.6 in OCSP vs 16.5%, 14.1-18.9 in OXVASC). However post 90-days up to 5 years, in contrast with the similar mortality risks after TIA, mortality risk after stroke fell from 45.1% (39.2-51.0) in OCSP to 36.1% (31.8-40.4) in OXVASC (p=0.004, Table 10.5).

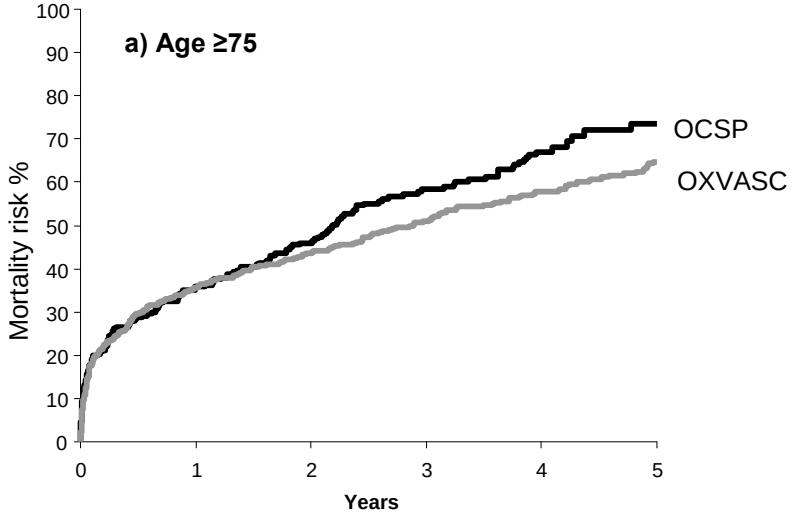
Table 10.4: Mortality (% risk, 95% CI) up to 5 years after TIA and stroke in OCSP and OXVASC

	1981-1986			2002-2010			
	Patients	Deaths	% risk	Patients	Deaths	% risk	p
TIA	152	36	30.8 (21.8-39.8)	486	96	27.8 (22.7-32.9)	0.98
Stroke	474	229	54.6 (49.3-59.9)	896	350	46.7 (42.8-50.6)	0.013
All events	626	265	48.9 (44.4-53.4)	1382	446	40.2 (37.1-43.3)	0.001

Table 10.5 Post 90-day mortality risks up to 5 years after TIA and stroke in OCSP and OXVASC

	1981-1986			2002-2010			
	Patients	Deaths	% risk	Patients	Deaths	% risk	p
TIA	151	35	30.3 (21.3-39.3)	470	80	25.3 (20.2-30.4)	0.5
Stroke	392	147	45.1 (39.2-51.0)	748	202	36.1 (31.8-40.4)	0.004
All events	543	182	41.1 (36.2-46.0)	1218	282	32.2 (28.9-35.5)	0.001

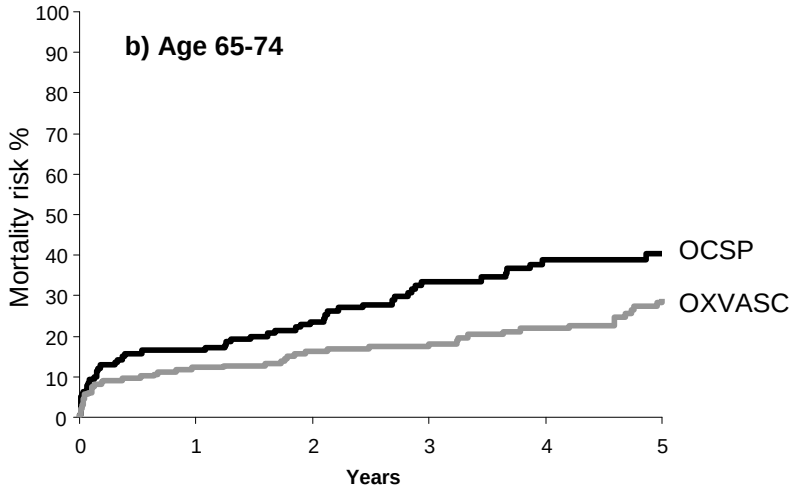
Figure 10.4 Risk of mortality up to 5 years after stroke in OCSP and OXVASC by age



HR 0.86 (0.71-1.05)

Adj HR 0.86 (0.71-1.05)

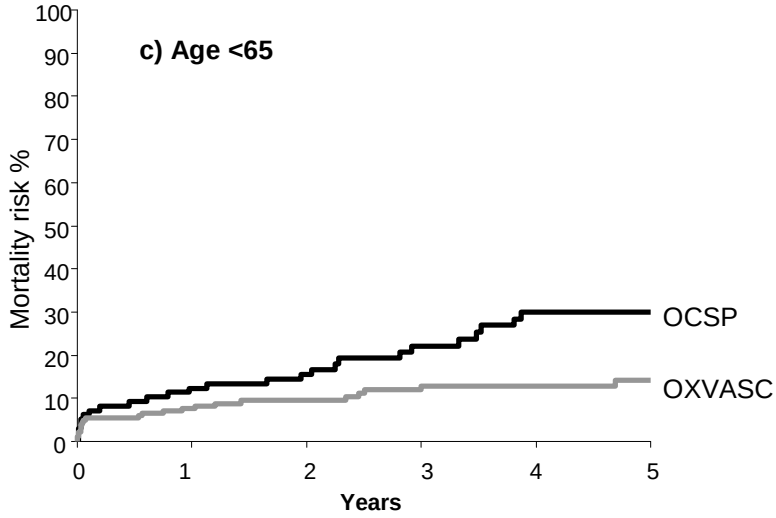
p=0.08



HR 0.68 (0.46-1.0)

Adj HR 0.68 (0.46-1.0)

p=0.05



HR 0.48 (0.28-0.83)

Adj HR 0.48 (0.28-0.83)

p=0.01

In OXVASC, there were 29 cardiac deaths at 5 years (Table 10.6). Of these, 13 deaths were due to fatal MI and 16 were due to sudden cardiac death (SCD).

Table 10.6: Risk of fatal MI or sudden cardiac death (% risk, 95% CI) up to 5 years after TIA and ischaemic stroke in OCSP and OXVASC

	1981-1986			2002-2010			
	Patients	Fatal MI/SCD	% risk	Patients	Fatal MI/SCD	% risk	p
TIA	152	10	10.5 (3.4-17.6)	486	12	4.6 (1.9-7.3)	**0.04**
Stroke	474	53	18.5 (13.4-23.6)	896	17	2.9 (1.3-4.5)	**<0.0001**
All events	626	63	16.2 (12.1-20.3)	1382	29	3.6 (2.2-5)	**<0.0001**

The 5-year risk of cardiac death after all ischaemic events in OXVASC was 3.6%, which was much lower than in OCSP (16.2% (12.1-20.3), p<0.0001, Figure 10.5a i). After adjusting for age and sex, the risk of cardiac death after all ischemic events has fallen by 81% (HR 0.19 (0.12-0.30), p<0.001). After TIA, the age and sex adjusted risk of cardiac death has fallen by 62% (HR 0.38 (0.16-0.89), p=0.04, Figure 10.5a ii). However, the greatest fall in risk of cardiac death was after stroke (18.5% (13.4-23.6) vs 2.9% (1.3-4.5)). After adjusting for age and sex, the risk of cardiac death has fallen by 84% after stroke (HR 0.16 (0.9-0.27), p<0.0001).

In contrast, the risk of fatal recurrent stroke has not changed since OCSP (Figure 10.5b). In OXVASC, there were 53 deaths from recurrent stroke (17 after TIA, 36 after stroke, Table 10.7).

Table 10.7: Risk of fatal recurrent stroke (% risk, 95% CI) up to 5 years after TIA and ischaemic stroke in OCSP and OXVASC

	1981-1986			2002-2010			
	Patients	Fatal recurrent stroke	% risk	Patients	Fatal recurrent stroke	% risk	p
TIA	152	7	6.0 (1.5-10.5)	486	17	4.7 (2.3-7.1)	0.77
Stroke	474	15	5.0 (2.5-7.5)	896	36	6.9 (4.5-9.3)	0.45
All events	626	22	5.3 (2.9-7.7)	1382	53	6.0 (4.2-7.8)	0.67

The age and sex adjusted risk of fatal recurrent stroke has remained the same when compared with OCSP (6.0% (4.2-7.8) vs 5.3% (2.9-7.7), HR 0.88 (0.53-1.46), p=0.67, Figure 10.5b i). Regarding event type, there has been no change in the risk of fatal recurrent stroke after either TIA or stroke (Figures 10.5b ii and 10.5b iii).

The fall in risk of cardiac death after TIA and stroke, is mainly accounted for by a fall in fatal MI after stroke. Figure 10.6 shows the risk of fatal MI compared with the risk of SCD after TIA and stroke in OXVASC and OCSP. After adjusting for age and sex, the risk of fatal MI after TIA and stroke has fallen by 85% (HR 0.15, (0.08-0.28), p<0.001), the age-adjusted risk of SCD has fallen by 75% (HR 0.25 (0.13-0.47), p<0.001).

Figure 10.5. Risk of a) fatal MI or sudden cardiac death (SCD)

b) fatal recurrent stroke up to 5 years in OCSP and OXVASC

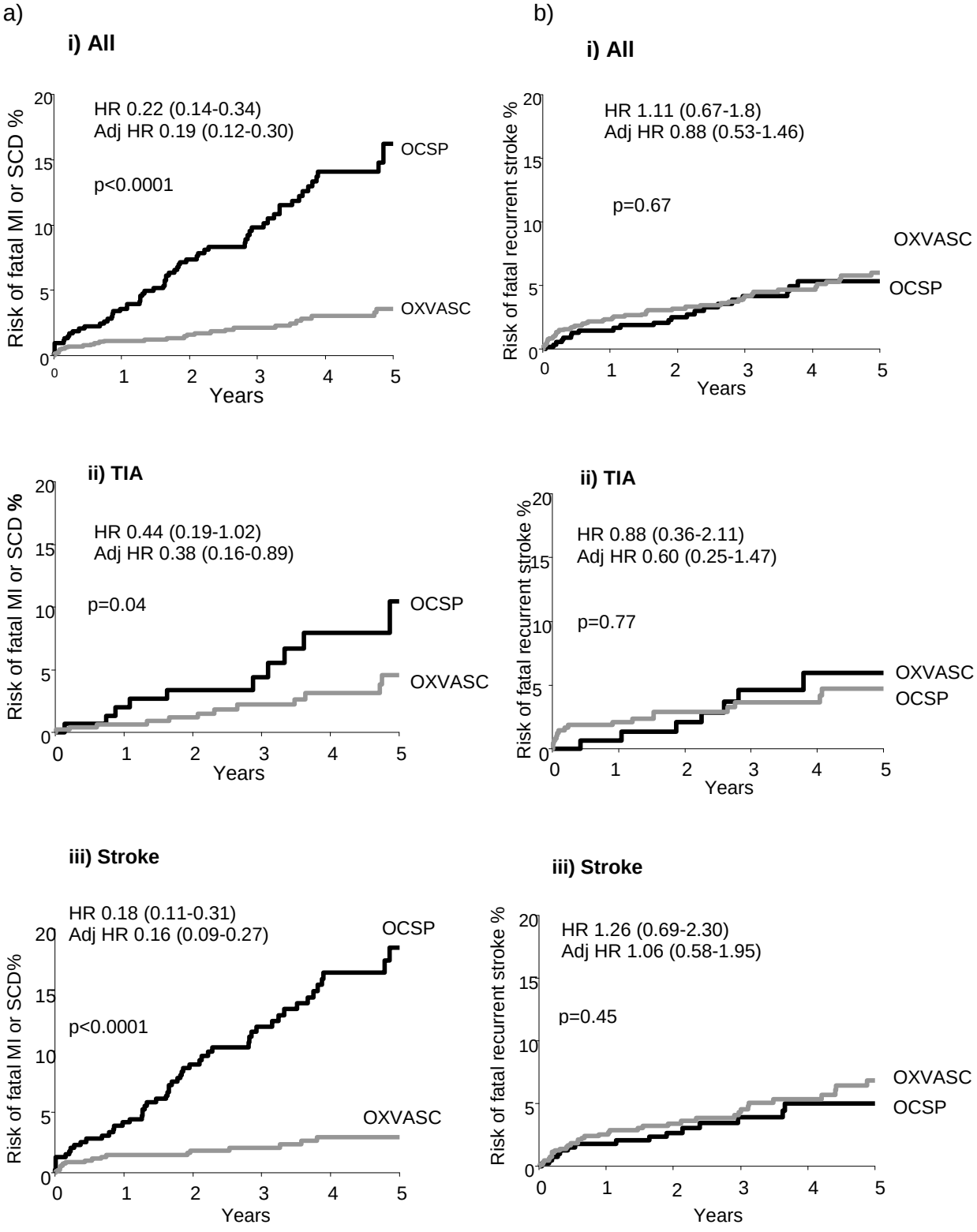
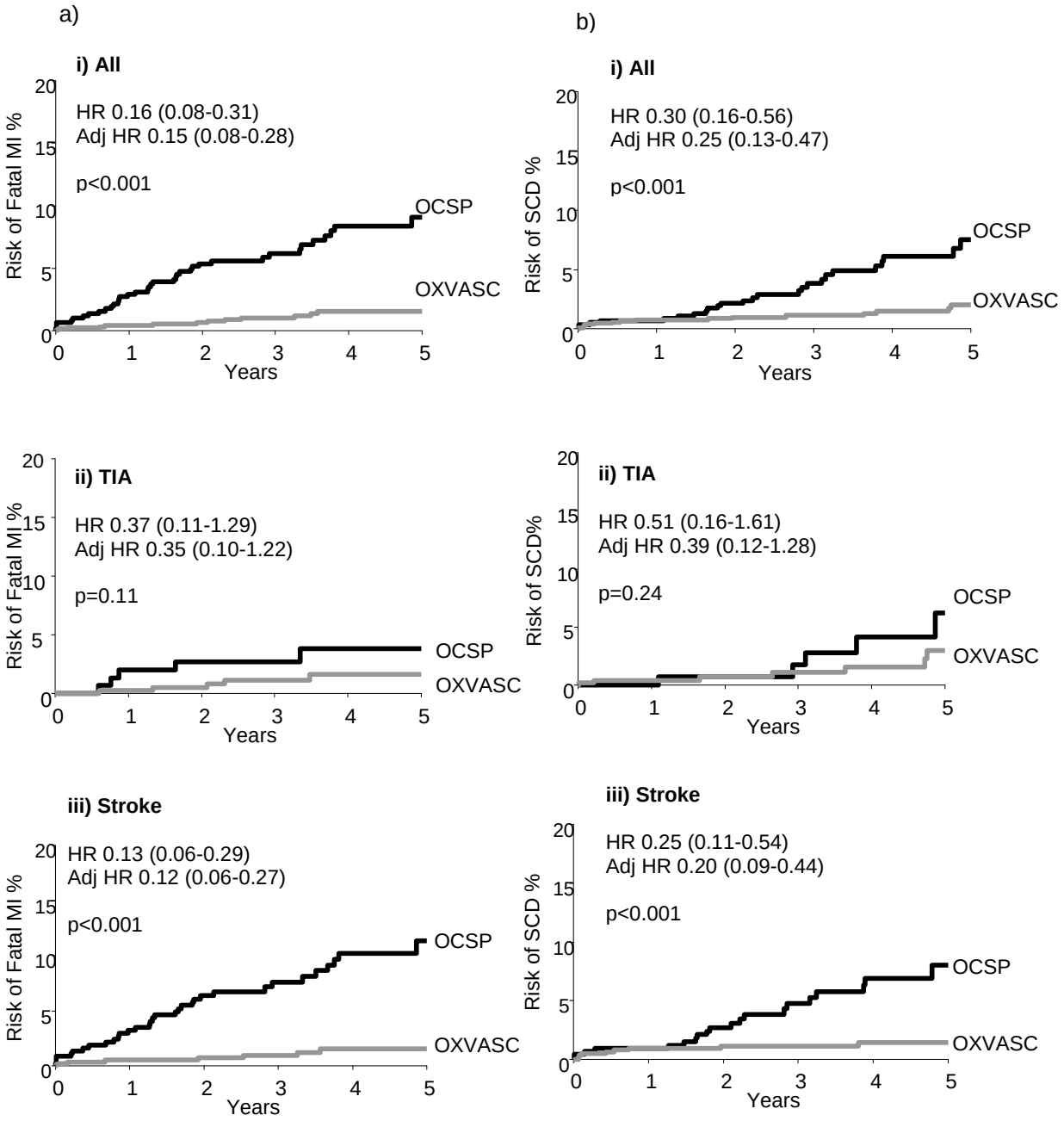


Figure 10.6. Risk of a) fatal MI and

b) SCD up to 5 years in OCSP and OXVASC



10.4 Discussion

In this study I have shown that since OCSP, the age and sex adjusted post 90-day recurrent stroke risks up to 5 years after TIA and stroke in Oxfordshire have fallen by 63% and 52% respectively. The age and sex adjusted mortality risk has fallen by 31% after stroke but has remained stable after TIA. The age and sex adjusted 5-year risk of cardiac death after TIA and stroke has fallen by 80%. The 5-year risk of fatal recurrent stroke has not changed.

There have been many improvements in secondary prevention since OCSP. Randomised trials have shown the effectiveness of aspirin plus dipyridamole in 1987, warfarin for patients with atrial fibrillation in 1993, carotid endarterectomy for severe symptomatic carotid stenosis in 1991, clopidogrel in 1996, blood-pressure reduction in 2001, and cholesterol reduction with simvastatin in 2004 and atorvastatin in 2006.[22] It has been estimated from modeling studies using the observed treatment effects from randomised trials, that treatment of all major risk factors can reduce the recurrent stroke risk by about 80% compared with no treatment.[23] Although levels of use of secondary prevention at follow-up in the OCSP cohort were not available for this analysis, it is likely that high levels of use of antiplatelets, warfarin, antihypertensives, statins after events in OXVASC (chapter 9) largely accounts for the reductions in later risk. Improvements in public awareness and public education into stroke risk factors with better acute stroke care and better management of complications could have also contributed to reduced recurrence rates and mortality.

My results are in keeping with other studies, the Perth Community Study reported a non-significant decrease in the 1 year cumulative recurrent stroke risk from 16.2% to 9% from 1989-1996.[24] A larger cohort in Northern Sweden found yearly declines in recurrence rates of 1.7% in non-diabetic men and 2.7% in non-diabetic women between 1985 and 2003.[25] A study of 5 year recurrent hospitalisation and mortality risks after hospitalisation for first stroke in Scotland from

1986-2001 found a 27% reduction in stroke recurrence risk and 28% reduction in mortality risk.[26] In their study, risks were adjusted for age, sex, socioeconomic status and co-morbidities, however, hospital coding data were used to measure outcomes which can be a less reliable method to estimate recurrent events.[26] Use of secondary prevention measures over time was not presented, however the authors also proposed this as the likely main reason for the fall in recurrence risk.[26]

Previous studies have reported that death following TIA is more commonly due to cardiac disease than due to further stroke.[11,27-29] In these studies, death due to coronary artery disease was responsible for 24-62% of deaths in the first 5-10 years after a TIA, whilst stroke accounted for 12-28% deaths.[11,27-29] In OCSP, those with stroke surviving beyond 30 days were also more likely to die of cardiac causes than recurrent stroke.[12] In this study I have shown that the long-term risk of cardiac death after TIA and stroke has fallen. Less smoking, increased antiplatelet and statin use over time may account for this reduction in fatal MI. It may be that, after a TIA or stroke, secondary stroke prevention is targeting asymptomatic coronary atheromatous disease, resulting in a lower MI risk. Other time-trend studies have observed a falling in incidence of MI in the general population,[30] which may be reflected in my data, independent of secondary prevention. However it is important to remember that patients with recurrent events within OXVASC are different to the general population in that they have already had a cerebrovascular event, and may be less amenable to secondary prevention. It may be that that advances in the treatment of MI since OCSP, such as rapid access to thrombolysis or primary angioplasty mean that there is now less chance of dying from MI. Another possibility is that the lower rates of cardiac death in OXVASC are due to removal of a hazard that was present during OCSP, for example there may have been higher use of alpha-blockers in the treatment of hypertension during OCSP which has been associated with an increased risk of cardiac events.[31] A comparison of secondary prevention measures at follow-up in both cohorts are needed to

explore this further and is a topic of future study. It would have been useful to study the incidence of MI after ischaemic events rather than death due to MI, however the changing definition of MI over time meant that I was unable to directly compare the risk of MI in the two cohorts. A broader definition of MI is used currently, making a comparison of MI risk with OCSP difficult. Since the definitions of fatal MI and sudden cardiac death are similar in both cohorts, I feel this comparison is valid.

By presenting post-90 day mortality risks, I attempted to show the excess in mortality attributable to death from causes other than the incident stroke. The risk of death from recurrent stroke remained stable between 1981 and 2010. The 5 year mortality risk after stroke in population-based studies varies between 41% and 72%.[14] In a hospital based cohort of 755 patients in Hong Kong, the 5 year mortality risk was 39.7%.[32] However, hospital-based studies do not include those with minor deficits, those who refused admission, those who died before admission and those admitted to other hospitals, therefore population-based studies provide better estimates of risk.

This study has some limitations. First, although I attempted to keep the inclusion of cases similar in both cohorts by restricting the analysis to incident cases with a probable or definite diagnosis of TIA or stroke, improvements in diagnostic methods and imaging, for example diffusion weighted MRI, could have increased the numbers of incident cases with TIA and minor stroke identified in OXVASC compared with OCSP. Such cases may have a better prognosis which could explain the lower mortality after stroke in OXVASC, however the mortality after TIA has remained unchanged, therefore this is unlikely. Second, there were differences in ascertainment of recurrent event cases: OXVASC included any new neurological event after improvement or stabilization of the first event as a recurrent event whereas in OCSP, only recurrent events 21 days after the initial event were included. This difference in diagnosis of recurrence based on

timing could have resulted in possible under ascertainment of early recurrent events in OCSP compared with OXVASC, although this should not have affected later, post-90 day risks. Again, improvements in imaging may have increased the numbers of recurrent events diagnosed in OXVASC although this would be expected to produce less of a fall in risk between the cohorts. Third, although hazard ratios were adjusted for age and sex, other differences in the two cohorts at baseline may account for the differences. The OCSP cohort included fewer 'very old' cases and patients were less frail, therefore the OCSP cohort may have had a better prognosis. The change in pre-morbid vascular risk factors over time, such as less smoking, and increase in use of pre-morbid anti-platelets, lipid-lowering and antihypertensive medications has been associated with falls in stroke incidence over time, and may also reduce long-term recurrence risk. Fourth, the definition of fatal recurrent stroke included deaths beyond 30 days due to complications from the recurrent stroke. This definition is useful as it reflects the impact of recurrent stroke on later mortality by including cases that die from complications of stroke, such as pneumonia due to immobility. However this definition is also open to individual interpretation, inter-rater reliability of classification of cause of deaths was not done in this study but could be an area for future work.

In summary, I have shown the later recurrent stroke risk, cardiac death risk and mortality risks up to 5 years after stroke have fallen in Oxfordshire since 1981. However the risk of recurrent fatal stroke has remained stable. Improvements in premorbid vascular risk factors and increased secondary prevention use may explain the fall in recurrent stroke risk and cardiac death risk. More data on changes in secondary prevention use over this time period are needed to explain these findings. Precise data on secondary prevention medication used in OCSP was not available for this sub-study but could be an area of future study. The high recurrent stroke risk beyond the acute phase supports the need for long-term secondary prevention after TIA and stroke.

10.5 References

1. Rothwell PM, Coull AJ, Giles MF, Howard SC et al. Change in stroke incidence, mortality, case-fatality, severity and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular study). Lancet 2004;363:1925-1933
2. Islam MS, Anderson CS, Hankey GJ, Hardie K, Carter K, Broadhurst R, Jamrozik K. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. Stroke 2008; 39: 776–782.
3. Béjot Y, Aouba A, de Peretti C, Grimaud O, Aboa-Eboulé C, Chin F, Woimant F, Jougla, E, Giroud M. Time trends in hospital-referred stroke and transient ischemic attack: result of a 7-year nationwide survey in France. Cerebrovasc Dis 2010; 30: 346–354.
4. Corso G, Bottacchi E, Giardini G, De la Pierre F, Meloni T, Pesenti Campagnoni M, Ponzetti C, Veronese Morosini M. Community-based study of stroke incidence in the Valley of Aosta, Italy. Neuroepidemiology 2009; 32: 186–195.
5. Chau PH, Woo J, Goggins WB, Tse YK, Chan KC, Lo SV, Ho SC. Trends in stroke incidence in Hong Kong differ by stroke subtype. Cerebrovasc Dis. 2011;31(2):138-46.
6. Hong K-S, Yegiaian S, Lee M, Lee J, Saver JL. Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. Circulation 2011; 123: 211-2119
7. Allen NB, Holford TR, Bracken MB, Goldstein L, Howard G, Wang Y, Lichtman JH. Trends in one-year recurrent ischaemic stroke among the elderly in the USA: 1994-2002. Cerebrovasc Dis 2010;30:525-532
8. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370(9596):1432-1442.
9. Lavallee PC, Meseguer E, Abboud H, et al. A transient ischemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6(11):953-960.
10. Calvet D, Lamy C, Touze E, Oppenheim C, Meder JF, Mas JL. Management and outcome of patients with transient ischemic attack admitted to a stroke unit. Cerebrovasc Dis. 2007;24(1):80-85.
11. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischaemic attacks in the Oxfordshire Community Stroke Project. Stroke. 1990; 21:848-853.
12. Dennis M, Burn JPS, Sandercock PAG, Bamford JM, Wade DT, Warlow C. Long-term survival after first-ever stroke: The Oxfordshire Community Stroke Project. Stroke. 1993; 24:796-800.

13. Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke. 2005 Dec; 36(12):2748-55.
14. Pendlebury ST, Rothwell PM. Risk of recurrent stroke, other vascular events and dementia after transient ischaemic attack and stroke. Cerebrovasc Dis. 2009; 27 Suppl 3:1-11.
15. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, Vessey M, Fowler G, Molyneux A, Hughes T, Burn J, Wade D. A prospective study of acute cerebrovascular disease in the community: the Oxford Community Stroke Project 1981-86. 1 Methodology, demography and incident cases of first-ever stroke. JNNP 1988;51:1373-1380.
16. Rothwell PM, Coull AJ, Silver LE, 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). Lancet. 2005;366(9499):1773-1783.
17. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke. 2004;35(9):2041-2045.
18. Dennis MS, Bamford JM, Sandercock PAG, Warlow CP. Incidence of transient ischaemic attacks in Oxfordshire, England. Stroke 1989;20:333-339
19. Burn J, Dennis M, Bamford J, Sandercock P, wade Derrick, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke 1994;25:333-337.
20. Coull A, Lovett JK, Rothwell PM, on behalf of the Oxford Vascular Study. Population based study of early risk of stroke after a transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004; 328: 326–28.
21. Coull A, Rothwell PM. Under-estimation of the early risk of recurrence after first stroke by the use of restricted definitions. Stroke 2004; 35: 1925–29.
22. Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. Lancet 2011; 377:1681-92.
23. Hackam DG, Spence JD. Combining multiple approaches for the secondary prevention of vascular events after stroke: a quantitative modeling study. Stroke 2007:38:1881-85.
24. Hardie K, Jamrozik K, Hankey GJ, Broadhurst RJ, Anderson C. Trends in five-year survival and risk of recurrent stroke in the Perth Community Stroke Study. Cerebrovasc Dis 2005;19:179-185
25. Rautio A, Eliasson M, Stegmayer B. Favourable trends in the incidence and outcome in stroke in nondiabetic and diabetic subjects: findings from the Northern Sweden MONICA Stroke registry in 1985 to 2003. Stroke 2008; 39:3137-3144.

26. Lewsey J, Jhund PS, Gillies M, Chalmers JWT, Redpath A, Briggs A, Walters M, Langhorne P, Capewell S, McMurray JJV, MacIntyre K. Temporal trends in hospitalization for stroke recurrence following incident hospitalization for stroke in Scotland. BMC Medicine 2010;8:23-30. http://www.biomedcentral.com/1741-7015/8/23 accessed September 11th 2011
27. Cartlidge NE, Whisnant JP, Elveback LR. Carotid and vertebral-basilar transient ischaemic attacks. A community study, Rochester, Minnesota. Mayo Clin Proc 1977;52:117-120,
28. Hankey GJ, Slattery JM, Warlow CP. The prognosis of hospital-referred transient ischaemic attacks. JNNP 1991;54:793-802.
29. Muuronen A, Kaste M. Outcome of 314 patients with transient ischaemic attacks. Stroke. 1982; 13:24-31.
30. McManus DD, Piacentine SM, Lessard D, Gore JM, Yarzebski J, Spencer FA, Goldberg RJ. Thirty-year (1975 to 2005) trends in the incidence rates, clinical features, treatment practices, and short-term outcomes of patients <55 years of age hospitalized with an initial acute myocardial infarction. Am J Cardiol 2011;108 (4):477-82
31. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid Lowering Treatment to prevent heart attack trial (ALLHAT). JAMA 2000;283:1967-75
32. Cheng CM, Tsoi TH, Hon SFK, Au-Yeung M, Shiu KL, Lee CN, Huang CY. Outcomes after first-ever stroke. Hong Kong Med J 2007;13:95-9.

CHAPTER 11

Conclusions and further research

11.1 Introduction 246

11.2 Time trends in patient behaviour after TIA and minor stroke 246

11.3 Population based study of capsular warning syndrome and prognosis after early recurrent TIA 247

11.4 Population-based study of NINDS-defined TIA: evidence of substantial under-diagnosis of posterior circulation events 248

11.5 Utility of FAST test in prediction of early stroke risk after TIA and minor ischaemic stroke: implications for public education 249

11.6 Feasibility, safety and cost of outpatient management of acute minor ischaemic stroke: a population-based study 250

11.7 Prognosis of TIA and minor stroke in the subacute phase 250

11.8 Treating blood pressure to target levels in patients with TIA and non-disabling stroke: Feasibility, acceptability and blood pressure control with intensive Bluetooth home BP-monitoring 251

11.9 Long term outcomes after TIA and stroke 252

11.10 Change in late recurrent stroke, fatal stroke and fatal cardiac event risk after TIA and stroke in Oxfordshire from 1981- 2010 253

11.1 Introduction

This thesis presents data from the Oxford Vascular Study (OXVASC), a prospective, population-based study of acute vascular events in all territories in Oxfordshire, UK, which started in April 2002 and is ongoing. The study population comprises approximately 91,000 individuals of all ages, defined by registration with nine general practices. Multiple overlapping methods of “hot” and “cold” pursuit are used to ensure near complete ascertainment of all patients with stroke, TIA, acute coronary syndrome, acute peripheral vascular events and those undergoing elective vascular investigations and interventions. Following ascertainment and consent, individuals are interviewed, examined, and followed up while clinical data including premorbid risk factors and investigation results are recorded. It is based on the Oxfordshire Community Stroke Project (OCSP), a similarly high quality population-based incidence study of stroke and TIA performed in a similarly defined population in the 1980’s.

The focus of this thesis has been to identify areas for improvement in the effectiveness of acute and long-term secondary prevention during the patient journey after TIA and minor stroke.

11.2 Time trends in patient behaviour after TIA and minor stroke

The early risk of recurrent stroke after TIA and minor stroke is high and this can be reduced by early assessment and treatment. However, there has been limited research on delays to treatment in this crucial period. I studied the initial perceptions and actions of 1357 consecutive TIA and minor stroke patients in relation to clinical characteristics and risk of recurrent stroke. I also studied the characteristics of 63 patients who had a TIA or minor stroke but only sought medical attention after an early recurrent stroke. I was able to show about 70% of patients fail to recognise their TIA or minor stroke and about 30% delay

seeking medical attention for over 24 hours. Reassuringly, those at higher early stroke risk had shorter delays, however 30% of early recurrent strokes occurred prior to any attempt to do so. I found that recognition of symptoms was associated with shorter delays in seeking medical attention after TIA, although not after minor stroke. During the seven year study period, I found the median delay in seeking medical attention after TIA and minor stroke did not change, the proportion of patients seeking medical attention within 24 hours remained around 70%.

The FAST television campaign was launched in 2009 with additional posters and leaflets. Television advertising has the potential to reach more people than posters and leaflets and may have affected public perception and behaviours after TIA, minor stroke and major stroke. OXVASC continues to collect data on patients' perceptions and behaviour following cerebrovascular events and the results of this data will be used to analyse the impact of the mass media campaign.

11.3 Population based study of capsular warning syndrome and prognosis after early recurrent TIA

Current guidelines recommend urgent assessment and treatment for patients with 2 or more TIAs within 7 days, perhaps in recognition of the capsular warning syndrome. However, whether all patients with multiple TIAs are at high early risk of stroke is not known. By studying the clinical characteristics and TOAST subtype of 1000 patients with TIA, I was able to show that the risk of recurrent stroke after recurrent TIA was highest in those of SVD origin, up to 42%. The recurrent stroke risk after recurrent TIAs of other aetiologies was much lower. Furthermore, the ABCD2 score appropriately classifies these high-risk small vessel TIAs. This has implications for secondary care providers who need to be aware of this high-risk syndrome. This work will need to be validated in larger numbers of TIAs and in other settings.

In further work, I aim to study the predictive power of ABCD2 score in relation to TOAST subtype using area under receiver operator characteristic curve (AUC) analyses. The capsular warning syndrome is rare (1.5% of TIA presentations) but has a poor prognosis. Further work is needed to explore the relationship between aetiology and stroke risk after TIA as a potential explanation of the pathophysiology of the ABCD2 score.

11.4 Population-based study of NINDS-defined TIA: evidence of substantial under-diagnosis of posterior circulation events

The diagnosis of TIA is usually based on the history. Transient isolated brainstem symptoms are not classified as TIAs by the NINDS diagnostic criteria, however there are too few data on their prognosis to be confident of their nature. I prospectively studied all those with a first definite TIA or ischaemic stroke and analysed data on any TIA or transient neurological attack (TNA) in the preceding 90 days. I was able to show that in patients with definite posterior circulation TIA or stroke, preceding TNAs occurred in 26%. TNAs were almost three times more common in the 90-days prior to definite vertebrobasilar territory events than prior to carotid territory events. Furthermore, TNAs were particularly associated with the presence of ≥50% symptomatic vertebrobasilar arterial stenosis. Despite this close temporal link and the association with ≥50% stenosis, only 11% of the preceding events satisfied the NINDS definition of a TIA.

Although the patients in my study were ascertained prospectively, details on TNAs were obtained from asking patients and assessing records retrospectively. To help eliminate recall bias, I would like to prospectively study the outcomes of transient isolated symptoms presenting to a daily TIA clinic. Prospective studies of TNAs are needed to establish reliable estimates of stroke risk and the particular clinical features, such as the characteristics of vertigo, associated with stroke risk. In OXVASC, work is continuing to determine the nature

(using DWI MRI) and prognosis of common TIA-like syndromes. All patients in OXVASC with 20 specific possible TIA syndromes (e.g. isolated slurred speech, isolated diplopia etc) have been prospectively ascertained and followed up since 2002. With these cases, it is hoped that the short and long-term prognosis of each syndrome can be determined. Patients attending the OXVASC clinic now have same-day MRI and MRA, therefore the proportion of patients with each syndrome that have acute ischaemia on DWI or relevant large artery stenotic disease can be determined.

11.5 Utility of FAST test in prediction of early stroke risk after TIA and minor ischaemic stroke: implications for public education

I studied the FAST test result of 1000 patients with TIA and 775 patients with minor ischaemic stroke, I found that a positive FAST test did not predict early recurrent stroke risk. The test also had limited potential to improve access to care, being positive in only 42% of TIA patients who delayed seeking medical attention >24 hours and in only 39% of TIA or stroke patients who did not seek medical attention until after a recurrent stroke. Moreover, there was potential for false reassurance in the 64% FAST negative patients who did seek attention within 24 hours. However, the test was not designed to be used in patients with TIA and minor stroke, further work is needed to show the impact of improving recognition of stroke symptoms and reducing delays in seeking medical attention in those with major stroke in OXVASC. I also hope to look at the impact of the FAST television campaign on delays in seeking medical attention and symptom recognition up to 2 years after its launch, as the campaign may have had long-lasting effects. I also intend to include the impact on patients with intracerebral haemorrhage (about 100 cases within OXVASC from 2002-2010). Such patients also need to access medical care quickly and this group may also act differently in light of the campaign.

11.6 Feasibility, safety and cost of outpatient management of acute minor ischaemic stroke: a population-based study

Outpatient management is safe and effective in preventing early recurrent stroke after TIA, but this approach may not be safe in patients with acute minor stroke. I studied outcomes of clinic and hospital-referred patients with TIA or minor stroke within OXVASC from 2002-2007. In patients with minor ischaemic stroke, I found that the rates of recurrent stroke, 30-day readmission and utilisation of secondary prevention measures after clinic discharge were no worse than those after hospital discharge. After adjusting for characteristics different at baseline, the mean 30-day care costs of clinic based care were six times less than hospital based care. Outpatient management of clinic-referred minor stroke therefore appears feasible and may be as safe as inpatient care. Uptake and maintenance of secondary prevention was also high in clinic managed patients. Additional data on the outcomes of patients with minor stroke in OXVASC since 2007 would help to validate our findings. OXVASC also collects data on disability at 1 month, 6 months, 1 year and 5 year follow-up in patients treated in either setting, analysis of this data would be an additional measure of the outcomes of either process of care.

11.7 Prognosis of TIA and minor stroke in the subacute phase

The early risk of recurrence following TIA and minor stroke is high. However, whether the timing of recurrent events in the subacute phase differs between TIA and stroke is less clear. I studied the timing of recurrent ischaemic events after TIA and minor ischaemic stroke up to 2 years after the event. I was able to show that the time course of recurrent stroke risk varied according to type of presenting event. The risk of recurrent stroke after TIA was about double that after minor stroke at 7-days (10.6% vs 5.1%, OR 2.19, 95% CI 1.30-.3.70, p=0.002), however, at 8 to 90 days from seeking medical attention, recurrent stroke risk was higher after MIS than after TIA (7.2% vs 2.6%, p=0.02). Therefore, stroke recurrence risk after minor

stroke is delayed compared with TIA, and is high during the subacute phase despite current best medical treatment. The higher proportion of recurrences after cardioembolic events may be related to underuse of warfarin after minor events or under-detection of AF. Further work in OXVASC is currently underway to establish the incidence of AF related stroke and use of anticoagulants. Since 2011, the OXVASC clinic cohort have 5-day ambulatory cardiac monitoring and echocardiography as routine investigations after TIA or stroke in order to improve detection of AF and other cardiac sources of embolism. The effect of this on recurrent stroke risks in the subacute phase is an area of future work.

11.8 Treating blood pressure to target levels in patients with TIA and non-disabling stroke: Feasibility, acceptability and blood pressure control with intensive Bluetooth home BP-monitoring

Hypertension is a major modifiable risk factor for recurrent stroke. I aimed to treat BP in patients after TIA or minor stroke to target levels using Bluetooth home monitoring. Monitoring resulted in 1175 changes in antihypertensive medication. Mean BP was 151/83mmHg at entry and 127/72mmHg at 6-months. I was able to show that Bluetooth-based home BP monitoring after TIA or minor stroke was feasible, irrespective of age, and patient satisfaction was high. Monitoring detected high levels of masked hypertension, informed titration of medication, and was associated with good BP control at six months. The Bluetooth home BP monitoring study is continuing with the aim of recruiting 1000 patients, including those managed as inpatients, with follow-up for 5 years to determine associations between BP variability and risks of recurrent stroke, cognitive decline and dementia and to study the effect of BP-stabilisation. Patients within the Bluetooth study are also currently undergoing cardiovascular physiological tests to determine associations between blood pressure variability and arterial stiffness, baroreceptor function and sympathetic over-activity. Using cerebral perfusion imaging techniques, the effects of blood pressure variability and blood-pressure lowering drugs on cerebral perfusion will also be studied. More work on the

adverse effects of treating BP to target in this group of patients is needed, for example the rates of falls, fractures and hospital admission. Further work is also needed on the tolerability of combinations of BP-lowering drugs and rates of stopping drugs due to their adverse effects. The relationship between BP variability and white matter lesion load, disability and cognitive outcomes is also being studied in OXVASC.

11.9 Long term outcomes after TIA and stroke

There is limited available data on the long-term prognosis after TIA and minor stroke within the modern era. I assessed the exact timing of all recurrent strokes, cardiac events and deaths up to 8 years after event onset. I also determined cause of death and secondary prevention use at 1 month and 1 year follow-up. I was able to show that the risk of recurrent stroke after TIA was about double that after minor stroke at 7-days, but the recurrence risk after minor stroke was higher at 8-90 days. After major stroke, the pattern of risk was similar to minor stroke. In all patients, the 8 year risk of a cardiac event was half the risk of a recurrent stroke (10.4%, 6.7-14.2 vs 24.6%, 21.5-27.7). Levels of secondary prevention use were high. I concluded that stroke recurrence risk after minor stroke is delayed compared with TIA, and remains high during the late phase despite current best medical treatment. The long-term cardiac risk after TIA and ischaemic stroke is low. Further work is needed on the impact of recurrent stroke in terms of disability, cognitive function and place of residence. OXVASC routinely collects this data up to 5 years follow up, I aim to analyse these outcomes for the recurrent events that I have presented here. The predictors of late recurrent stroke, cardiac events and mortality are also areas of future work.

11.10 Change in late recurrent stroke, fatal stroke and fatal cardiac event risk after TIA and stroke in Oxfordshire from 1981- 2010

Previous work has shown that the early recurrent stroke risk after TIA and stroke in Oxfordshire has fallen with increased use of preventative treatments and improved risk factor control. However, whether long-term outcomes have changed is not known. I compared the risks of recurrent stroke, death, fatal recurrent stroke and cardiac death up to 5 years after TIA and stroke in the OXVASC cohort to those of patients in the Oxford Community Stroke Project (OCSP) cohort from 1981-1986. I was able to show that since OCSP, post 90 days up to 5 years from event onset, the age and sex adjusted recurrent stroke risk has fallen by 62% after TIA and by 49% after stroke. There were also improvements in mortality after stroke: compared with OCSP, the age and sex adjusted 5-year mortality risk after stroke has fallen by 31%. However, after TIA, 5-year mortality risk has remained stable. Further data is needed on secondary prevention use during follow-up in the two cohorts, it is likely that secondary prevention measures after TIA and stroke are better in the modern era and that their effects persist into the late phase. Data on levels of secondary prevention use in both cohorts could help determine the reason for differences in post-90day recurrent stroke risk and mortality. The effect of secondary prevention on disability also needs to be assessed. Further work is also needed on whether stroke aetiology has changed over time. It may be that differences exist in the aetiology of recurrent events in the two cohorts, which may reflect different management of atherosclerosis compared with that of cardioembolism in the modern era.

In conclusion, this thesis focuses on how secondary prevention after TIA and minor stroke can be improved, by reducing delays in seeking medical attention, improving diagnosis, and managing risk factors beyond the acute phase. This has implications for public education and care-delivery. Future directions include the impact of improved acute and long-term secondary prevention on disability and cognitive outcomes.

Appendix 1 Royal College of Physicians TIA management algorithm[1]

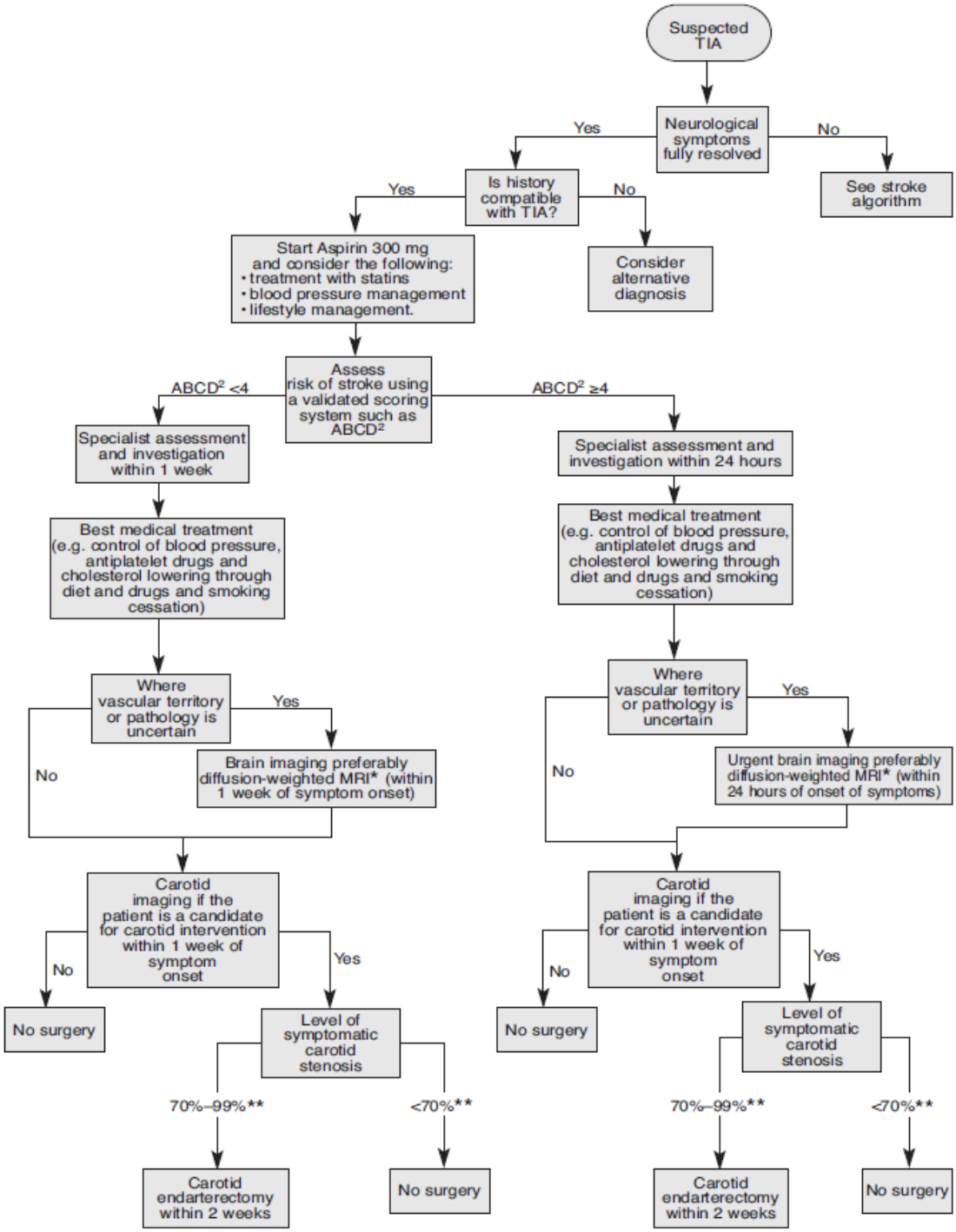


Figure 3.1 Transient ischaemic attack (TIA) algorithm

*except where contraindicated, in which case computed tomography (CT) should be used

**according to the European Carotid Surgery Trial (ECST) criteria

1. National Collaborating Centre for Chronic Conditions. Stroke: National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). London: Royal College of Physicians, 2008.

Appendix II ICD-10 diagnostic codes

ICD-10 Ischaemic Heart Disease

I200	Unstable angina
I201	Angina pectoris with documented spasm
I208	Other forms of angina pectoris
I209	Angina pectoris, unspecified
I210	Acute transmural myocardial infarction of anterior wall*
I211	Acute transmural myocardial infarction of inferior wall*
I212	Acute transmural myocardial infarction of other sites*
I213	Acute transmural myocardial infarction of unspecified site*
I214	Acute subendocardial myocardial infarction*
I219	Acute myocardial infarction, unspecified*
I220	Subsequent myocardial infarction of anterior wall
I221	Subsequent myocardial infarction of inferior wall
I228	Subsequent myocardial infarction of other sites
I229	Subsequent myocardial infarction of unspecified site
I230	Haemopericardium as curr comp follow acute myocardial infarct
I231	Atrial sept defect as curr comp following acute myocardial infarct
I232	Ventric sep defect as curr comp following acute myocardial infarct
I233	Rup cardac wall without haemopercard as cur comp foll acute MI
I234	Rup chordae tendinae as curr comp foll acut myocard infarct
I235	Rup papilary muscle as curr comp foll acute myocard infarct

I236	Thromb atrium/auric append/vent as curr comp foll acute MI
I238	Other current comp following acute myocardial infarction
I240	Coronary thrombosis not resulting in myocardial infarction
I241	Dressler's syndrome
I248	Other forms of acute ischaemic heart disease
I249	Acute ischaemic heart disease, unspecified
I250	Atherosclerotic cardiovascular disease, so described
I251	Atherosclerotic heart disease
I252	Old myocardial infarction
I253	Aneurysm of heart
I254	Coronary artery aneurysm
I255	Ischaemic cardiomyopathy
I256	Silent myocardial ischaemia
I258	Other forms of chronic ischaemic heart disease
I259	Chronic ischaemic heart disease, unspecified
I460	Cardiac arrest with successful resuscitation
I460	Successful resuscitation
I461	Sudden cardiac death, so described
I469	Cardiac arrest, unspecified

ICD-10 Cerebrovascular disease

G450-G468	Vascular brain syndromes
H340-H432	Retinal artery occlusion

H348	Retinal artery occlusions
I600-I609	Subarachnoid Haemorrhage
I610-I619	Intracerebral Haemorrhage
I620-I629	Other intracranial haemorrhages
I630-I64X	Cerebral infarction-stroke non specified
I650-I670	Cerebral artery occlusion and dissection of cerebral arteries
I671- I698	Acute and chronic cerebrovascular diseases

ICD-10	**Haemorrhage**
I850	Oesophageal bleeding
K55-K63	Lower gastrointestinal bleeding
K250-K922	Upper gastrointestinal bleeding
N938-N939	Uterine bleeding
R040-R049	Respiratory bleeding

SUBJECT ID NO:

Patient identification label
(check address is current)

Was patient interviewed		**Y**	**N**	**U**
If NO why not?	Please tick			
1	Refused interview			
2	Aphasic and relatives could not be contacted			
3	Too unwell/ multiple medical problems			
4	Dementia (need to record MMSE or AMTS) and relatives could not be contacted			
5	Late ascertainment and no reply to invitation to join study			
6	Ascertainment after death			
7	Diagnosis uncertain			
9	Unknown			

Patient contact details	
Telephone (day)	
Telephone (evening)	
Mobile	
Fax number	
Email address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone (day)	
Telephone (evening)	
Mobile phone no	
Fax number	
Email addres	

OXVASC db: Name

11 digit OXCODE for notification event										

Consultant	

1 Physician	5 Vascular surgeon
2 Physician with stroke interest	6 Cardiologist
3 Neurologist	7 Neurosurgeon
4 General surgeon	9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name or Initials					

Summary Diagnosis		Specify:
S= Stroke T= TIA A= Amaurosis fugax	R= Retinal artery Occlusion M= MI	B= Burden Z= Other (specify)

Is this the first ever in a lifetime (incident) stroke? *	**Y**	**N**	**U**
Is this the first ever in a lifetime (incident) TIA? *	**Y**	**N**	**U**

* Please tick as appropriate

Date of notification event (DD-MM-YY)	

Location of interview	1 JRH inpatient 2 RI in patient 3 Community hosp	4 Outpatients 5 Home 6 Other (specify)		Specify:
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up	4 Other (specify) 6 No follow-up 7 Home visits		Specify:
Info on form obtained from	1 Patient 2 Relative 3 GP 4 hospital records	5 Death certificate 6 Other (specify)		Specify:
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify)	5 Health authority search 6 Death 7 Troponin 9 Other (specify)		Specify:

Other sources of notification (select all appropriate)	1	2	3	4
	Specify:	Specify:	Specify:	Specify:

If one had not identified the patient via the route of 1st notification would patient have been identified by other source of ascertainment? (please circle)	Y	N	U

OXVASC db: 1

HISTORY OF NOTIFICATION EVENT	Please tick if:	All fields unknown on page 3+4

Narrative history & examination

Did patient have PRANS events?	Y	N	U	Date most recent	OXCODE for PRANS event:
				U	

Details:

Notification event*		What did you think was wrong? OXVASC db: 2
Date DD-MM-YY	**Time** 24 hr clock	
U	: U	

* The event that led to first seeking medical attention

Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
Were you alone?	**Y**	**N**	**U**
If you were with someone who was it?	U		
Who called for help?	U		
If you did not call for help at time of event, why not?	U		

Who did you 1st call for help?	1= Medical 2=Non-Medical 9= Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
1st call for ANY help non-medical or medical			Please give date/time for any 1st call *	
				: U
1st call for MEDICAL help GP/ A&E / 999/ NHS direct			Please give date/time for 1st medical call	
				: U

* This could be the same date and time as the first call for medical help (please provide anyway)

Calls for medical attention		**Date** DD-MM-YY	**Time** 24 hr clock
GP by telephone	**Y / N**		:
GP in person	**Y / N**		:
Telephoned 999	**Y / N**		:
Went to A&E in person	**Y / N**		:
Telephoned NHS direct	**Y / N**		:
Went to OEH	**Y / N**		:
Other (Specify)	**Y / N**		:

Outcome of first call for medical assistance

				Date DD-MM-YY	Time 24 hr clock
Seen by GP / A&E <u>in person</u>?	**Y**	**N**	**U**		: U
If GP referred subject to OXVASC clinic: **Notification by GP to OXVASC**					: U
If subject was not referred to OXVASC: **Admitted to hospital?**	**Y**	**N**	**U**		: U
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					: U
Assessment by OXVASC staff					: U

HISTORY OF NOTIFICATION EVENT	**Please tick if:**	**All fields unknown on page 5+6**

Duration of symptoms Please leave blank for stroke				Hrs:	Mins:
Onset on wakening from sleep?				**Y**	**N** **U**
Time awake (ignore if onset not on wakening from sleep) 24 hr clock				: U	
Activity at onset (within 2 hrs of onset)					1= Asleep 2= Sedentary 3= Mild-moderate 6= Strenuous 9= Unknown
What were you doing in the same 2 hrs on the day prior to the event?					
Drugs within previous hour				**Y**	**N** **U**
Meal within previous hour				**Y**	**N** **U**
Record exact activity				U	
Location of event	1 Home 2 Work 3 Leisure (non-sport)		4 Sport 8 Other (specify) 9 Unknown		Specify:

OXVASC db: 3

ONSET ANGER SCALE		Anger level
Onset NOT on wakening from sleep	In the **two hours prior to the event** what best describes your emotional state from the list provided?	
	In the **exact same two hours on the day prior to your event** which best describes your mood?	
OR:		
Onset ON wakening from sleep	If you had your event on wakening how were you in the **two hours before you went to bed**?	

1 = **Calm**
2 = **Busy** (but not hassled)
3 = **Mildly angry** (irritated and hassled, but does not show)
4 = **Moderately angry** (so hassled it shows in your face)
5 = **Very angry** (body tense, clenching fists or teeth)
6 = **Furious** (almost out of control, very angry, pound table, slam door)
7 = **Enraged** (lost control, throwing objects, hurting yourself or others)
9= **Unknown**

Was there a further event between notification event and assessment?	Y	N	U

If yes to above please indicate number of events between any of the following:	
	No. events
Between notification event and seeing GP/ other medical opinion (including notification event)	# U
Between seeing GP and notification by GP to OXVASC	# U
Between notification by GP and OXVASC assessment	# U

Were there any events in the month preceding the notification event?	Y	N	U
How many events were there in the month before notification event?	#		U

Has this patient had a recurrent event between notification event and OXVASC assessment?	Y	N	U

This question is identical to the one at the top, answers should be the same.

HISTORY OF NOTIFICATION EVENT

Event	History of events between notification event and assessment		
1	**Notification event itself**		
2		**Event date*:** U	**Time** : U
3		**Event date*:** U	**Time** : U
4		**Event date*:** U	**Time** : U
5		**Event date*:** U	**Time** : U

Use extra piece of paper for event 6 onwards. * DD-MM-YY 24 Hr clock

If admitted as a result of the notification event (use ambulance sheet)

Was subject admitted to hospital? as a direct result of the notification event	Y	N	U

If YES then please answer:

Was subject admitted by ambulance?	Y	N	U

If admitted by ambulance:	**Date** DD-MM-YY	**Time** 24 hr clock
Arrival of emergency service with patient	U	: U
Arrival of emergency service in Hospital *	U	: U

* If not on ambulance sheet use blue admissions

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						**Cerebral**						**Peripheral**		
	NSTEMI			**STEMI**			**TIA**			**CVA**					
Prior acute events?	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
	Possible*			Possible*			Possible*			Possible*					
# of events	U			U			U			U			U		
Date of most recent	U			U			U			U			U		

* Please circle if it is unclear what type of event it was

OXVASC db: 4

BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U	Age at diagnosis

Please tick if:	All No	All U	Tick if:	All age U

Angina U

Hypertension U

Myocardial infarction U

Diabetes Mellitus U

Treatment								
Diet			Tablets			Insulin		
Y	N	U	Y	N	U	Y	N	U

Valvular heart disease U

Nature: U

Intermittent Claudication U

Peripheral vascular intervention U

Age at 1st intervention:

Site:

1 Arm
2 Leg
3 Bowel
4 Carotid
5 Abdo aneurysm
6 Thoracic aneurysm
7 Other
8 Uncertain

Type:	Angiogram			Angioplasty			Bypass			Amputation		
	Y	N	U	Y	N	U	Y	N	U	Y	N	U

Result: U

Atrial fibrillation U

1 Current
2 Previous
9 Unknown

Choose from above:

TREATMENT
1=Cardioversion
2=Paroxysmal
3=Persistent
4=Permanent
9=Unknown

Choose from above:

Pace maker			Type pacemaker
Y	N	U	U

Hyper lipidaemia U

Treatment								
Diet			Statin			Other		
Y	N	U	Y	N	U	Y	N	U

Cardiac failure U

Treated (loop diuretic)**?** Y N U

	Y/N/U	Age at diagnosis

OXVASC db: 6

CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U choose	Age at:											
Please tick if:	**All No**	**All U**	**Tick if:**	**All age U**									
Migraine					**With Aura?**			**Prolonged aura (>1hr)**					
					Y	**N**	**U**	**Y**	**N**	**U**			
Epilepsy			**Age @ Diagnosis**										
			U										
Cardiac intervention			**Age @ 1st Intervention**	**Number**	**Angiogram**			**Angioplasty**			**Stent**			**Bypass**		
			U		**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
			Results of angiogram:		U											
Carotid: Endarterectomy			**Age @ 1st operation**	**Side**												
			U	**Left**			**Right**			**Both**						
Carotid: Stent			**Age @ 1st operation**	**Side**												
			U	**Left**			**Right**			**Both**						
Asthma																
Liver disease																
COAD																
Peptic ulcer disease																
Previous venous thromboses				**Number**		**Details:** Please enter U if not known										
Any other past medical history			**Details:** Please enter U if not known													
SLE Look in notes			**Age @ Diagnosis**	**Anticardiolipin antibodies (aCL)**				**Lupus anticoagulant (LA)**					
			U	**Y**	**N**	**U**		**Y**	**N**	**U**			

OXVASC db: 7

CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U choose		
Please tick if:	**All No**	**All U**	
Autoimmune disease		**Diagnosis**	U
Allergies	Please list all. If no allergies or unknown please enter No or Unknown.		
Nosebleeds			
Bleeding after dental extraction			
Any cancer			
End stage renal failure/ dialysis			

LIST OF MEDICATION BEFORE ONSET OF NOTIFICATION EVENT

Aspirin	Y	N	U	**Dose** mg/day	U
Dipyridamole	Y	N	U		
Clopidogrel	Y	N	U		
Warfarin	Y	N	U	**INR**	U

Do you currently take any vitamin supplements?		Y	N	U
Vitamin B	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U

Names of (other) current vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter "No other".

OXVASC db: 8

Was your BP measured at any time prior to the notification event?	**Y**	**N**	**U**
Date of most recent BP measurement prior to notification Event DD-MM-YY			U
How many times have you had your BP measured in the last year?			U

Have you ever been on OCP?	**Y**	**N**	**U**
Have you ever been on HRT?	**Y**	**N**	**U**
No of years in lifetime on HRT and/or OCP			U

		1	2		3	4	5	
Previous stroke or TIA? Y N U		**Date most recent event** DD-MM-YYYY Prior to notification event	**Any other previous ?**		**No. of previous events** ALL events prior to notif. Event	**Date 1st event** DD-MM-YY Provide date even if same as most recent (number previous events = 1)	**Duration** (mins) **recent**	**longest**
Hemi-spheric stroke carotid	**R**		Y	N	#			
	L		Y	N				
Hemi-spheric TIA carotid	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Vertebro-basilar stroke			Y	N				
Vertebro-basilar TIA			Y	N			Mins: U	Mins: U
Stroke unknown territory			Y	N				
TIA unknown territory			Y	N			Mins: U	Mins: U
Amau-rosis fugax	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Retinal infarc-tion	**R**		Y	N				
	L		Y	N				

Comments:

OXVASC db: 9

MEDICATION

Was subject taking medication <u>at the time of</u> the notification event? If YES provide names below	Y	N	U

	NAME DRUG	Y	N	U	Dose mg/day	Other unit? Please specify
1	**Aspirin**				U	U
2					U	U
3					U	U
4					U	U
5					U	U
6					U	U
7					U	U
8					U	U
9					U	U
10					U	U
11					U	U
12					U	U
13					U	U
14					U	U
15					U	U
16					U	U

Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter "No other" here.

OXVASC db: 9

BACKGROUND FAMILY HISTORY

Patient is adopted	**Y**	**N**	**U**	**Twin**	**Y**	**N**	**U**
Total number of siblings (inc)				**Any vascular history**	**Y**	**N**	**U**

Oldest → Youngest

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	**Y/N/U**														
	Age 1st*														
MI	**Y/N/U**														
	Age 1st*														
PVD	**Y/N/U**														
	Age 1st*														
BrainHaem	**Y/N/U**														
	Age 1st*														
Diabetes	**Y/N/U**														
	Age 1st*														
Hyperlip aedemia	**Y/N/U**														
	Age 1st*														
Hyper tension	**Y/N/U**														
	Age 1st*														
	Sibling* is:														

T = Twin **M** = Half-sibling mother's side **S** = Sibling **F** = Half-sibling father's side

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	**A**	**D**	**U**			U	U
Father	**A**	**D**	**U**			U	U
Sib1 oldest	**A**	**D**	**U**	**M**	**F**	U	U
Sib 2	**A**	**D**	**U**	**M**	**F**	U	U
Sib 3	**A**	**D**	**U**	**M**	**F**	U	U
Sib 4	**A**	**D**	**U**	**M**	**F**	U	U
Sib 5	**A**	**D**	**U**	**M**	**F**	U	U
Sib 6	**A**	**D**	**U**	**M**	**F**	U	U
Sib 7	**A**	**D**	**U**	**M**	**F**	U	U
Sib 8	**A**	**D**	**U**	**M**	**F**	U	U
Sib 9	**A**	**D**	**U**	**M**	**F**	U	U
Sib 10	**A**	**D**	**U**	**M**	**F**	U	U
Sib 11	**A**	**D**	**U**	**M**	**F**	U	U
Sib 12 youngest	**A**	**D**	**U**	**M**	**F**	U	U

Total number of subject's children ☐ **# Male** ☐ **# Female** ☐

please fill in "U" if unknown

OXVASC db: 10

AUTOIMMUNE HISTORY- Personal			
Do you have an autoimmune disease?	**Y**	**N**	**U**
Thyroid	**Y**	**N**	**U**
Early onset diabetes	**Y**	**N**	**U**
Pernicious anaemia	**Y**	**N**	**U**
Rheumatoid arthritis	**Y**	**N**	**U**

SMOKING			
Have you ever smoked?	**Y**	**N**	**U**
Are you a lifetime non-smoker?	**Y**	**N**	**U**
Smoking oddities (pipes etc)			U
Are you an ex-smoker?	**Y**	**N**	**U**
If so at what age did you stop?	Age:		U
<u>If you have stopped</u>: How many years did you smoke?	# Years:		U
Do you currently smoke?	**Y**	**N**	**U**
How many do you smoke per day?	Number:		U
<u>If you are still smoking</u>: How many years have you smoked?	# Years:		U

OXVASC db: 11

Premorbid modified Rankin

Do you have any symptoms?	**Y**	**N**	**U**
Are you able to look after yourself and carry out normal activities?	**Y**	**N**	**U**
Does anyone else help pay the bills, do the shopping, cleaning etc?	**Y**	**N**	**U**
Do you need someone to help you walk?	**Y**	**N**	**U**
Do you need help to wash yourself?	**Y**	**N**	**U**
Do you need to be lifted in and out of bed?	**Y**	**N**	**U**

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	Score

Rose PVD: IHD questionnaire

NOTE: ALL QUESTIONS RELATE TO SYMPTOMS <u>PRIOR</u> TO THE NOTIFICATION EVENT

PART A

a) Have you ever had any pain or discomfort in your chest?		**Y**	**N**	**U**	n: **go to part C**
b) Do you get the pain or discomfort when you walk up hill or hurry?		**Y**	**N**	**U**	n: **go to part B**
c) Do you get it when you walk at an ordinary pace on the level?		**Y**	**N**	**U**	
d) When you get any pain or discomfort in your chest what do you do?	1=stop 2=slow down 3= continue at same pace 9= unknown				
e) Does it go away when you stand still?		**Y**	**N**	**U**	
f) How soon?	**1**=10 minutes or less **2**= > 10 minutes **9**= unknown				

PART B

Have you ever had severe pain across the front of your chest lasting half an hour or more?	**Y**	**N**	**U**

PART C

a) Do you get pain in either leg when you are walking?	**Y**	**N**	**U**	
b) Does this pain ever begin when you are standing still or sitting?	**Y**	**N**	**U**	
c) Do you get this pain in your calf (or calves)	**Y**	**N**	**U**	
d) Do you get it when you walk up hill or hurry?	**Y**	**N**	**U**	
e) Do you get it when you walk at an ordinary pace on the level?	**Y**	**N**	**U**	
f) Does the pain ever disappear while you are still walking?	**Y**	**N**	**U**	
g) What do you do if you get it when you are walking?	**1**=stop **2**=slow down **3**=continue at same pace ***9*=** unknown			
h) What happens if you stand still?	1=usually continues for more than 10 minutes **2**= usually disappears in 10 minutes or less **9**= unknown			

OXVASC db: 12

<u>Premorbid</u> Barthel

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres 3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

OXVASC db: 13-16

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

Interviewer's perception of patient personality		1 Very relaxed 2 Fairly relaxed 3 Average 4 Prone to stress 5 Highly stressed 9 Unknown	
In terms of stress what kind of person are you?			
Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing 5 Care home 8 Other (specify) 9 Not known	**8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?**	**SPOUSE or:**
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility	
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer 4 Community services (specify) 5 No assistance needed 9 Not known	**4-Specify:**
Marital status		1 Married 2 Widow 3 Single 4 Separated 5 Partner 9 Not known	
Employment status		1 Working FT 2 Working PT 3 Caring for home 4 Unemployed 5 Unable to work 6 Retired 7 Student 9 Not known	
Most recent occupation (spouse's occupation if not employed)		U	
Socioeconomic class		1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner) 4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**	
Ethnic origin		1 White 2 Black Carribean 3 Black African 4 Indian 5 Pakistani 6 Bangladeshi 7 Chinese 8 Other 9 Not known	
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average 3 Normal 4 Above average 9 Not known	
Alcohol units per week*		* *Please use guidelines provided below*	
Age left school	U		
Education		1 Basic 2 Further 3 Higher 9 Not known	
Age left full-time education	U		

(Sparkling) wine and Champagne					
	ml		**10%-units**		**14% -units**
M glass	175		1.75		2.5
L glass	250		2.5		3.5
Bottle			7.5		10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)			
		ml	**Units**
Small		25	1
Large		35	1.3
Double		50	2
L double		70	2.8

Lager, Beer and Cider					
	ml		**4% -units**		**9%-units**
Bottle	330		1.3		3
Can	440		1.8		4
Pint	568		2.3		5.1

275 ml bottle alcopops	
	1.4 units

50 ml glass Sherry/ Port	
	1 Unit

OXVASC db: 17

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP

What is the likelihood of you dozing in the following three situations:

1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
Do you take medications for high blood pressure?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8= I don't know 9= Unknown
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION

How is your appetite?		1= Good 2= Normal 3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U	
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U	
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed 4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week 4= 1 /day 5= 2-4 /day 6= > 4 /day 9= Unknown

OXVASC db: 18

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	**Y**	**N**	**U**	
DRIVING	Do you drive?	**Y**	**N**	**U**	
Handedness	Left/Right/Both/Unknown				R= Right L= Left B= Both U= Unknown
Clinical impression of frailty (corrected for age)					1= Frail 2= Normal 9= Unknown

LIFE EVENTS

Have any of these events happened to you over the last year*?	**Y**	**N**	**U**	**How upset were you by these events?**
Death or serious illness of close friend or relative	**Y**	**N**	**U**	
Financial difficulty	**Y**	**N**	**U**	
Divorce or break up of close friend or relatives	**Y**	**N**	**U**	
Major conflict with children or grandchildren	**Y**	**N**	**U**	
Muggings, robberies, accidents	**Y**	**N**	**U**	

1= Very much
2= Moderately
3= Not too much
9= Unknown

OTHER

AMTS

Age	**0**	**1**
Time (nearest hour)	**0**	**1**
Year	**0**	**1**
Name or place	**0**	**1**
Recognition of 2 persons	**0**	**1**
Date and month of birth	**0**	**1**
Date of 1st World War	**0**	**1**
Queen's name	**0**	**1**
Count 20-1 backwards	**0**	**1**
5 mins recall full street address	**0**	**1**

0= Fail
1= Pass

If AMTS not done explain why not

*Data entry instructions: N should be changed to Y if any of the answers below are answered as Y or if OTHER has been filled in.

OXVASC db: 19

GENERAL EXAMINATION					
	cm*			**inches***	
Collar size					U
Waist measurement					U
Hip measurement					U
Height					U
	kg*			**stone***	
Weight					U
Arcus	Y	N	U		
Xanthelasma	Y	N	U		
Nicotine staining	Y	N	U		
Ear crease	Y	N	U		
Own teeth/ denture	O	D	U	O= own teeth D= denture U= unknown	

*Data entry instructions: If it is obvious that "cm" measurements have been placed in the "inches" column and vice versa please ensure data is entered on the db in the correct field. A note with initials is required on this form to make a note of this data change. The same is valid for incorrect kg/stone entries.

For all patients: **1st HEART RATE and BLOOD PRESSURE post event**				
		Date DD-MM-YY	**Time** 24 hr clock	
		U	:	U
Blood pressure 1st BP post event		**Sys**	**Dias**	U
Heart rate 1st HR post event				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

OXVASC db: 20

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE at admission				
Temp on admission		ºC		U
Admission Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
BP on admission		Sys	Dias	U
Sats/air		**%**		U
BM				U

For all subjects: HEART RATE and BLOOD PRESSURE at assessment				
BP on assessment		Sys	Dias	U
Heart rate on assessment				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Cardiac murmur?		Y	N	U
Cardiac failure?		Y	N	U
Any pre-existing neurological disability?		Y	N	U

OXVASC db: 20

STROKE	Normal exam		All Unknown	

Prestroke disability	U	**Predicted 30 day Rankin**	U

SYMPTOMS AT ONSET

	Weakness		**Sensory**			**Eyes/vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemia nopia**			**Dys phasia**	
Arm					**Mono cular**			**Dys arthria**	
Hand								**Vertigo**	
Leg					**Diplopia**			**Head ache**	

FINDINGS ON EXAMINATION:

Glasgow Coma Scale			
Eyes	**/4**	1 – No eye opening 2 – Eye opening in response to pain	3- Eye opening in response to speech 4- Spontaneous eye opening
Motor	**/6**	1 – No response to pain 2 – Extensor posturing to pain 3 - Flexor response to pain	4 – Withdrawal to pain 5 - Localizing response to pain 6 – Obeys commands
verbal	**/5**	1 – No speech 2 – Incomprehensible speech 3 – Inappropriate speech	4 – Confused conversation 5 – Oriented

	Weakness		**Sensory**			**Eyes/ vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemia nopia**			**Dys phasia**	
Arm					**Gaze palsy**			**Dys arthria**	
Hand					**Nystag mus**			**Ataxia**	
Leg								**Neglect**	

NIH STROKE SCALE For instructions see separate sheet						Tick if:	NOT DONE	
LOC		LOC questions		LOC commands			Best gaze	
Best visual		Facial Palsy		Right arm			Left arm	
Right leg		Left leg		Limb ataxia			Sensory	
Language		Dysarthria		Neglect			**TOTAL**	

STROKE PROGNOSIS

OXVASC db: 21

Date of prognostic markers DD-MM-YY	U

Please tick:	**All fields normal**	**All fields unknown**

Hemianopia	1= No deficit 2= Mild 3= Moderate 4= Severe 9= Unknown	
Inattention		
Dysarthria		
Swallowing		
Dysphasia		

Limb deficit (able to lift both arms to horizontal MRC≥3)	**Y**	**N**	**U**
Unable to sit independently	**Y**	**N**	**U**
Unable to stand independently	**Y**	**N**	**U**
Unable to walk independently (Cannot walk without help of another or aid)	**Y**	**N**	**U**
Urinary incontinence	**Y**	**N**	**U**
Catheterised	**Y**	**N**	**U**

ABCD^2 score

A (Age); 1 point for age ≥60 years

B (Blood pressure) ≥ 140/90 mmHg); 1 point for hypertension at the acute evaluation

C (Clinical features); 2 points for unilateral weakness, 1 for speech disturbance without weakness

D (Symptom duration); 1 point for 10-59 minutes, 2 points for ≥60 minutes

D (Diabetes); 1 point

Total

MANAGEMENT - DISCHARGE

MANAGEMENT			
Did you discuss the need to change diet with subject?	**Y**	**N**	**U**
Did you discuss the need to reduce weight with subject?	**Y**	**N**	**U**
Did you discuss the need to quit smoking with subject?	**Y**	**N**	**U**

DRUG MANAGEMENT

	New				**Continued**				**Contra-indicated**		
Aspirin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Dipyridamole	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Clopidrogel	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Warfarin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Low molecular weight heparin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
GPIIIa/IIb	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Unfractionated heparin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Lipid lowering	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Ace inhibitors	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Thiazide diuretics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Loop diuretics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Beta blockers	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Other antihypertensive	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Antiarrythmics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**

Other (Please specify new Y/N/U, continued Y/N/U, contra-indicated Y/N/U)

OXVASC db: M, D

Appendix IV

Ascertainment form for Acute Coronary Syndrome

SUBJECT ID NO:

Patient identification label

Was patient interviewed	Y	N	U
If NO why not? Please tick			
1	Refused interview		
2	Aphasic and relatives could not be contacted		
3	Too unwell/ multiple medical problems		
4	Dementia (need to record MMSE or AMTS) and relatives could not be contacted		
5	Late ascertainment and no reply to invitation to join study		
6	Ascertainment after death		
7	Diagnosis uncertain		
8	Diagnosis changed after assessment from diagnosis not requiring interview (eg Trop>1) to diagnosis requiring interview (eg NSTEMI)		
9	Unknown		

Patient contact details	
Telephone (day)	
Telephone (evening)	
Mobile	
Fax number	
mail address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone (day)	
Telephone (evening)	
Mobile phone no	
Fax number	
Email addres	

Consider asking if this patient can provide a control: | |

All: Name

11 digit OXCODE for notification event										

STEMI, NSTEMI

Consultant	

1 Physician
2 Physician with stroke interest
3 Neurologist
4 General surgeon
5 Vascular surgeon
6 Cardiologist
7 Neurosurgeon
9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name: or Initials:					

Summary Diagnosis for: STEMI / NON-STEMI				
Non ST elevation MI (NSTEMI)	Y	N	U	*Data entry: if Y use NSTEMI*
ST elevation MI (STEMI)	Y	N	U	*Data entry: if Y use STEMI*
Lytic	Y	N	U	
Unstable angina	Y	N	U	*Data entry: if Y use ANGINA*

Is this the first ever in a lifetime (incident) NSTEMI?	Y	N	U
Is this the first ever in a lifetime (incident) STEMI?	Y	N	U

Date of notification event (DD-MM-YY)				
Location of interview	1 JRH inpatient 2 RI in patient 3 Community hosp 4 Outpatients 5 Home 6 Other (specify)		Specify:	
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up 4 Other (specify) 6 No follow-up 7 Home visit		Specify:	
Info on form obtained from	1 Patient 2 Relative 3 GP 4 hospital records 5 Death certificate 6 Other (specify)		Specify:	
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify) 5 Health authority search 6 Death 7 Troponin 9 Other (specify)		Specify:	
Other sources of notification (select all appropriate)		1 Specify:	2 Specify:	3 Specify:	4 Specify:
If one had not identified the patient via the route of 1st notification would patient have been identified by other source of ascertainment? (circle)		Y	N	U	

All: 1

STEMI and NON-STEMI

Narrative history & examination

SYMPTOMS						
Chest pain					**Y**	**N**	**U**
Radiation to arms & neck					**Y**	**N**	**U**
SOB	**Y**	**N**	**U**		Description:		
Duration of chest pain in minutes					Mins: U		

Any previous chest pain, SOB, diagnosis of angina or cardiac investigation/ intervention	Y	N	U

CHARACTERISTICS OF ANGINA (if known angina)			
More severe	Y	N	U
More prolonged	Y	N	U
More frequent	Y	N	U
Angina at rest	Y	N	U
Angina on minimal exertion (lower threshold)	Y	N	U
New onset angina within last 2 months with minimal exertion	Y	N	U
ECG changes compatible with ischaemia	Y	N	U
History of, or new, positive exercise test	Y	N	U
Prior or new percutaneous catherisation (≥ 50% stenosis)	Y	N	U
Prior or new coronary intervention or CABG	Y	N	U
Any potential secondary aetiology If YES please tick below	Y	N	U

Arrythmia	**Anaemia**	**Thyroid disease**	**Sepsis**	**Surgery**	**Other:**

HISTORY OF NOTIFICATION EVENT	Please tick if:	All	STEMI: 2 NSTEMI: 2 ANGINA: 2	on

STEMI and NON-STEMI

Notification event*		What did you think was wrong?
Date DD-MM-YY	**Time** 24 hr clock	
	: U	

* The event that led to first seeking medical attention

Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
Were you alone?	**Y**	**N**	**U**
If you were with someone who was it?	U		
Who called for help?	U		
If you did not call for help at time of event, why not?	U		

Who did you 1st call for help?	1= Medical 2=Non-Medical 9=Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
			Please give date/time* for <u>any</u> 1st call	
1st call for ANY help non-medical or medical				: U
			Please give date/time for 1st <u>medical</u> call	
1st call for MEDICAL help GP/ A&E / 999/ NHS direct				: U

* This could be the same date and time as the first call for medical help

Outcome of first call for medical assistance

STEMI: 2
NSTEMI: 3
ANGINA: 3

HISTORY OF NOTIFICATION EVENT

STEMI and NON-STEMI

				Date DD-MM-YY	**Time** 24 hr clock
Seen by GP / A&E <u>in person</u>?	**Y**	**N**	**U**		**:** U

If subject was not referred to OXVASC: **Admitted to hospital?**	**Y**	**N**	**U**		**:** U
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					**:** U
Assessment by OXVASC staff					**:** U

STEMI: 2
NSTEMI: 3
ANGINA: 3

HISTORY OF NOTIFICATION EVENT

STEMI

Onset on wakening from sleep?			**Y**	**N**	**U**
Time awake (ignore if onset not on wakening from sleep) 24 hr clock			:		U
Activity at onset (within 2 hrs of onset)				1= Asleep 2= Sedentary 3= Mild-moderate 6= Strenuous 9= Unknown
What were you doing in the same 2 hrs on the day prior to the event?				
Drugs within previous hour			**Y**	**N**	**U**
Meal within previous hour			**Y**	**N**	**U**
Record exact activity					U
Location of event	1 Home 2 Work 3 Leisure (non-sport)	4 Sport 8 Other (specify) 9 Unknown		Specify:	

ONSET ANGER SCALE		**Anger level**
Onset NOT on wakening from sleep	In the **two hours prior to the event** what best describes your emotional state from the list provided?	
	In the **exact same two hours on the day prior to your event** which best describes your mood?	
OR:		
Onset ON wakening from sleep	If you had your event on wakening how were you in the **two hours before you went to bed**?	

1 = **Calm**
2 = **Busy** (but not hassled)
3 = **Mildly angry** (irritated and hassled, but does not show)
4 = **Moderately angry** (so hassled it shows in your face)
5 = **Very angry** (body tense, clenching fists or teeth)
6 = **Furious** (almost out of control, very angry, pound table, slam door)
7 = **Enraged** (lost control, throwing objects, hurting yourself or others)
9= unknown

STEMI: 3

STEMI and NON-STEMI

If admitted (use ambulance sheet)

Was subject admitted by ambulance?	Y	N	U

If admitted:	Date DD-MM-YY	Time 24 hr clock
Arrival of emergency service		:
Arrival in Hospital *		:

* If not on ambulance sheet use blue admissions

STEMI and NON-STEMI

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						Cerebral						Peripheral		
	NSTEMI			STEMI			TIA			CVA					
Prior acute events?	Y	N	U	Y	N	U	Y	N	U	Y	N	U	Y	N	U
	Possible*			Possible*			Possible*			Possible*					
# of events			U			U			U			U			U
Date of most recent DD-MM-YY			U			U			U			U			U

STEMI: 4
NSTEMI: 4
ANGINA: 4

BACKGROUND MEDICAL HISTORY

	Y/N/U	Age at diagnosis

Please tick if:	All No	All U	Tick if:	All age U

Angina U

Hypertension U

Myocardial infarction U

Diabetes Mellitus U

Treatment								
Diet			Tablets			Insulin		
Y	N	U	Y	N	U	Y	N	U

Valvular heart disease U

Nature: U

Intermittent Claudication U

Peripheral vascular intervention U

Age at 1st intervention:

Site:

1 Arm
2 Leg
3 Bowel
4 Carotid
5 Abdo aneurysm
6 Thoracic aneurysm
7 Other
8 Uncertain

Type:

Angiogram			Angioplasty			Bypass			Amputation		
Y	N	U	Y	N	U	Y	N	U	Y	N	U

Result: U

Atrial fibrillation U

1 Current
2 Previous
9 Unknown

Choose from above:

1=Cardioversion
2=Paroxysmal
3=Persistent
4=Permanent
9=Unknown

Choose from above:

Pace maker			Type pacemaker
Y	N	U	U

Hyper lipidaemia U

Treatment								
Diet			Statin			Other		
Y	N	U	Y	N	U	Y	N	U

Cardiac failure U

Treated (loop diuretic)**?** Y N U

	Y/N/U	Age at diagnosis

STEMI: 5
NSTEMI: 5
ANGINA: 5

CONTINUING BACKGROUND MEDICAL HISTORY

	Y/N/U choose	Age at:
Please tick if:	**All No** / **All U**	**Tick if:** / **All age U**

Migraine			**With Aura?**			**Prolonged aura (>1hr)**		
			Y	**N**	**U**	**Y**	**N**	**U**
Epilepsy		**Age @ Diagnosis**						
		U						
Cardiac intervention		**Age @ 1st Intervention**	**Number**	**Angiogram**			**Angioplasty**			**Stent**			**Bypass**		
		U		**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
		Results of angiogram:	U												
Carotid: Endarterectomy		**Age @ 1st operation**	**Side**		
		U	**Left**	**Right**	**Both**
Carotid: Stent		**Age @ 1st operation**	**Side**		
		U	**Left**	**Right**	**Both**
Asthma					
Liver disease					
COAD					
Peptic ulcer disease					
Previous venous thromboses		**Number**		**Details:** Please enter U if not known	
Any other past medical history		**Details:** Please enter U if not known			
SLE Look in notes		**Age @ Diagnosis**	**Anticardiolipin antibodies (aCL)**			**Lupus anticoagulant (LA)**		
		U	**Y**	**N**	**U**	**Y**	**N**	**U**

STEMI: 6
NSTEMI: 6
ANGINA: 6

CONTINUING BACKGROUND MEDICAL HISTORY

	Y/N/U choose		
Please tick if:	**All No**	**All U**	
Autoimmune disease		**Diagnosis**	U
Allergies	Please list all. If no allergies or unknown please enter N or U.		
Nosebleeds			
Bleeding after dental extraction			
Any cancer			
End stage renal failure/ dialysis			

LIST OF MEDICATION BEFORE ONSET OF NOTIFICATION EVENT

Aspirin	Y	N	U	**Dose** mg/day	U
Dipyridamole	Y	N	U		
Clopidogrel	Y	N	U		
Warfarin	Y	N	U	**INR**	U

Do you take any vitamin supplements?		Y	N	U
VitB	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U

Names of (other) Vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter “No other”.

STEMI: 7
NSTEMI: 7
Angina: 7

STEMI and NON-STEMI

Was your BP measured at any time prior to the notification event?	**Y**	**N**	**U**
Date of most recent BP measurement prior to notification event DD-MM-YY			U
How many times have you had your BP measured in the last year?			U

Have you ever been on OCP?	**Y**	**N**	**U**
Have you ever been on HRT?	**Y**	**N**	**U**
No of years in lifetime on HRT and/or OCP			U

		1	2		3	4	5	
Previous stroke or TIA? Y N U		**Date most recent event** DD-MM-YYYY Prior to notification event	**Any other previous ?** Y	N	**No. of previous events** ALL events prior to notif. Event	**Date 1st event** DD-MM-YY Provide date even if same as most recent (number previous events = 1)	**Duration** (mins) **recent**	**longest**
Hemi-spheric stroke carotid	**R**		Y	N	#			
	L		Y	N				
Hemi-spheric TIA carotid	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Vertebro-basilar stroke			Y	N				
Vertebro-basilar TIA			Y	N			Mins: U	Mins: U
Stroke unknown territory			Y	N				
TIA unknown territory			Y	N			Mins: U	Mins: U
Amau-rosis fugax	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Retinal infarc-tion	**R**		Y	N				
	L		Y	N				

Comments:

STEMI: 8
NSTEMI: 8

MEDICATION

Was subject taking medication <u>at the time of</u> the notification event? If YES provide names below	Y	N	U

	NAME DRUG	Y	N	U	Dose mg/day	Other unit? Please specify
1	**Aspirin**				U	U
2					U	U
3					U	U
4					U	U
5					U	U
6					U	U
7					U	U
8					U	U
9					U	U
10					U	U
11					U	U
12					U	U
13					U	U
14					U	U
15					U	U
16					U	U

Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter “No other” here.

STEMI: 8
NSTEMI: 8
Angina: 8

BACKGROUND FAMILY HISTORY: STEMI, NON-STEMI

Patient is adopted	**Y**	**N**	**U**	**Twin**	**Y**	**N**	**U**
Total number of siblings (inc)				**Any vascular history**	**Y**	**N**	**U**

Oldest → Youngest

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	**Y/N/U**														
	Age*														
MI	**Y/N/U**														
	Age*														
PVD	**Y/N/U**														
	Age*														
Brain Haem	**Y/N/U**														
	Age*														
Diabetes	**Y/N/U**														
	Age*														
Hyperlip aedemia	**Y/N/U**														
	Age*														
Hyper tension	**Y/N/U**														
	Age*														
	Sibling* is:														

T = Twin **M** = Half-sibling mother's side **S** = Sibling **F** = Half-sibling father's side

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	**A**	**D**	**U**			U	U
Father	**A**	**D**	**U**			U	U
Sib1 oldest	**A**	**D**	**U**	**M**	**F**	U	U
Sib 2	**A**	**D**	**U**	**M**	**F**	U	U
Sib 3	**A**	**D**	**U**	**M**	**F**	U	U
Sib 4	**A**	**D**	**U**	**M**	**F**	U	U
Sib 5	**A**	**D**	**U**	**M**	**F**	U	U
Sib 6	**A**	**D**	**U**	**M**	**F**	U	U
Sib 7	**A**	**D**	**U**	**M**	**F**	U	U
Sib 8	**A**	**D**	**U**	**M**	**F**	U	U
Sib 9	**A**	**D**	**U**	**M**	**F**	U	U
Sib 10	**A**	**D**	**U**	**M**	**F**	U	U
Sib 11	**A**	**D**	**U**	**M**	**F**	U	U
Sib 12 youngest	**A**	**D**	**U**	**M**	**F**	U	U

Total number of subject's children ☐ **# Male** ☐ **# Female** ☐

please fill in "U" if unknown

STEMI: 9
NSTEMI: 9
Angina: 9

FAMILY TREE (Number siblings and children)

SMOKING			
Have you ever smoked?	Y	N	U
Are you a lifetime non-smoker?	Y	N	U
Smoking oddities (pipes etc)			U
Are you an ex-smoker?	Y	N	U
If so at what age did you stop?	Age:		U
<u>If you have stopped</u>: How many years did you smoke?	# Years:		U
Do you currently smoke?	Y	N	U
How many do you smoke per day?	Number:		U
<u>If you are still smoking</u>: How many years have you smoked?	# Years:		U

STEMI: 10
NSTEMI: 10
Angina: 10

Premorbid modified Rankin

STEMI and NON-STEMI

Do you have any symptoms?	**Y**	**N**	**U**
Are you able to look after yourself and carry out normal activities?	**Y**	**N**	**U**
Does anyone else help pay the bills, do the shopping, cleaning etc?	**Y**	**N**	**U**
Do you need someone to help you walk?	**Y**	**N**	**U**
Do you need help to wash yourself?	**Y**	**N**	**U**
Do you need to be lifted in and out of bed?	**Y**	**N**	**U**

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	Score

Rose PVD: IHD questionnaire

NOTE: ALL QUESTIONS RELATE TO SYMPTOMS PRIOR TO THE NOTIFICATION EVENT

PART A

a) Have you ever had any pain or discomfort in your chest?			**Y**	**N**	**U**	n: **go to part C**
b) Do you get the pain or discomfort when you walk up hill or hurry?			**Y**	**N**	**U**	n: **go to part B**
c) Do you get it when you walk at an ordinary pace on the level?			**Y**	**N**	**U**	
d) When you get any pain or discomfort in your chest what do you do?	1=Stop 2=Slow down	3= continue at same pace 9= Unknown				
e) Does it go away when you stand still?			**Y**	**N**	**U**	
f) How soon?	**1**=10 minutes or less	**2**= > 10 minutes **9**= unknown				

PART B

Have you ever had severe pain across the front of your chest lasting half an hour or more?	**Y**	**N**	**U**

PART C

a) Do you get pain in either leg when you are walking?			**Y**	**N**	**U**
b) Does this pain ever begin when you are standing still or sitting?			**Y**	**N**	**U**
c) Do you get this pain in your calf (or calves)			**Y**	**N**	**U**
d) Do you get it when you walk up hill or hurry?			**Y**	**N**	**U**
e) Do you get it when you walk at an ordinary pace on the level?			**Y**	**N**	**U**
f) Does the pain ever disappear while you are still walking?			**Y**	**N**	**U**
g) What do you do if you get it when you are walking?	1=Stop 2=Slow down	3=Continue at same pace 9**=** Unknown			
h) What happens if you stand still?	**1**=Usually continues for more than 10 minutes **2**= Usually disappears in 10 minutes or less **9**= Unknown				

STEMI: 11
NSTEMI: 11
Angina: 11

Premorbid Barthel

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres 3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

STEMI: 12-15
NSTEMI: 12-13
Angina: 12-13

STEMI and NON-STEMI

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

Interviewer's perception of patient personality		1 Very relaxed 2 Fairly relaxed 3 Average 4 Prone to stress 5 Highly stressed 9 Unknown
In terms of stress what kind of person are you?		
Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing 5 Care home 8 Other (specify) 9 Not known **8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?** **Spouse** Or:
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer 4 Community services (specify) 5 No assistance needed 9 Not known **4-Specify:**
Marital status		1 Married 2 Widow 3 Single 4 Separated 5 Partner 9 Not known
Employment status		1 Working FT 2 Working PT 3 Caring for home 4 Unemployed 5 Unable to work 6 Retired 7 Student 9 Not known
Most recent occupation (spouse's occupation if not employed)		U
Socioeconomic class	U	1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner) 4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**
Ethnic origin		1 White 2 Black Carribean 3 Black African 4 Indian 5 Pakistani 6 Bangladeshi 7 Chinese 8 Other 9 Not known
Exercise (Clinician judgement on amount of physical activity – age corrected- per week)		1 None 2 Below average 3 Normal 4 Above average 9 Not known
Alcohol units per week*		* Please use guidelines provided below
Age left school	U	
Education		1 Basic 2 Further 3 Higher 9 Not known
Age left full-time education	U	

(Sparkling) wine and Champagne					
	ml		**10%-units**		**14% - units**
M glass	175		1.75		2.5
L glass	250		2.5		3.5
Bottle			7.5		10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)			
		ml	**Units**
Small		25	1
Large		35	1.3
Double		50	2
L double		70	2.8

Lager, Beer and Cider					
	ml		**4% - units**		**9%-units**
Bottle	330		1.3		3
Can	440		1.8		4
Pint	568		2.3		5.1

275 ml bottle Alcopops	
	1.4 units

50 ml glass Sherry/ Port	
	1 Unit

STEMI: 16
NSTEMI: 14

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP

What is the likelihood of you dozing in the following three situations:

1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
Do you take medications for high blood pressure?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8= I don't know 9= Unknown
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION

How is your appetite?		1= Good 2= Normal 3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U	
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U	
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed 4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week 4= 1 /day 5= 2-4 /day 6= > 4 /day 9= unknown

STEMI: 17
NSTEMI: 15
Angina: 15

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	Y	N	U	
DRIVING	Do you drive?	Y	N	U	
Handedness	Left/Right/Both/Unknown				R= Right L= Left B= Both U= Unknown
Clinical impression of frailty (corrected for age)					1= Frail 2= Normal 9= Unknown

LIFE EVENTS					
Have any of these events happened to you over the last year*?	Y	N	U	**How upset were you by these events?**	*Data entry instructions: N should be changed to Y if any of the answers below are answered as Y or if OTHER has been filled in.
Death or serious illness of close friend or relative	Y	N	U		1= Very much 2= Moderately 3= Not too much 9= Unknown
Financial difficulty	Y	N	U		
Divorce or break up of close friend or relatives	Y	N	U		
Major conflict with children or grandchildren	Y	N	U		
Muggings, robberies, accidents	Y	N	U		
OTHER life events					
					1= Very much 2= Moderately 3= Not too much 9= Unknown

STEMI: 18
NSTEMI: 16
Angina: 16

STEMI

GENERAL EXAMINATION

	cm*	inches*	
Collar size			U
Waist measurement			U
Hip measurement			U
Height			U
	kg*	**stone***	
Weight			U

Arcus	Y	N	U	
Xanthelasma	Y	N	U	
Nicotine staining	Y	N	U	
Ear crease	Y	N	U	
Own teeth/ denture	O	D	U	O= own teeth D= denture U= unknown

*Data entry instructions: If it is obvious that "cm" measurements have been placed in the "inches" column and vice versa please ensure data is entered on the db in the correct field. A note with initials is required on this form to make a note of this data change. The same is valid for incorrect kg/stone entries.

STEMI and NON-STEMI

New

FIRST POST-EVENT RECORDS

		Date DD-MM-YY	Time 24 hr clock	
		U	:	U
Blood pressure		**Sys**	**Dias**	U
Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

New

New

STEMI: 19
NSTEMI: 17

STEMI

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE				
Temp on admission		ºC		U
Admission Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
BP on admission		Sys	Dias	U
Sats/air		**%**		U
BM				U

For all subjects				
BP on assessment		Sys	Dias	U
Heart rate on assessment				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Cardiac murmur?		Y	N	U
Cardiac failure?		Y	N	U
Any pre-existing neurological disability?		Y	N	U

STEMI: 19

STEMI			
MYOCARDIAL INFARCTION			
		Date DD-MM-YY	**Time** 24Hr clock
Reperfusion treatment?	Tick if: **No reperfusion**	U	: U
Delay from arrival in hospital to reperfusion treatment Leave blank if no reperfusion		Hrs: Mins:	
First cardiac arrest	Tick if: **No cardiac arrest**	U	: U

If cardiac arrest: please fill in below. If no cardiac arrest: leave blank

Territory	1 Anterior 2 LBBB	3 Inferior	4 Other	
Cardiac arrest	1 No arrest 2 Before ambulance 3 After ambulance	4 A&E 5 CCU	6 Medical ward 7 Elsewhere in hospital	
Presenting rhythm	1 No arrest 2 Asystole	3 VF/ pulseless VT 4 EMD	9 N/A or Unknown	
Outcome	1 No return circulation 2 Return spontaneous circulation, died in hosp	3 Discharged from hosp with neuro deficit 4 Discharged, no neuro deficit 5 Resuscitation not attempted	5 Resuscitation not attempted 6 No arrest 9 Not applicable/ Unknown	
Admission diagnosis	1 Definite MI 2 Probable MI	3 Unstable angina 4 Chest pain	5 Other initial diagnosis 6 Already in hospital	
ECG determining treatment	1 ST elevation 2 LBBB 3 ST depression	4 T wave change 5 Other	6 Normal 9 Unknown	

STEMI investigations				
Reperfusion attempted	1 Thrombolysis 2 PTCA	3 Rescue PTCA 4 Ci to reperfusion	5 Not attempted 9 Unknown	
Did patient receive aspirin	1 Already on 2 Given out of hosp 3 After arrival	4 Ci to aspirin 5 Other antiplatelet 6 None	7 On Warfarin 8 Not known	
Admission unit	1 CCU 2 AMAU 3 Gen med ward	4 ITU 5 Other 6 Died A&E	7 Cardiac ward 8 Stepdown	
Killip	1= Class I No clinical signs of heart failure 2= II/ III/ IV 3= Class II Rales or crackles in the lungs, an S_3 gallop and elevated jugular venous pressure 4= Class III Frank acute pulmonary edema 5= Class IV Cardiogenic shock or hypertension (measured as systolic blood pressure < 90mmHg) and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating) 9= Unknown			
Diuretic initiated or increased for heart failure?				Y N U

STEMI: 20

INVESTIGATIONS: CARDIAC ENZYMES				
	Date	**CK**	**AST**	**troponin**
Admission day				
Day 1				
Day 2				
Day 3				

Coded ECG	1 AF 2 BBB 3 ST Segment change 4 LVH	5 Acute MI 6 Old MI 7 Normal 9 Other (specify)		Specify:

STEMI: 20

STEMI: 20.2

NON-STEMI

TIMI – NSTEMI SCORE		
Age ≥65		0 no 1 yes
≥3 CAD risk factors =1, (FHx HBP Raised chol, DM)		0 no 1 yes
Known CAD, Stenosis ≥ 50%		0 no 1 yes
ASA use in past 7 days		0 no 1 yes
Recent (≤24 hrs) angina		0 no 1 yes
Raised cardiac markers		0 no 1 yes
ST deviation ≥ 0.5 mm		0 no 1 yes

TIMI-NSTEMI Total	

Notes

STEMI

TIMI – STEMI SCORE		
Age		0 < 65 2 65-74 3 ≥ 75
DM or HBP or angina		0 no 1 yes
SBP <100		0 no 3 yes
HR> 100		0 no 2 yes
Killip II-IV See p23		0 no 2 yes
Weight < 67kg		0 no 1 yes
Anterior STE/LBBB		0 no 1 yes
Time to Tx > 4		0 no 1 yes

TIMI – STEMI Total	

Notes

STEMI: 21
NSTEMI: 18
Angina: 17-18

MANAGEMENT – DISCHARGE

MANAGEMENT			
Did you instruct subject to change diet?	**Y**	**N**	**U**
Did you instruct subject to reduce weight?	**Y**	**N**	**U**
Did you instruct subject to quit smoking?	**Y**	**N**	**U**

	DRUG MANAGEMENT								
	New			**Continued**			**Contra-indicated**		
Aspirin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Dipyridamole	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Clopidrogel	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Warfarin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Low molecular weight heparin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
GPIIIa/IIb	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Unfractionated heparin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Lipid lowering	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Ace inhibitors	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Thiazide diuretics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Loop diuretics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Beta blockers	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Other antihypertensive	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Antiarrythmics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Other (Please specify new Y/N/U, continued Y/N/U, contra-indicated Y/N/U)

Oxvasc db: M,D

INVESTIGATIONS AND PROCEDURES / GENERAL COMMENTS

Oxvasc db: Proc

Appendix V

Classification of Vascular Deaths in OXVASC

All deaths in the OXVASC population that were recorded and assigned were coded as follows (in increasing order of validity):

i. *All certified deaths due to vascular disease*: All deaths with the underlying cause coded for the purposes of national statistics as being due to "ischaemic heart disease" (ICD I219,I251,I259), "cerebrovascular disease" (ICD I607, I609, I610,I619, I620,I634,I635, I639,I64X,I678,I679, I694, I698), or "peripheral vascular disease" (ICD I709, I710, I711, I713, I714, I718, I719 ,I728, I739).

ii. *All certified acute vascular deaths*: All deaths where the underlying cause of death was coded for the purposes of national statistics as being due to "acute ischaemic heart disease" (ICD I219, I251), "acute cerebrovascular disease" (ICD I607, I609, I610, I619, I620, I634, I635, I639, I64X), or "acute peripheral vascular disease" (ICD I710, I711, I713, I714, I718, I719, I728).

iii. *Probable or definite acute vascular deaths*: All deaths in (ii) excluding unclassifiable sudden deaths (as defined below) and other deaths that after evaluation of the clinical and/or post-mortem data were considered to have been incorrectly attributed (i.e. there was definite evidence of another cause), and with the addition of any deaths not in (ii) that were considered by the OXVASC researchers to have been due to an acute vascular event. This definition includes all probable or definite sudden cardiac deaths as defined in the methods section.

iv. Definite acute vascular deaths: All deaths in (iii) excluding sudden deaths for which the only supporting evidence was a previous history of symptomatic vascular disease in

the relevant arterial territory (unless there was a documented acute myocardial infarction, acute stroke or acute peripheral vascular event within the previous 28 days). *Unclassifiable deaths,* which were mainly out-of-hospital deaths, were deaths certified as having a vascular cause which had no witness description of the event or of preceding symptoms to suggest acute vascular disease in a specific territory, no post-mortem evidence of an acute vascular event or other cause of death, no post-mortem evidence of clinically significant coronary atherosclerosis, and no past history of symptomatic vascular disease in a relevant arterial territory.

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1st June 2005

OREC A: 05/Q1604/70
Version 2

Study title: The Oxford Vascular Study (OXVASC)

You are being invited to take part in a research study. 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 others 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 wish to take part.

What is the purpose of the study?

The purpose of this study is to find out how common vascular disease (e.g. heart attacks, strokes, transient ischaemic attacks and other circulatory problems) is in Oxfordshire and how it affects people's lives. This has never been done before for different types of vascular disease at the same time and in the same population. We hope the study will provide us with useful information on the best way of providing a service for those who suffer from these common problems. We hope we can build up a detailed picture of the way that people recover and the subsequent changes in health over several years.

Why have I been chosen?

You have been chosen because you are registered with one of the nine GP practices in Oxfordshire which are collaborating in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to read and be asked to sign a consent form. You will be given a copy of the information sheet and signed consent form to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part you would agree to an interview and a clinical examination by the researcher. It would also involve taking an extra sample of blood in the hospital or clinic. We would also like to gather some information on risk factors for vascular disease from both your hospital and GP notes. The study would also involve being followed up by telephone or at home by a researcher in thirty days time, in six months, at one year, two years and five years. All the information collected will be completely confidential.

What do I have to do?
This is an observational study and taking part in the study will not affect your current or future care. No investigations, new drugs or other treatments will be tested.

What are the possible disadvantages and risks to taking part?
You will be required to give a blood sample which will cause mild discomfort. Where possible this will be taken at the same time as those collected in the course of your normal medical care. There are no additional risks involved.

What are the possible benefits of taking part?
We hope the information we get from this study may help us to treat future patients with vascular disease better.

What if something goes wrong?
If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
It is likely that the results of this study will be published in medical journals after completion of the research. If you decide to take part in the study you will not be identified in any report.

Who is organising and funding the research?
This research is being organised by Professor Rothwell at The Stroke Prevention Research Unit, University of Oxford in collaboration with the Department of Primary Health Care, the Department of Cardiology and your participating General Practice. The study is funded by the Stroke Association and the Medical Research Council.

Who has reviewed the study?
The Oxfordshire Research Ethics Committee has approved the study.

Contact for Further Information
If you would like any further information please ask the researcher who is discussing this information sheet with you or by contacting the Oxford Vascular Study Office on 01865 231601.

Thank you for reading this.

Professor Peter Rothwell - Consultant Neurologist, Dr Adrian Banning - Consultant Cardiologist, Professor David Mant - Professor of General Practice
Dr Sarah Pendlebury – Senior Research Fellow, Dr Lucy Binney, Dr Nicola Paul , Dr Michela Simoni , Dr Alastair Webb and Dr Gabriel Yiin, Dr Dominic Howard and Dr Linxin Li - Clinical Research Fellows
Louise Silver, Linda Bull, Nikki Radcliffe, Rachel Teal and Sarah Welch– Clinical Research Nurses
Fiona Cuthbertson and Michelle Wilson – Clinical Research Therapists
Robyn Cary - Clinical Research Secretary
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OREC A: 05/Q1604/70
Version 2

28th December 2006

CONSENT FORM

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul, Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson, Michelle Wilson.

Please tick the relevant box	**Yes**	**No**
1. I confirm that I have read and understand the information sheet dated 1st June 2005 for the above study and have had the opportunity to ask questions.	☐	☐
2. I agree to take part in the above study.	☐	☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status.	☐	☐
4. I understand future research using the blood sample I give may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for me personally.	☐	☐
5. I agree to take part in the follow up study that involves being interviewed at home or a place of my choice, by telephone or in person at 1, 3, 6 , 12 and 60 months.	☐	☐
6. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐	☐

Name of Patient	Date	Signature
Name of Witness	Date	Signature
Researcher	Date	Signature

Professor Peter Rothwell - Consultant Neurologist, Dr Adrian Banning - Consultant Cardiologist, Professor David Mant - Professor of General Practice
Dr Sarah Pendlebury – Senior Research Fellow, Dr Lucy Binney, Dr Nicola Paul , Dr Michela Simoni , Dr Alastair Webb and Dr Gabriel Yiin, Dr Dominic Howard and Dr Linxin Li - Clinical Research Fellows
Louise Silver, Linda Bull, Nikki Radcliffe, Rachel Teal and Sarah Welch– Clinical Research Nurses
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Robyn Cary - Clinical Research Secretary
Oxford Vascular Study Telephone 01865 231601 Fax 01865 234629

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OREC A: 05/Q1604/70
Version 1

ASSENT FORM

21st March 2005

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul, Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson, Michelle Wilson.

	Please initial box	**Yes**	**No**
1.	I confirm that I have read and understand the information sheet dated 1st June 2005 for the above study and have had an opportunity to ask questions.	☐	☐
2.	I understand that the participation of my relative is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐	☐
3.	I understand that sections of any of my relative's medical notes may be looked at by responsible individuals where it is relevant to taking part in research. I give assent for these individuals to have access to these records.	☐	☐
4.	I understand future research using the blood sample my relative gives may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for my relative personally.	☐	☐
5.	I agree for my relative to take part in the above study.	☐	☐

Name of Next of Kin	Date	Signature
Researcher	Date	Signature