Determinants of

medium-term blood pressure variability

and the related risks of stroke and dementia.

Thesis submitted for degree of Doctor of Philosophy

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For Mum and Dad, for the love, life and opportunities you have given me,

and, above all, for Amanda, Joshua and Sophie,

who have been there for me through everything,

with love.

ABSTRACT

Determinants of medium-term blood pressure variability and the related risks of stroke and dementia.

Visit-to-visit variability in blood pressure (BP) increases stroke risk, independent of mean BP. However, its physiological validity, the ideal method of measurement and the mechanisms increasing cardiovascular risk are unclear.

In meta-analyses of individual patient data, I pooled associations between BP variability and risk of stroke, all cardiovascular events and death. I then determined antihypertensive drug-class differences in cardiovascular risk, intra-individual (I-VR) and inter-individual BP variability (M-VR). In 500 Oxford Vascular Study (OXVASC) patients undergoing thrice-daily home (HBPM) and awake ambulatory monitoring (ABPM), associations between mean, maximum or variability in BP (CV-BP) were determined with premorbid BP, hypertensive arteriopathy (creatinine, aortic stiffness, cognitive impairment, stroke versus TIA and leukoaraiosis) and cardiovascular events. In 200 patients, I determined associations with pulsatility or stiffness (pulse wave velocity) in cerebral and aortic vessels.

There was a 21% and 27% increased risk of stroke and myocardial infarction per standard deviation of CV-SBP in 318700 patients, independent of mean SBP. In 244,479 patients, SBP variability was reduced by CCBs and diuretics within (I-VR=0.89, 95% CI=0.82-0.96, p=0.0001) and between individuals (M-VR 0.83, 0.77-0.89, p<0.0001), especially in the first year of treatment, explaining drug class differences in stroke risk (OR=0.76, 0.68-0.87, p<0.0001). In OXVASC, drug class differences on day-to-day SBP variability were greatest immediately after waking.

Residual hypertension after treatment on HBPM but not ABPM (BP>135/85) predicted recurrent cardiovascular events (HR 2.82, 1.44-5.51, p=0.002 vs. 1.48, 0.68-3.23, p=0.33), reflecting stronger associations with premorbid BP and hypertensive arteriopathy, due largely to inaccuracy of ABPM in patients aged >65 years. Furthermore, day-to-day maximum and CV-SBP were associated with premorbid BP, hypertensive arteriopathy and cardiovascular events, with no additional predictive value of mean SBP when analysed with maximum SBP. Maximum SBP was greater in men and CV-SBP in women, whilst age and creatinine determined both. Increased stroke risk may partly be due to the association between BP variability and cerebral pulsatility, which was correlated with leukoaraiosis (p=0.01) and determined by aortic stiffness (p=0.016) and pulsatility (p<0.001).

BP variability is clinically significant and physiologically valid, and is treatable with CCBs and diuretics. After TIA or minor stroke, HBPM best identifies residual hypertension and demonstrates the predictive value of BP variability and maximum BP, but associated arterial changes might explain some of the increased stroke risk.

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Submitted for the degree of Doctor of Philosophy, Trinity Term 2013

Declarations

I certify that this thesis entitled 'Determinants of medium-term variability in blood pressure and the related risks of stroke and dementia' was performed whilst I was a fulltime postgraduate student at the University of Oxford.

I declare that this thesis is my own work. I personally performed the searches, the majority of the collection of papers and the data extraction for the systematic reviews incorporated in this thesis. The systematic reviews included in this thesis include updates of systematic reviews that were published prior to the inception of this DPhil, including those published as part of my MSc by research, but I have now used individual patient data obtained from direct communication with trial authors. For the past 2 years I have also been the physician responsible for the day-to-day running of the blood pressure monitoring cohort described in chapters 5-8, monitoring BP readings on a daily basis and treating patients. I reviewed, cleaned and analysed all the data included in this thesis. I also designed, carried out, developed the analysis programs and analysed data for the physiological assessments included in the physiological substudy in chapters 9-10, although MRI assessments were additionally performed by a consultant neuroradiologist (W Kuker) and a Stroke Prevention Research Unit clinical fellow specializing in this area (L Li). I was supported in the statistical approaches and analyses by my supervisor, Prof Rothwell, and the statisticians associated with the group, Ziyah Mehta and Sally Howard. Finally, this thesis was drafted in its entirety by myself, but extensively reviewed by my supervisor, Prof Rothwell. Sections of this thesis have been published in peer-reviewed scientific journals as stated below, but have not been used in the application for or submission of any other degree.

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Papers Produced from this Work (in chronological order)

Published Papers

Webb AJS, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM. Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. *Stroke*. 2012 Oct;43(10):2631-6. Epub 2012 Aug 23

Webb AJS, Rothwell PM. The effect of antihypertensive treatment on headache and blood pressure variability in randomized controlled trials: a systematic review. *J Neurol*. 2012 Sep;259(9):1781-7.

Webb AJS, Li L, Wilson M, Paul NP, Fischer U, Tarassenko L, Rothwell PM. Frequency, validity and prognostic value of residual hypertension on home versus ambulatory blood pressure after TIA or non-disabling stroke. *BMJ*; Under review

Papers in Preparation

Webb AJS, Rothwell PM. Prognostic implications of day-to-day and visit-to-visit blood pressure variability in prospective studies: a systematic review and meta-analysis.

Rothwell PM, Webb AJS, Mehta Z, on behalf of the Blood Pressure Lowering Triallists' Collaboration. Effects of antihypertensive drug class on consistency of control of blood pressure and risk of stroke: analysis of over 2 million readings in 229,732 participants.

Webb AJS, Cuthbertson F, Paul N, Lovett N, Fischer U, Tarasenko L, Rothwell PM. Validity of day-to-day variability and maximum systolic blood pressure on multi-day home monitoring versus single-day ambulatory monitoring: frequency versus duration?

Webb AJS, Pendlebury ST, Mehta Z, Rothwell PM. Validation of Montreal Cognitive Assessment (MoCA) versus Mini-Mental State Examination (MMSE) against hypertension and hypertensive arteriopathy in patients with TIA or minor stroke.

Webb AJS, Michelle Wilson MSc, Nicola Paul DPhil, Urs Fischer MD, Rothwell PM. Determinants of within-individual antihypertensive drug effects on variability in home blood pressure: An analysis after TIA and minor stroke

Presentations

Webb AJS, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM. Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. European Stroke Conference 2012.

Webb AJS, Rothwell PM. The effect of antihypertensive treatment on headache and blood pressure variability in randomized controlled trials: a systematic review. European Stroke Conference 2012 and Association of British Neurologists 2012.

Webb AJS, Rothwell PM. Blood pressure variability in patients with recent TIA or minor stroke: visit-to-visit office measures versus Bluetooth home monitoring versus 24-hour ABPM. European Stroke Conference 2012.

Webb AJS, Li L, Wilson M, Paul NP, Fischer U, Tarassenko L, Rothwell PM. Frequency, validity and prognostic value of residual hypertension on home versus ambulatory blood pressure after TIA or non-disabling stroke. European Stroke Conference 2013 and Association of British Neurologists 2013.

Webb AJS, Rothwell PM. Clinical and physiological validity of maximum systolic BP: home versus ambulatory monitoring. European Stroke Conference 2013.

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CHAPTER ONE

Introduction

1.1 Stroke and Hypertension

1.1.1 The burden of stroke and hypertension

Stroke is the leading cause of morbidity in the United Kingdom and the third leading cause of death. Approximately 1,200,000 people are living with the consequences of stroke, with 150,000 new strokes per year,[1] including 56,000[2] fatal events. It costs the National Health Service approximately 6% of its total budget[3] in direct costs, and is a major cause of dementia.[4] As result, its prevention and treatment as part of the National Stroke Strategy[5] forms a major part of the National Service Framework for Older People.[6]

Hypertension is one of the most prevalent diseases worldwide and the strongest modifiable risk factor for stroke. It affected over a quarter of the world's population in 2000 and is set to rise to approximately 29% of the population by 2025, affecting 1.56 billion people.[7, 8] A mean systolic blood pressure (SBP) >115mmHg explains 50-60% of the worldwide population attributable risk of stroke[9-11] and an increment of 20mmHg SBP doubles the risk of stroke between 40-69 years of age.[9] Randomisation to a treatment which reduces mean SBP results in a significant reduction in cardiovascular events with a 5-6mmHg decrease in diastolic pressure resulting in a 33-50% reduction in stroke and a 4-22% reduction in acute coronary events.[12] Nonetheless, only approximately 50% of patients with hypertension receive treatment in both the UK[13] and the rest of the world,[14] resulting in a significant excess burden of cerebrovascular disease.[15]

1.1.2 The pathophysiology of hypertension and stroke

The pathophysiological relationship between hypertension and stroke is complex. Firstly, hypertension causes accelerated atherosclerosis, contributing to the pathogenesis of large artery disease;[16] secondly, it causes hypertensive and ischaemic heart disease resulting in atrial fibrillation[17] and post-infarction mural thrombosis, with subsequent cardioembolic stroke; thirdly it is associated with arteriosclerosis, lipohyalinosis and the

development of leukoaraiosis, lacunar strokes and vascular dementia.[18] A strong relationship between small vessel disease and hypertension has been suggested by hospital-based cohort studies, although these studies probably overestimate this relationship when population based cohorts are also included.[19] Nonetheless, there are clear relationships between hypertension and all aetiological subtypes of stroke.

1.1.3 A potential new risk factor

Professor Peter Rothwell recently demonstrated that medium-term systolic blood pressure variability from one clinic visit to another (visit-to-visit variability) and the maximum blood pressure recorded are strongly predictive of the subsequent risk of stroke, independent of mean SBP.[20, 21] Both variability in SBP and risk of stroke were reduced by amlodipine, a calcium channel blocker, and increased by atenolol, a beta-blocker.[22] This represents a major shift in our understanding of hypertension and its treatment, although only the latest in the long line of paradigm shifts which have characterised hypertension research. This newly identified risk factor was initially only thoroughly investigated by one group, and although other groups have since confirmed its importance, it still creates more questions than answers, both in terms of its validity, its pathophysiological basis and its relevance to clinical practice. However, before these questions can even be framed, it is necessary to understand how this finding fits into our overall understanding of hypertension.

1.2 The Epidemiology of Hypertension

1.2.1 Hypertension as a risk factor for cardiovascular disease

Systolic blood pressure, measured by palpation, was the first measureable index of blood pressure following its discovery by Rev Stephen Hales,[23] until Riva-Rocci developed his sphygmomanometer.[24] This invention allowed Korotkoff to hear five transitions in blood pressure on auscultation of a partially occluded brachial artery, so identifying the diastolic pressure.[25] Diastolic blood pressure then dominated clinical practice, even though there was no specific evidence that it was more closely associated with cardiovascular outcomes

than any other index. This probably reflected the clinical experience of practicing physicians in treating malignant hypertension and its complications in younger patients, such as that which took the life of Franklin Roosevelt.[26] The clinical benefits of lowering diastolic blood pressure were then confirmed in trials of patients with malignant hypertension, before any reliable evidence existed that the chronic treatment of blood pressure reduced cardiovascular disease, reinforcing the prevailing view that diastolic blood pressure was of primary importance.[27, 28]

The first epidemiological evidence that chronically elevated blood pressure was associated with cardiovascular events and mortality arose from actuarial[29] and industrial data.[30] These findings were soon confirmed in a series of prospective observational studies.[31-34] The five most comparable of these studies were combined in the first major attempt to combine observational data measuring the association between risk factors and cardiovascular outcomes, the Epidemiology Pooling Project,[35] which demonstrated a strong, continuous relationship between diastolic or systolic blood pressure and the incidence of cardiovascular events and mortality, with approximately twice the risk of coronary events for patients in the top quintile of either diastolic or systolic BP compared to the bottom quintile. However, although this reported an 'almost identical' relationship with diastolic or systolic BP, it was commonly misinterpreted as demonstrating a stronger relationship with DBP.[36] This propagated the view that DBP alone provided sufficient information to base both clinical decision-making and further research upon. This is shown by its use as the sole blood pressure inclusion criterion in the early randomised controlled trials of antihypertensive treatment,[37-40] and as the most commonly reported intermediate outcome measure, often without reporting of SBP. Such was the dominance of DBP that systolic blood pressure did not appear in the Joint National Committee's guidelines on the diagnosis and management of hypertension until 1993. [41]

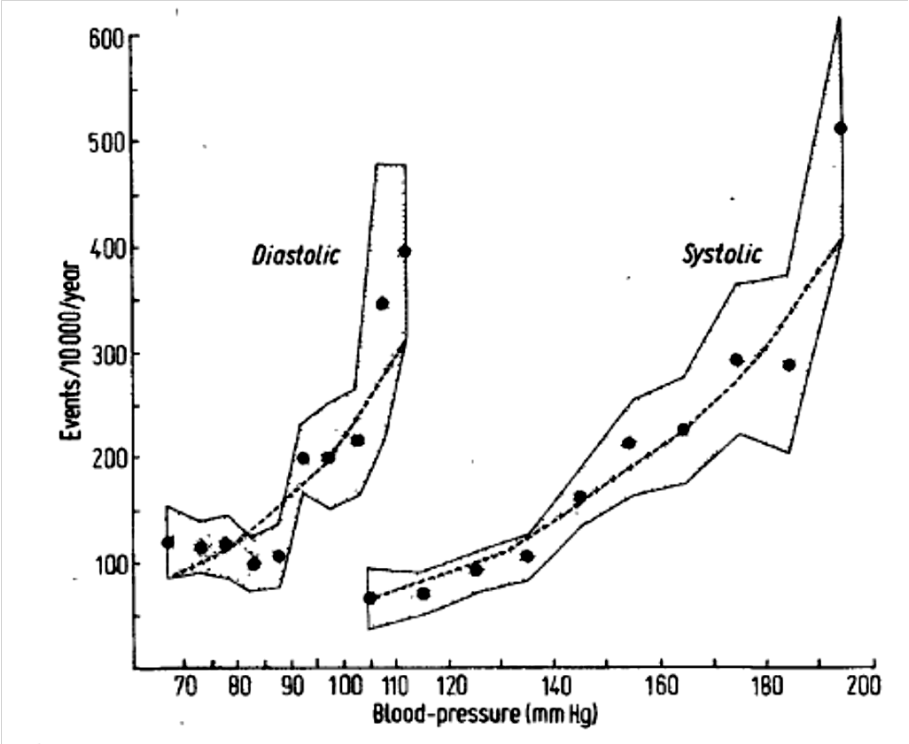


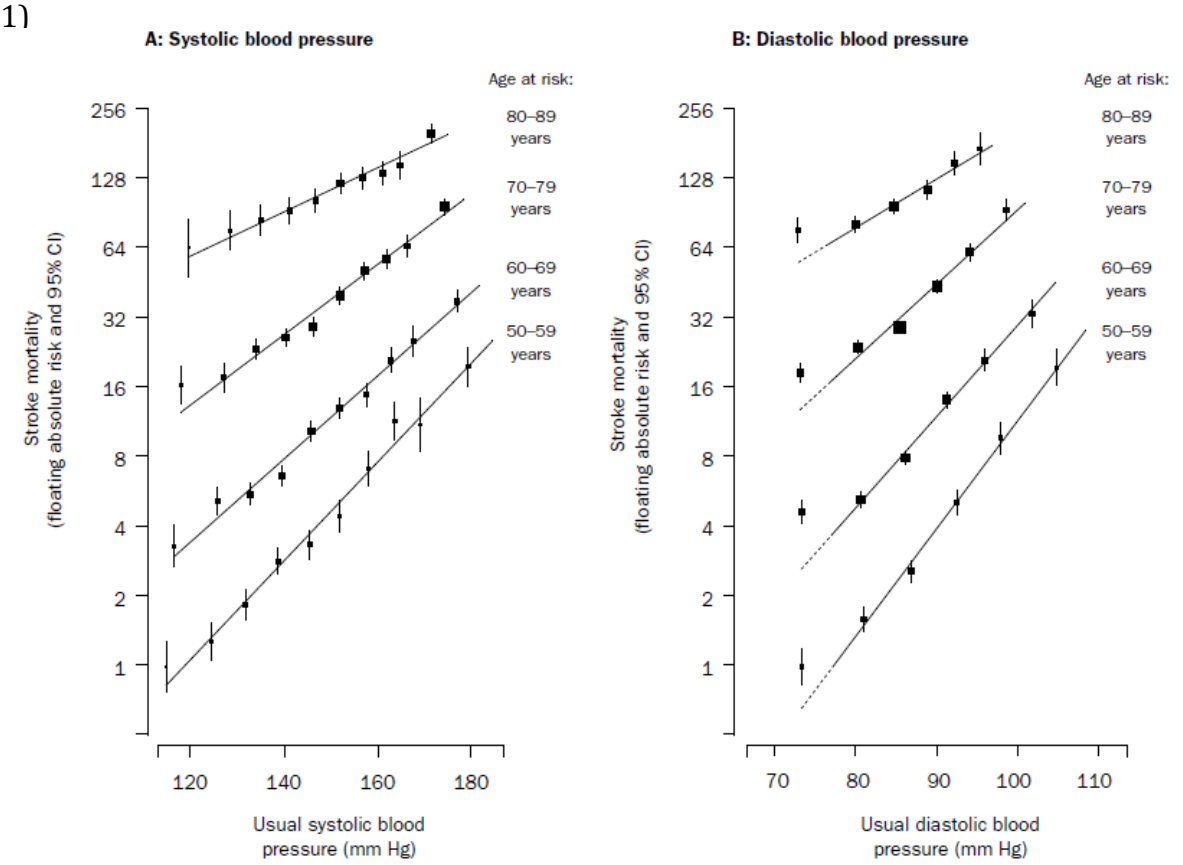
Figure 1.1 Annual incidence of cardiovascular events at Framingham after 18 years of follow up. Data is presented by level of diastolic or systolic blood pressure, pooled for men and women. Derived from Anderson et al.[34]

1.2.2 Usual blood pressure

Although there had been extensive research into the relationship between blood pressure and cardiovascular disease, a precise quantification of the relationship between diastolic blood pressure and cardiovascular events was only reached in 1990 with the concept of 'Usual' blood pressure. [12, 42] This population-based statistical measurement uses the 'regression dilution ratio' to adjust the risk relationship between measured blood pressure and cardiovascular events for the effect of regression to the mean. This systematic bias occurs when patients at the extremes of a distribution tend to have blood pressures closer to the population mean at follow up, independent of intervention, resulting in an under-estimation of the risk of subsequent cardiovascular events for a given blood pressure. Using this technique, it has been shown that there is a continuous relationship between average diastolic or systolic blood pressure and vascular mortality,[9] coronary artery disease,[9, 42] stroke,[9, 42] heart failure,[43] peripheral artery disease[44] and end-stage

renal failure.[45] An individual patient meta-analysis of more than 1 million adults[9] demonstrated that for each 20mmHg decrease in systolic blood pressure or 10mmHg difference in the diastolic blood pressure, the rate of vascular mortality at 40-49 years of age is halved, with one-third less at 80-89 years old, with a greater decrease in stroke mortality (hazard ratio (HR)=0.36, 95% CI 0.32-0.40) than in ischaemic heart disease (HR=0.49, 0.45-0.53). This relationship is continuous down to at least 115mmHg / 75mmHg, is similar for all other vascular causes of death (HR=0.43, 0.38-0.48), and is even seen, although less strongly, for non-vascular causes of death (HR=0.88, 0.87-0.89). The relative risk for all outcomes decreases with age, but as the absolute risk increases with age, the absolute increase in risk with increasing blood pressure is greater in older individuals. Furthermore, the risk relationship is steepest for stroke, resulting in the largest cause of long-term morbidity. However coronary artery disease is more common worldwide and therefore the population attributable risk of BP-related vascular mortality is greatest for ischaemic heart disease in many regions.[46]

1)



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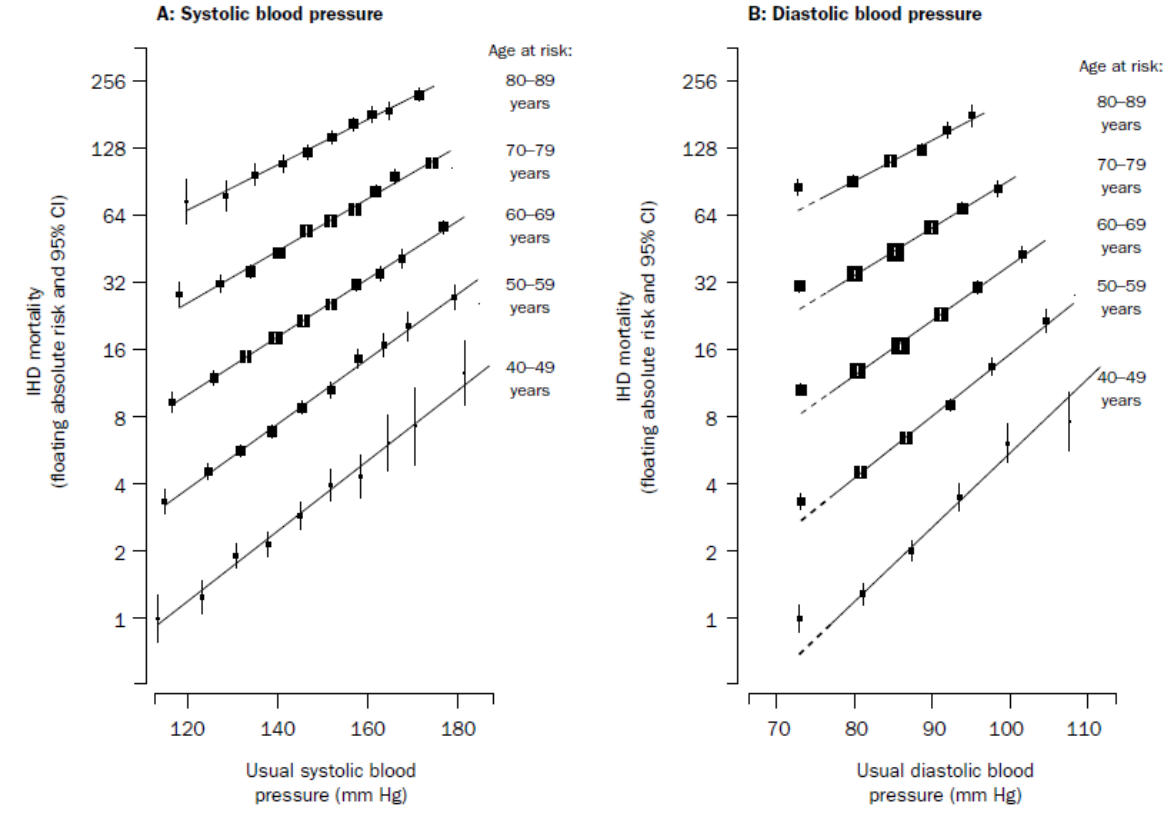

Figure 1.2 Mortality rate in each decade of age versus usual blood pressure at the start of the decade for 1) Stroke and 2) Ischaemic heart disease. Derived from Lewington et al.[9]

1.2.3 The importance of systolic blood pressure

Belief in the primary importance of DBP persisted until the mid-1990s, with the earliest derivations of 'Usual' blood pressure being based solely upon DBP.[12, 42] This was probably due to the influence of the Epidemiology Pooling Project,[35] clinical teaching and the impact of the early randomised clinical trials of antihypertensive drugs, recruitment to which was almost entirely based upon diastolic blood pressure. This trial criterion resulted from the FDA only requiring drug companies to show a reduction in DBP, not SBP. However, even as early as 1971 the Framingham study had demonstrated that systolic blood pressure was more informative for predicting coronary artery disease risk than diastolic blood pressure in a specified population.[47] Stamler et al. then demonstrated the importance of SBP across the entire US population,[48] and a number of studies in elderly populations have since demonstrated an inverse relationship between diastolic blood pressure and cardiovascular outcomes for any given systolic blood pressure.[49-51] The most precise estimate available, from the Prospective Collaborative Study Group, showed that diastolic and systolic BP were equally informative in the prediction of stroke and coronary artery disease, although this analysis was dominated by studies in younger individuals.[9] Overall, these studies reflect the fact that DBP falls with age whilst SBP rises, causing an increase in the prevalence of isolated systolic hypertension.[49, 52] Systolic hypertension is therefore the most prevalent form in this highest risk group, resulting in a greater proportional burden of disease due to systolic hypertension than diastolic hypertension. This has led to a number of trials in patients with isolated systolic hypertension,[53, 54] that have demonstrated that the treatment of isolated systolic hypertension >160mmHg still has significant benefits with a 13% reduction in total mortality, a 23% reduction in coronary events and a 30% reduction in stroke,[51] with similar effects even in the very elderly.[55]

1.3 The treatment of hypertension

1.3.1 The efficacy of blood pressure reduction

The earliest trials of blood-pressure lowering drugs demonstrated that the acute control of blood pressure in the setting of malignant hypertension provided significant reductions in mortality, renal failure and heart failure.[56-59] However doubts persisted about whether chronic control of less severe hypertension would be of benefit, especially in patients with established cerebrovascular disease due to concerns that a reduction in blood pressure would impair cerebral perfusion. The first small, randomised controlled trials demonstrated that new blood pressure lowering therapies such as chlorothiazide[28] or pronethanol[60] were safe. Then a series of trials from the Veterans Administration demonstrated a relative risk reduction in all cardiovascular events of >90% for active treatment of patients with a diastolic blood pressure >115mmHg,[38, 39] and 73% for patients with a DBP 90-114mmHg, with similar effects in stroke survivors.[40] This started 30 years of intensive investigation of antihypertensive agents versus placebo in a wide range of clinical circumstances, from the first Australian National Blood Pressure study[61] through to the MRC trials in mild hypertension, [62] and the elderly,[63] amongst others,[64, 65] all demonstrating a significant reduction in cardiovascular risk from the reduction of average blood pressure in a wide range of patients, with a greater reduction with more aggressive treatment.[66, 67] Pooled analyses of these trials confirmed the relationship demonstrated by the observational studies described above, with randomisation to a treatment which lowers DBP by 5-6mmHg reducing incidence of stroke by 35-40% and coronary artery disease by 20-25%.[12, 68]

The early trials focused on diuretics and beta-blockers in comparison to placebo, demonstrating the efficacy of blood pressure lowering at different levels of baseline blood pressure,[69] in men and women,[70] in isolated systolic hypertension,[53] in patients with

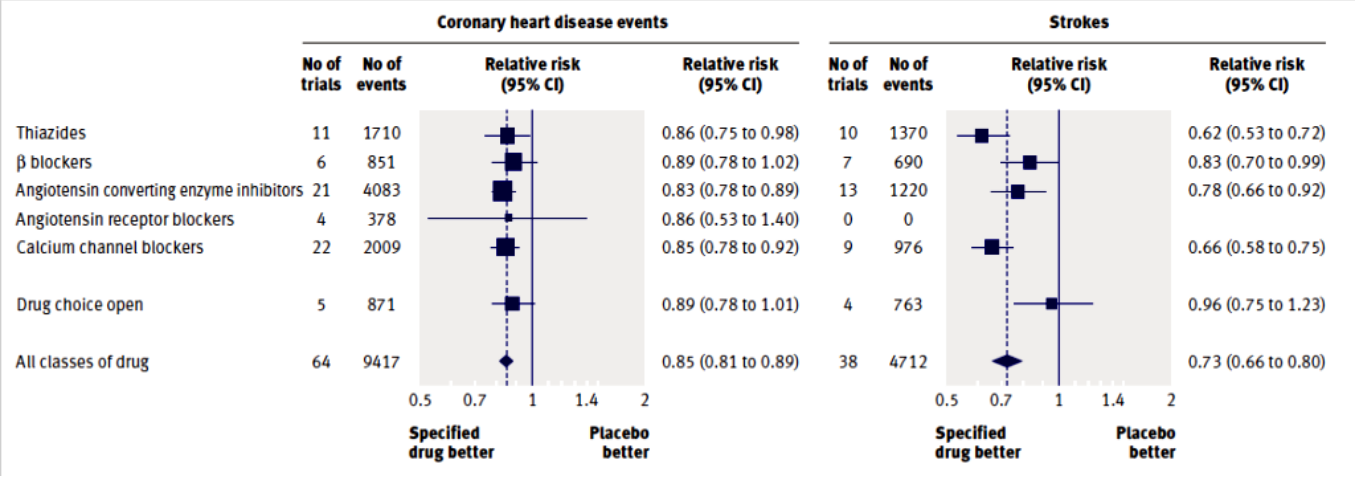

Figure 1.3 Relative risk reduction following randomisation to each class of antihypertensive drug compared to placebo for coronary heart disease and stroke. Derived from Law et al.[68]

diabetes,[71] and for many other demographic characteristics. Across all patient groups, blood pressure lowering was shown to be efficacious in the reduction of subsequent cardiovascular events, including in the secondary prevention of stroke, with a 24% reduction in the risk of recurrent stroke across all trials[72] and a 43% reduction in the risk of recurrent stroke following randomisation to a combination of perindopril and indapamide in particular.[73] Whether to reduce blood pressure below 130/80 is still debated, with proponents for and against the existence of a J-shaped curve. Nonetheless, virtually all trials have demonstrated a continuous reduction in the subsequent risk of stroke with lowering blood pressure, without an apparent threshold below which there is no benefit. This is in contrast to coronary artery disease in which some trials suggest an increased mortality at lower BP levels,[74-76] but recent trials such as Cardio-SIS[77] demonstrated that treating to a target below 130/80 in hypertensive people is still associated with further reductions in mortality (HR=0.50, 0.31-0.79).

1.3.2 Differences between blood–pressure lowering drug classes

Differences in the incidence of cardiovascular outcomes between drug classes are less clear than their absolute effectiveness in lowering blood pressure. Given the proven efficacy of blood pressure lowering treatment, it became unethical to carry out further

placebo-controlled trials. Therefore the 1990s and 2000s were dominated by trials comparing different drug regimens, and specifically comparing newer agents such as angiotensin converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARBs) or calcium channel blockers (CCBs) with diuretics or beta-blockers. The majority of these trials, such as STOP-2,[54] did not demonstrate major differences between the newer and older agents and a number of meta-analyses have demonstrated no difference or only small differences between drug classes in effects on cardiovascular outcomes (figure 1.3).[68, 69, 78] Unfortunately, most studies allow a high rate of add-on use of drugs from other classes, obscuring drug class differences. Despite this, a number of trials have shown specific differences between agents which are not explained on the basis of blood-pressure lowering alone. These include the marked difference in the risk of stroke between amlodipine+/-perindopril and atenolol+/-bendroflumethiazide in the ASCOT-BPLA trial[79] (combined endpoint HR=0.90, 0.79-1.02, stroke HR=0.77, 0.66-0.89).

Although relatively small, the differences seen in randomized trials result in frequent class-effects. In comparison to other agents, in most trials calcium channel blockers show an average 10% greater reduction in the subsequent risk of stroke, [68, 69] although there is an increase in the subsequent risk of heart failure. Similarly, angiotensin receptor blockers may show a greater reduction in the subsequent risk of stroke, independent of their effects on mean BP, but results have been inconsistent between trials with the effect being non-significant in meta-analyses.[68, 72] In contrast, beta-blockers are superior to other agents in the secondary prevention of ischaemic heart disease, particularly in the first three years after a myocardial infarction,[68, 80] but are less effective in the primary prevention of stroke, so much so that they are no longer indicated as first-line treatment for hypertension.[81, 82]

1.3.3 Current guidelines on the management of hypertension

National guidelines from the Joint National Committee VII[83] and the European Societies Joint Task Force,[46] and more locally from the National Institute for Clinical Excellence (NICE)[84] and the British Hypertension Society,[85] have consolidated the huge breadth of evidence on the treatment of hypertension into a set of consistent principles:

1. Treatment should be based on the demonstration of a persistently elevated systolic or diastolic blood pressure on repeated measurements, as part of a global assessment of cardiovascular risk;
2. Lifestyle interventions such as exercise, alcohol and salt reduction are a vital part of management, and may be sufficient in mild hypertension;
3. Patients should be treated to a target of <140/90, with some guidelines advocating a target of <130/80 in high risk groups (stroke, diabetes, chronic kidney disease);
4. Specific indications exist for the use of certain antihypertensive agents as first-line agents;
5. In the absence of specific indications, treatment should be initiated with a calcium channel blocker, ACEI (or ARB) or low-dose diuretic. There is minimal difference between these agents and guidelines differ on the first choice, with JNC VII advising a low-dose diuretic first, whilst NICE favour calcium channel blockers in the elderly (or diuretics when CCBs are contraindicated) and ACEi in younger patients, followed by addition of the alternative agent then diuretics. Beta-blockers are no longer indicated as first line treatment and have now been superseded by spironolactone as the fourth choice agent;
6. The majority of hypertensive patients will ultimately require treatment with more than one class of blood-pressure lowering drug, and so combination therapy may be appropriate as a first line treatment option.

1.4 Short-term blood pressure variability

Although the prognostic significance of diastolic or systolic blood pressure have been more extensively investigated than almost any other patient characteristic, with well over a million patients examined in prospective observational cohorts[9] and more than 500,000 patients randomized to blood pressure lowering treatments,[68, 69] the importance of variations in blood pressure have largely been ignored. Although it was recognized as early as 1931 that there are marked variations in blood pressure from one clinic visit to the next, with greater fluctuations in higher risk patients,[86] the prognostic significance of this measure has not been systematically investigated. This is due, at least in part, to the greater logistical challenges in both the measurement and statistical analysis of blood pressure variability,[87, 88] especially in the era preceding automated blood pressure measuring devices. With the unequivocal demonstration of the importance of absolute measures of blood pressure, it appears that any potential prognostic significance of blood pressure variability was largely ignored in favour of the definition and treatment of absolute hypertension. However, with the advent of automated monitoring blood pressure devices, the investigation of short-term variation in blood pressure became possible, focusing particularly on situational and diurnal variations in blood pressure.

1.4.1 Diurnal blood pressure variability

In 1988, O'Brien et al demonstrated that the absence of the normal 10-20% dip in nocturnal blood pressure was associated with an increased risk of stroke.[89] Further studies confirmed that increases in the night-day blood pressure ratio, and either non-dipping or extreme nocturnal dipping were associated with increased cardiovascular risk, independent of average 24 hour blood pressure.[90] Similarly, a greater surge in blood pressure in the morning independent of the baseline level is associated with increased mortality and cardiovascular events,[91] and the pattern of the surge closely follows the increased risk of stroke in this time period.[92] Overall, variability across 24 hours[93] or during the awake

period,[94] independent of the absolute blood pressure level, are associated with an increased risk of cardiovascular outcomes. However, the increase in risk for diurnal BP variability is only small in comparison to the predictive value of the average 24 hour blood pressure, contributing 1-10% of the risk of all cardiovascular outcomes.[93]

1.4.2 Situational blood pressure variability

The second advantage of automated, home blood pressure monitoring equipment was the ability to assess situational differences in blood pressure. This has demonstrated marked differences in individuals and populations between readings obtained in the clinic and at home, with home monitoring significantly improving blood pressure control, and likely therefore to have prognostic benefits.[95, 96] It has allowed the demonstration of both white-coat hypertension (a consistent elevation in blood pressure on clinic measurements compared to home) and 'masked' hypertension (an elevation on home monitoring, not detected on clinic measurements). The former of these was originally felt not to have prognostic value, but long-term follow-up suggests that it is predictive of future hypertension[97] and mortality,[98] whilst masked hypertension is a strong predictor of cardiovascular risk.[99] In addition, causes of transient increases in blood pressure are known triggers of stroke[100, 101] whilst orthostatic hypertension[102, 103] and hypotension[104] are both predictive of increased vascular risk. 'Post-stroke' hypertension is a commonly recognized phenomenon, but may actually represent the tail-end of a causative, pre-event hypertensive peak in some patients. This is suggested by a review of premorbid blood pressures in the OXVASC prospective cohort which demonstrated that 74% of patients had had at least one higher reading in the past, and that BP level is greater after TIA than major stroke.[105] This evidence is consistent with the 'cardiovascular reactivity' hypothesis: subgroups of patients, particularly those with hostile personality traits,[106] have greater blood pressure responses to situational stress and are at greater cardiovascular risk,[107] potentially through acute hypertension induced events.

1.5 Visit-to-visit blood pressure variability

Even though short-term variations in blood pressure have been known to provide additional prognostic information for more than 20 years, variations in blood pressure from one clinic visit to the next have been viewed as an obstacle to the accurate measurement of the underlying mean systolic and diastolic blood pressure.[108, 109] This is in spite of no systematic analysis of the prognostic importance of visit-to-visit blood pressure variability, coupled with a focus on the importance of the absolute blood pressure level. The aim of blood pressure measurement has been to estimate a patient's 'usual' or 'true' blood pressure by taking the average of multiple measurements. This reflects an inappropriate extrapolation of the concept of 'Usual' blood pressure, a statistically defined population measure, to the individual. For example, the current European guidelines state that 'Blood pressure…should be obtained over several months to define the patient's usual blood pressure as accurately as possible,[46] whilst the American Heart Association states 'conventional readings…are a surrogate for a patient's true blood pressure, which is conceived as an average over long periods of time.[110] This philosophy is epitomised by a recent analysis of the PROGRESS trial which suggested that visit-to-visit blood pressure variability is 'noise' masking detection of the 'signal' of true blood pressure to such an extent that blood pressure monitoring should be reduced or stopped once treatment has started.[111]

1.5.1 Previous evidence for the importance of visit-to-visit variability

In contrast to the prevailing view prior to March 2010, there was already evidence that visit-to-visit variability in blood pressure may be independently predictive of cardiovascular risk. Firstly, the statistical adjustment used in deriving the 'Usual' blood pressure is partly dependent upon the extent of within-individual variability in blood pressure. The greater the within-individual variability in BP, the greater the degree of regression to the mean, the larger the statistical adjustment,[88] and the greater is the amplification of the risk relationship between 'Usual' blood pressure and cardiovascular risk.

Secondly, the predictive value of mean blood pressure falls with age, whilst the incidence of systolic hypertension and stroke both increase with age,[15] even though the benefits of reduction of blood pressure in the elderly are maintained.[51, 55] This may partly be due to the increase in blood pressure variability with age or comorbidities.[88, 112] Thirdly, patients with prior cerebrovascular disease have greater visit-to-visit blood pressure variability.[87, 88, 112] Fourthly, limited evidence has been published from one observational cohort that medium-term blood pressure variability independently predicts the subsequent risk of cardiovascular events.[113, 114]

1.5.2 Visit-to-visit variability as a new, independent risk factor for stroke

The importance of visit-to-visit blood pressure variability in predicting the subsequent risk of stroke was demonstrated in a series of papers in the Lancet and Lancet Neurology in March 2010.[20-22] Prof Peter Rothwell presented analyses of five prospective cohorts of patients with hypertension or previous TIA or stroke (from the UK-TIA,[115] ESPS 2,[116] Dutch-TIA[117] and ASCOT-BPLA[79] trials) and two randomized controlled trials in hypertensive patients (ASCOT-BPLA[79] and MRC-elderly[63]). In the five prospective cohorts, there was a marked increase in the risk of stroke with increasing deciles of visit-to-visit variability in blood pressure, measured as either standard deviation (SD), the coefficient of variation (SD/mean) or other derived measures of variability, including variation independent of the mean (VIM). In the UK-TIA cohort, there was a >6 fold increase in the subsequent risk of stroke comparing the highest decile of SD with the lowest (HR=6.22, 95% CI 4.16-9.29), which was even greater when excluding patients with previous stroke (HR=8.23, 5.51-12.30) or evidence of previous infarction on CT (HR=10.44, 6.64-16.38), figure 1.6. The risk of stroke was most strongly predicted by the maximum blood pressure, adjusted for mean SBP (HR=15.01, 6.56-34.38). This demonstrates the importance of episodic hypertension, with patients with severe episodic hypertension (lowest SBP <140 and highest >180) being at greater risk than patients with stable hypertension (all readings >140mmHg) even though they had a lower mean SBP.

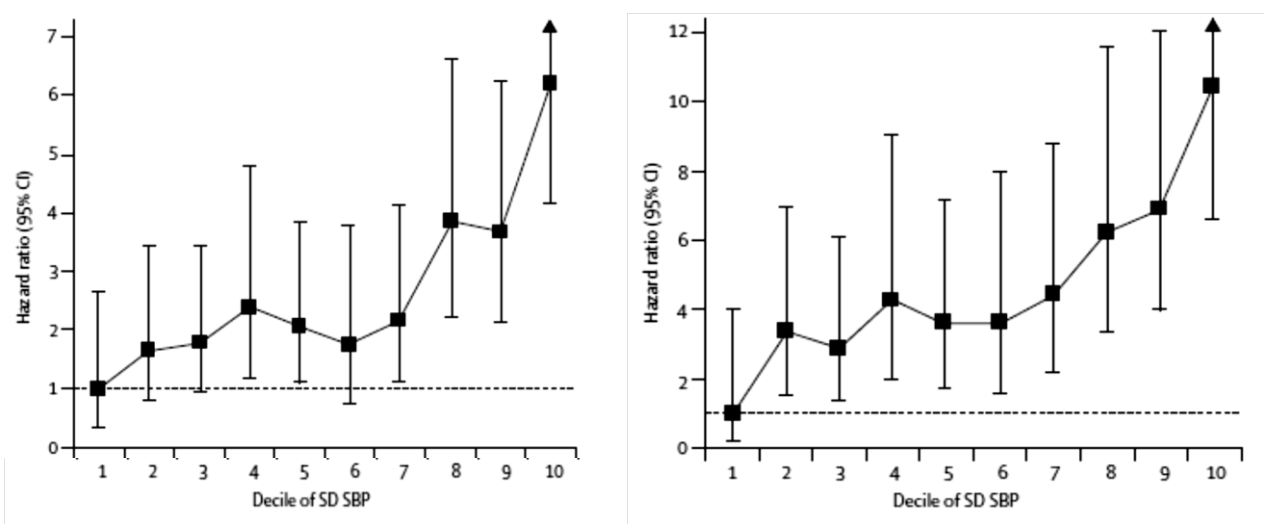

Figure 1.4 Hazard ratios for risk of any subsequent stroke by deciles of SD SBP based in the UK-TIA trial, with the first decile as the reference category. The left panel includes all patients. The panel on the right excludes patients with previous stroke. Derived from Rothwell et al.[20]

Visit-to-visit variability in SBP was a stronger predictor of the risk of stroke with increasing precision of measurement (top decile of SD-SBP versus bottom decile in the UK-TIA trial: 1-7 visits HR=6.22, 4.16-9.29; 1-10 visits HR=12.08, 7.40-19.72). The relationship was seen across all five cohorts, and it persisted with adjustment for mean SBP, age, sex and other baseline risk factors. Furthermore it was a stronger predictor of outcome than short-term, SD of daytime SBP measured in the ASCOT-BPLA 24 hour ABPM substudy, with only very weak predictive values for within-visit variability in SBP or the 'white-coat' effect. Finally, visit-to-visit variability was also a strong predictor of coronary events, heart failure and angina, although not to the same extent as stroke.

1.5.3 Randomised treatment reduces visit-to-visit variability and stroke risk

ASCOT-BPLA randomised 19257 hypertensive patients aged 40-79 with 3 or more additional cardiovascular risk factors to amlodipine with or without perindopril compared to atenolol with or without bendroflumethiazide, resulting in a significantly lower visit-to-visit variability in the amlodipine-based arm. Adjustment for differences in mean SBP alone explained less than one third of the difference in the risk of stroke between the groups, whilst adjustment for both mean SBP and SD-SBP explained all of the difference in

subsequent risk of stroke (unadjusted HR=0.78, 0.67-0.90; adjusted for mean SBP HR=0.84, 0.72-0.98, adjusted for mean SBP and SD-SBP HR=0.99, 0.85-1.16). In the MRC-elderly trial, randomisation to a beta-blocker resulted in a significantly greater SD-SBP than randomization to a thiazide diuretic, with a slightly greater CV even compared to placebo. Again, this correlated with a significantly greater risk of stroke in the beta-blocker group than the thiazide group during the first two years of follow-up, and a greater risk even than the placebo group, in spite of a significant reduction in blood pressure. Only following the addition of other antihypertensives to a beta-blocker was there a reduction in visit-to-visit variability in SBP, and a reduction in the risk of stroke compared to the placebo group.

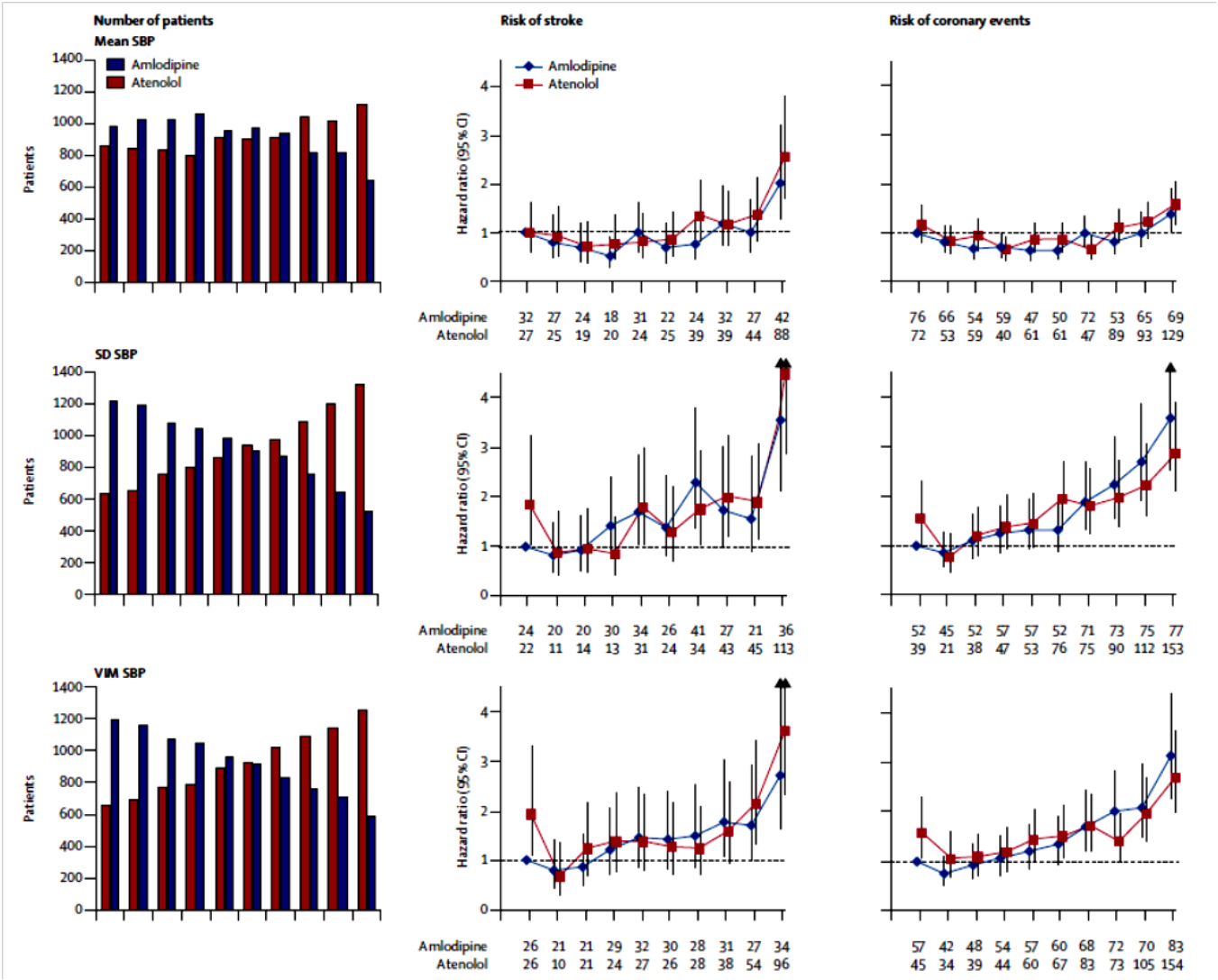

Figure 1.5 Distribution of patients in the two treatment groups in ASCOT-BPLA according to deciles of mean, SD and VIM of SBP (left) and the association of each of these variables with risk of stroke (middle) and risk of coronary events (right). The middle and right columns show the hazard ratios (95% CI) for risk of stroke and acute coronary events, by deciles of the same parameters. SBP=systolic blood pressure. VIM=variation independent of mean. Derived from Rothwell et al.[20]

The accompanying systematic review and meta-analysis[118] assessed the effects of all different classes of antihypertensive medication on intra-individual variability in systolic blood pressure in published trial reports. As no study at this time reported intra-individual variability in systolic blood pressure by randomized drug class, this study used the variation in SBP across each drug group (the standard deviation of the mean SBP at a specific time point) to derive a within-trial treatment effect on variability in SBP as the group variance ratio (G-VR= the ratio of the variance of mean SBP in each drug group). Further analyses of the 5 observational cohorts reported by Prof Rothwell demonstrated that in a linear regression model, intra-individual SBP variability explained more than 50% of the variance in group SD at a specific timepoint, with G-VR being a reliable surrogate measure of antihypertensive effects on within-individual variability in SBP in the ASCOT-BPLA and the MRC trials.[20]

This meta-analysis demonstrated that randomization to a calcium channel blocker was associated with the greatest reduction in VR compared to either placebo or all other drug classes, with smaller reductions in VR with thiazide and thiazide-like diuretics but increases in VR with ACE inhibitors, angiotensin receptor blockers and most significantly with beta-blockers (figure 1.6). These effects of antihypertensive drugs on variability in SBP were very similar to their effects on the subsequent risk of stroke seen in all trials. Furthermore, in trials reporting both VR and stroke risk, there was a strong relationship between randomized treatment effect on variability in SBP and risk of stroke, independent of mean SBP (r^2=0.473 p<0.0001, VR p=0.014, difference in mean SBP p=0.038). Further systematic reviews have since demonstrated that the correlation between drug class effects on VR and stroke risk is not due to confounding by atrial fibrillation,[119] persists when the agents are used in combination with other agents[120] and is dose dependent.[120] Finally, non-selective beta-blockers increase variability in SBP more than selective beta-blockers and are probably associated with a greater stroke risk as a result.[121]

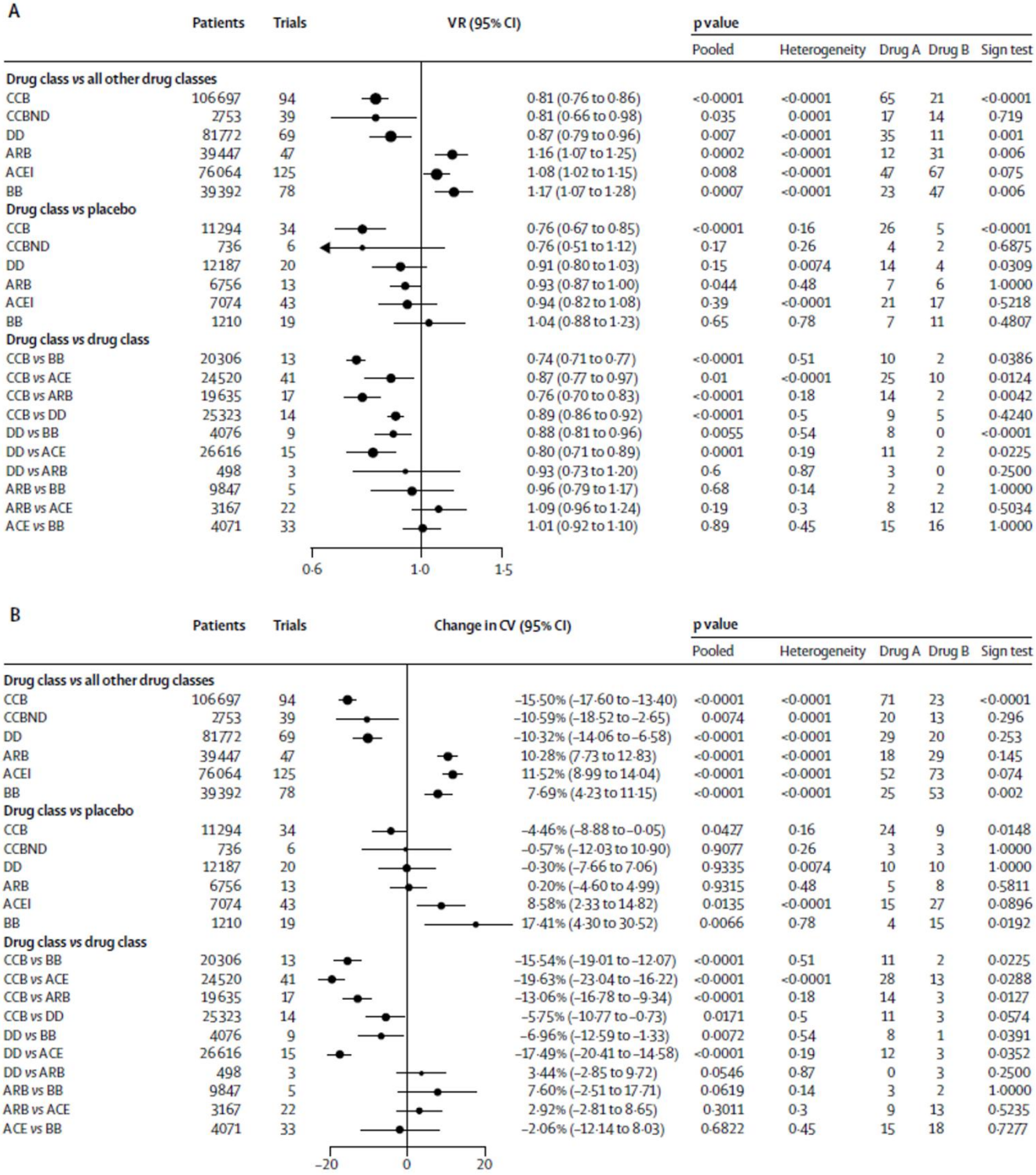

Figure 1.6 Pooled estimates of within-trial comparisons between drug classes at follow-up as the ratio of variances or the difference in percentage change in coefficient of variation compared to baseline. Confidence limits and p-values calculated according to random-effects meta-analysis and sign test. Error bars are 95% CI. The number of trials included in each analysis and the number of patients included in those trials (N) are given. NB. The sign tests analysis excludes trials in which there VR was 1.00 or the %CV was 0, and so the number of trials listed is less than the total. Derived from Webb et al[118]

1.6 Conclusions and Aims

Medium-term, visit-to-visit variability in SBP was a strong predictor of the risk of stroke independent of mean SBP in three cohorts of patients with previous TIA or stroke and in both arms of the ASCOT randomized controlled trial including hypertensive patients at an increased risk of cardiovascular events. In the ASCOT-BPLA and MRC-elderly studies and all available trial reports, randomisation to a calcium channel blocker reduced variability in SBP, as to a lesser extent did randomisation to a diuretic, whilst randomisation to a renin-angiotensin system inhibitor or a beta-blocker increased variability in SBP. These effects were associated with an increased risk of stroke.

Despite the robust nature of these findings a large number of questions remain. Are these findings replicable in independent populations with differing characteristics? Are antihypertensive effects on the surrogate measure of variability in SBP, the group variance ratio, truly reflective of effects on intra-individual variability? What is the optimal method of assessing blood pressure and blood pressure variability, particularly in the high-risk patients with recent TIA or minor stroke? How is variability in SBP related to clinical characteristics, hypertensive vascular disease and the risk of cardiovascular events? Is variability in SBP a truly causative factor resulting in increased stroke risk, or is it confounded by another strongly associated physiological change such as changes in the cerebral circulation? Given the strong relationship between stroke and dementia, is BPV increased in patients with cognitive decline? Which forms of BPV variability respond to treatment with different antihypertensive medications?

Therefore this thesis aims to:

1. Confirm and validate the observation that medium-term blood pressure variability is related to an increased risk of cardiovascular events in independent populations with a wider range of underlying conditions;

2. Further characterise the effects of different classes of antihypertensive agent on blood pressure variability and the related risk of stroke;
3. Determine the optimal method of assessing blood pressure variability;
4. Identify the clinical and physiological determinants of medium-term blood pressure variability;
5. Assess whether medium-term variability may be related to a risk of stroke or dementia through associated effects on cerebral haemodynamics;
6. Establish a large cohort of patients with extensive blood pressure monitoring and physiological assessment for future determination of cardiovascular risk.

These aims will be addressed through a number of methods: through systematic review and meta-analysis of published literature and meta-analysis of individual patient data from randomized controlled trials; through an observational cohort study within the Oxford Vascular Study population, incorporating home and ambulatory blood pressure monitoring after TIA and minor stroke; through prospective assessment of multiple physiological characteristics including cerebral haemodynamics in patients with BP monitoring and a recent TIA or minor stroke.

Through these studies, I aim to clarify the effect of medium-term variability in systolic blood pressure on the future risk of stroke, dementia and other cardiovascular events, gain a greater understanding of the pathophysiological basis of this relationship and more clearly delineate how it is affected by currently used antihypertensive medications.

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CHAPTER TWO

Prognostic implications of medium-term variability in blood pressure in prospective studies: systematic review and meta-analysis

2.1 Summary

Visit-to-visit variability in systolic blood pressure (SBP) was associated with an increased risk of stroke and other cardiovascular events in 5 cohorts with TIA or minor stroke. This novel risk factor is treatable, being reduced by calcium channel blockers and increased by beta-blockers, reducing the future risk of stroke. However, the relationship between SBP variability and cardiovascular events has been inconsistent in subsequent studies, raising concerns about its validity in other populations.

To resolve inconsistencies between published studies, I performed a systematic review and meta-analysis in 318700 patients in 43 cohorts, determining the relationship between intra-individual coefficient of variation in BP (CV = standard deviation/mean) with stroke, myocardial infarction or cardiovascular death. Summary group measures of intraindividual variability were obtained either from published reports, or calculated from individual patient level data for cohorts belonging to the Blood Pressure Lowering Triallists' Collaboration. Hazard ratios per standard deviation of CV were pooled by random effects meta-analysis, weighted by the inverse variance.

There was a clinically significant increase in stroke risk per SD of CV-SBP (HR=1.21, 95%CI 1.17-1.25, $p<1x10^{-10}$) and CV-DBP (HR=1.17, 95%CI 1.13-1.21, $p<1x10^{-10}$) with a similar relationship with myocardial infarction (HR=1.27, 95%CI 1.22-1.33, $p<1x10^{-10}$), and a less strong relationship with cardiovascular death (HR=1.05, 95%CI 1.00-1.09, p=0.049). These relationships persisted in trials with separate outcome periods, although they were stronger for cardiovascular death (HR=1.16, 95%CI 1.12-1.20, $p<1x10^{-10}$). Moderate heterogeneity between studies was partly explained by a stronger relationship in observational studies than randomised trials (stroke: HR=1.29, 1.14-1.46, p<0.001).

Variability in SBP and DBP was a reliable and clinically significant risk factor for stroke, myocardial infarction and cardiovascular death in a large meta-analysis of all available studies, and persisted in different study populations.

2.2 Introduction

As described in chapter 1, visit-to-visit variability in blood pressure (BP) and episodic hypertension in clinic were associated with an increased risk of stroke or all cardiovascular events, independent of mean BP in 5 cohorts of patients with cerebrovascular disease or hypertension.[1, 2] In the ASCOT-BPLA study, visit-to-visit variability was reduced by calcium channel blockers but increased with beta-blockers, explaining differences in stroke risk that were not explained by differences in mean SBP.[3, 4] A number of studies have subsequently found a similar association between variability in blood pressure and cardiovascular events[5] or death[6] in multiple populations, using both home[7] and clinic blood pressure measures to estimate blood pressure variability from day-to-day or visit-to-visit. However, the results of these studies have been inconsistent, due to variation in methods, populations, outcomes and the small size of some studies.[8, 9]

Despite strong associations in the five original cohorts, the clinical importance of variability in blood pressure has been questioned due to a number of concerns: doubts that it truly predicts future cardiovascular events, independent of mean SBP;[10] doubts that it is a reliable marker of a pathophysiological abnormality, particularly compared to awake ambulatory blood pressure variability; and doubts that the magnitude of the relationship is clinically significant.[11] Furthermore, it has been proposed that the relationship only exists in patients receiving antihypertensives[12] and that differences between agents are explained by drug half-life or compliance.[13] However, as a novel, treatable risk factor for stroke it offers the potential for immediate clinically important reductions in stroke risk as well as a target for future research and interventions.

Therefore I carried out a systematic review and meta-analysis to derive an unbiased estimate of the predictive value of variability in blood pressure for cardiovascular events.

2.3 Methods

2.3.1 Search Strategy and Data Collection

I searched Medline and EMBASE between inception and January 1st 2013 with the terms *(blood pressure OR hypertension OR BP) AND (office OR clinic OR visit-to-visit OR "visit to visit" OR home) AND (variability OR repeatability).* Non-English language papers were included. Reference lists of identified reviews and corresponding webtables were searched. Secondly, studies were identified by personal communication with authors and the BP Lowering Triallists' Collaboration (BPLTC). Data from all included reports was extracted prior to analysis and studies were assessed for quality by explicit criteria.

Studies reporting an association between any eligible measure of blood pressure variability (day-to-day variability on home monitoring or visit-to-visit variability on at least 3 consecutive clinic readings) and either cardiovascular death (CV-death), stroke or myocardial infarction were included, with all-cause mortality used as a surrogate for CV-death where CV-death was not reported. Studies reporting chronic cerebral ischaemia were included in the systematic review, but not in the meta-analysis. Available data was extracted from studies reporting an estimate of effect size (HR, Hazard Ratio; OR, Odds Ratio) and its precision (standard error or confidence interval) per standard deviation (SD), coefficient of variation (CV) or variation independent of the mean (VIM) of systolic or diastolic BP. Summary group measures of intraindividual variability were obtained either from published reports, or calculated from individual patient level data for BPLTC cohorts.

2.3.2 Statistical Analysis

For each cardiovascular outcome, HRs or ORs were pooled by both fixed (FE) and random-effects (RE) meta-analysis, weighted by the inverse variance, with significance of heterogeneity assessed by Cochran's Q and its magnitude by the I^2 statistic. Where available, the effect size was scaled to the reported population SD of that measure of BP variability for that study, or when available, to the average population SD across all studies. Only equivalent effect sizes (HRs or Ors) for equivalent measures of BP variability (SD, CV

or VIM) were pooled for each cardiovascular outcome, unadjusted and adjusted for age, gender and mean SBP or DBP where available. For the purposes of meta-analysis, hazard ratios, odds ratios and relative risks were deemed to be equivalent, although hazard ratio was used in preference.

Sensitivity analyses were performed for specific subgroups: studies reporting variability in BP during an exposure period that was temporally separated from the outcome period; studies reporting SD-SBP/DBP; for randomised controlled trials versus observational studies; and stratifying studies by age, baseline SBP and disease state. The presence of publication and reporting bias was assessed with funnel plots.

All analyses were performed in Matlab R2012a, Microsoft Excel 2010 and IBM SPSS 20.

2.4 Findings

2.4.1 Search Results

Data was available for 318700 patients from 43 cohorts identified by multiple methods. Firstly, the electronic search identified 858 citations, of which 173 abstracts and 68 potentially eligible papers were reviewed in full. Of these, 21 studies fulfilled criteria for inclusion in the systematic review whilst 12 studies (13 cohorts including two arms to ASCOT-BPLA)[2] could be included in the meta-analyses (table 2.1). Of the cohorts included in the meta-analysis, 11 reported outcomes as a function of standard deviation (SD) and 10 reported outcomes as a function of coefficient of variation (CV) or an equivalent measure. Outcome data was available for 9 studies for all-cause mortality, 7 studies for cardiovascular mortality, 7 studies for myocardial infarction and 8 studies for stroke risk, with the other studies reporting only the risk of a composite measure of cardiovascular disease. Secondly, results from 28 studies included in the Blood Pressure Lowering Trialists' Collaboration were obtained following direct communication with the authors. These 28 studies were all large randomised controlled trials in different patient groups, reporting CV death, stroke and myocardial infarction.

Table 2.1 Details of studies included in systematic review. C-C = case-control; RCT = randomised controlled trial; MI = myocardial infarction; CVA = stroke; HTN = hypertension; Pop. = population sample; yrs = years; TIA = transient ischaemic attack; RFs = risk factors; CVde = cardiovascular death; DM = diabetes; CHD = coronary heart disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; OR = Odds ratio; HR = hazard ratio; SD = standard deviation; CV = coefficient of variation.

Study	Start	Follow-up	Population	N	Outcomes	BP method	BP measures	Measure of Association
Studies Included in Meta-analysis								
Hata et al (2000)[14]	C-C	1	Stroke	488	CVA	Clinic	SBP / DBP Mean/ CV	OR
Hata et al (2002)[15]	C-C	1	MI	419	MI	Clinic	SBP / DBP Mean / CV	OR
Ohasama study[16]	Cohort	12	Pop.; >40yrs	2455	CVde; fatal CVA / MI	Home	SBP / DBP Mean / SD	HR
UKTIA[17]	RCT	4	TIA	2435	CVde; CVA; MI	Clinic	SBP / DBP Mean / SD / CV	HR
ESPS[18]	RCT	2	TIA / Stroke	1250	CVde; CVA; fatal MI	Clinic	SBP / DBP Mean / SD / CV	HR
Dutch-TIA[19]	RCT	2.6	TIA	3131	CVde; CVA; non-fatal MI	Clinic	SBP / DBP Mean / SD / CV	HR
ASCOT (amlodipine)[20]	RCT	5.5	HTN; RFs	9639	CVde; CVA; MI	Clinic	SBP / DBP Mean / SD / CV	HR
ASCOT (Atenolol)[20]	RCT	5.5	HTN; RFs	9618	CVde; CVA;MI	Clinic	SBP / DBP Mean / SD / CV	HR
NHANES[6]	Cohort	14	Pop.; >20 yrs	956	Death	Clinic	SBP / DBP SD / CV	HR
Finn-Home study[7]	Cohort	7.8	Pop.; 45-74 yrs	1866	Death;	Home	SBP / DBP Mean / SD	HR
Hsieh et al.(2012)[21]	Cohort	5.6	DM	2161	CVde	Clinic	SBP / DBP / MBP Mean / SD / CV	HR
WHI[5]	Cohort	5.4	Postmenopausal women	58228	CVA	Clinic	SBP SD	HR
Di Iorio et al. (2012)[22]	RCT	2.8	Pre-dialysis renal impairment	730	Death	Clinic	SBP CV	HR
TNT/IDEAL/CARDS[23]	RCT	-	RFs	20952	CVA / MI	Clinic	SBP / DBP SD	HR
PROSPER[24]	RCT	7	RFs; >70yrs	1808	CVde; CVA;MI	Clinic	SBP	HR

							SD	
ABCD[25]	RCT	5.3	DM	950	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
ADVANCE[26]	RCT	4.3	DM; RFs	11140	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
ALLHAT[27]	RCT	4.9	HTN; RFs	33357	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
ANBP2[28]	RCT	4.1	HTN; >65 yrs	6083	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
BENEDICT[29]	RCT	3.6	HTN; DM	1204	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
CAPPP[30]	RCT	6.1	HTN	10985	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
CONVINCE[31]	RCT	3.0	HTN; RFs	16746	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
DIABHYCAR[32]	RCT	3.9	DM; nephropathy	4912	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
ELSA[33]	RCT	4.0	HTN	2334	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
EUROPA[34]	RCT	4.2	CHD	12228	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
HOT[35]	RCT	3.8	HTN	18790	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
HYVET[36]	RCT	1.8	HTN; >80 yrs	2845	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
INVEST[37]	RCT	2.8	HTN; CHD	22576	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
JMIC-B[38]	RCT	3.0	HTN; CHD	1650	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
MOSES[39]	RCT	4.8	HTN; Stroke; RFs	1352	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
MRC1[40]	RCT	5.3	HTN; 35-64 yrs	17354	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
MRC2[41]	RCT	5.8	HTN; >65 yrs	4396	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
NICS-EH[42]	RCT	5.0	HTN; >60 yrs	429	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
NORDIL[43]	RCT	5.0	HTN	10881	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR

PART2[44]	RCT	4.7	CHD or stroke	617	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
PREVEND-IT[45]	RCT	3.8	Microalbuminuria	864	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
PREVENT[46]	RCT	3.0	CHD	825	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
PROGRESS[47]	RCT	3.9	Stroke	6105	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
SCAT[48]	RCT	4.0	CHD	460	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
STOP2[49]	RCT	5.0	HTN; >70 yrs	6614	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
SYST-EUR[50]	RCT	2.6	HTN; >60 yrs	4695	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
UKPDS[51]	RCT	8.4	HTN; DM	758	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
VHAS[52]	RCT	2.0	HTN	1414	CVde; CVA;MI	Clinic	SBP / DBP SD / CV	HR
Studies Included in Systematic Review only								
Havlik (2002)[53]	Cohort	20-31	Pop.; men	575	Leukoaraiosis	Clinic	SBP Residual SD	OR
Wingfield (2005)[54]	C-C	7.7	Pop.	1431	CVde; CVA;MI	Clinic	DBP Transient elevations	OR
Kilpatrick (2010)[55]	RCT	9	T1 DM	1441	Diabetic nephropathy	Clinic	SBP / DBP SD	OR
Brickman (2010)[56]	Cohort	4.7	Pop.; >65 yrs	686	Leukoaraiosis; Silent infarcts	Clinic	MBP SD	Linear regression
Nagai (2012)[57]	Cohort	1	RFs; >70 yrs	201	Cognitive impairment (MMSE)	Clinic	SBP / DBP SD, CV	OR
FOSIDIAL[58]	RCT	2	Haemodialysis patients	397	All CV events	Clinic	SBP / DBP SD, CV	HR

2.4.2 Relationship between BP variability and Risk of Stroke

Across 37 cohorts including 234095 patients with 6611 strokes, there was a 21% increase in risk of stroke per SD increase in CV-SBP, adjusted for age, gender, and mean SBP (figure 2.1), with a 24% increase in stroke risk with unadjusted effect sizes (table 2.2). There was moderate heterogeneity between studies (p<0.001%, I^2=59%), resulting in minimal difference between fixed and random effects meta-analysis with no evidence of reporting bias (figure 2.2). There was only an increased stroke risk of ~17% per SD of CV-DBP, before and after adjustment (table 2.2). The pooled effect size was similar for stroke risk per SD of SD-SBP (RE HR = 1.20, 1.16 – 1.25, p<0.001, I^2=62%) and SD of SD-DBP (RE HR = 1.26, 1.19 – 1.34, p<0.001, I^2=75%), and for trials in which baseline SD of CV-SBP was known (RE HR = 1.21, 1.16 – 1.26, p<0.001, I^2=60%).

Study	N	Events	HR	Cilow	Cihigh	p-value	p-het
NICS-EH	336	11	0.29	0.12	0.75	0.0101	
BENEDICT	870	4	0.64	0.20	2.07	0.46	
PART2	606	9	0.78	0.36	1.67	0.52	
JMIC-B	1338	20	0.96	0.59	1.56	0.87	
DIABHYCA	4351	177	1.00	0.85	1.17	0.98	
CONVINCE	14794	186	1.00	0.87	1.16	0.95	
INVEST	16790	263	1.04	0.92	1.18	0.53	
ABCD	849	32	1.05	0.75	1.47	0.79	
Dutch-TIA	3131	254	1.06	0.98	1.15	0.12	
MRC1	16373	151	1.10	0.94	1.28	0.22	
EUROPA	11859	166	1.10	0.95	1.27	0.2	
PROGRESS	5822	588	1.15	1.06	1.24	0.0007	
ELSA	1908	19	1.15	0.75	1.78	0.52	
MRC2	4060	202	1.16	1.01	1.33	0.0325	
HYVET	3283	77	1.16	0.92	1.46	0.21	
ESPS	1250	184	1.16	1.00	1.34	0.043	
STOP2	6326	567	1.17	1.10	1.25	<0.0001	
UKPDS	1037	59	1.18	0.90	1.55	0.22	
Di Lorio (2012)	374	209	1.19	1.05	1.33	0.0041	
ADVANCE	10614	356	1.21	1.10	1.34	0.0001	
ALLHAT	29158	1209	1.23	1.16	1.29	<0.0001	
CAPPP	10676	293	1.25	1.13	1.38	<0.0001	
UKTIA	2435	320	1.28	1.15	1.43	<0.0001	
VHAS	1277	8	1.29	0.67	2.48	0.45	
ASCOT - amlodipine	9639	327	1.29	1.17	1.43	<0.0001	
Ohasama (2008)	2455	83	1.30	1.07	1.61	0.0123	
HOT	17952	236	1.31	1.17	1.46	<0.0001	
ASCOT - atenolol	9618	422	1.31	1.20	1.43	<0.0001	
MOSES	1162	121	1.31	1.14	1.51	0.0002	
NORDIL	10501	294	1.33	1.20	1.48	<0.0001	
TNT/IDEAL/CARDS	20952	657	1.33	1.24	1.42	<0.0001	
PREVEND-IT	797	6	1.37	0.74	2.53	0.32	
SYST-EUR	3902	102	1.38	1.18	1.61	<0.0001	
ANBP2	5908	185	1.40	1.24	1.57	<0.0001	
PREVENT	760	6	1.43	1.11	1.84	0.0059	
Hata(2000)	488	138	1.46	1.21	1.74	<0.0001	
SCAT	444	10	1.58	0.89	2.79	0.12	
Fixed Effects	234095	6611	1.22	1.19	1.24	<0.0001	I'2 58.9%
Random Effects	234095	6611	1.21	1.17	1.25	<0.0001	<0.0001

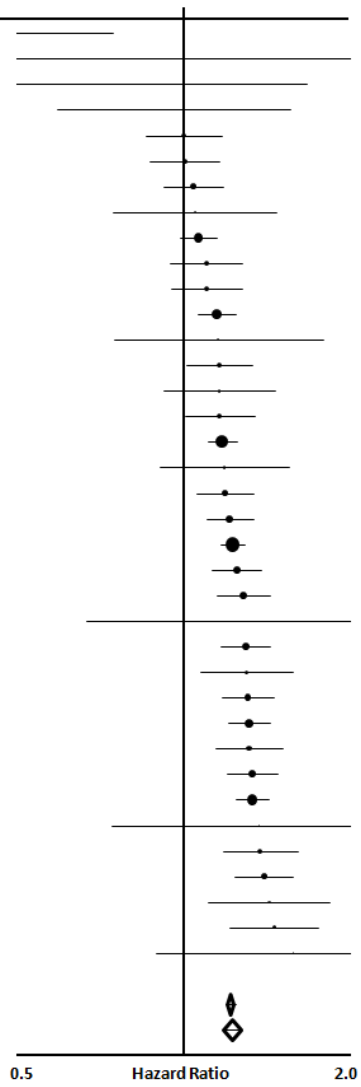

Figure 2.1 Forest plot of the relationship between CV-SBP and risk of stroke, adjusted for age, gender and mean SBP. Pooled estimates are presented as both fixed and random effects meta-analysis per SD of CV-SBP.

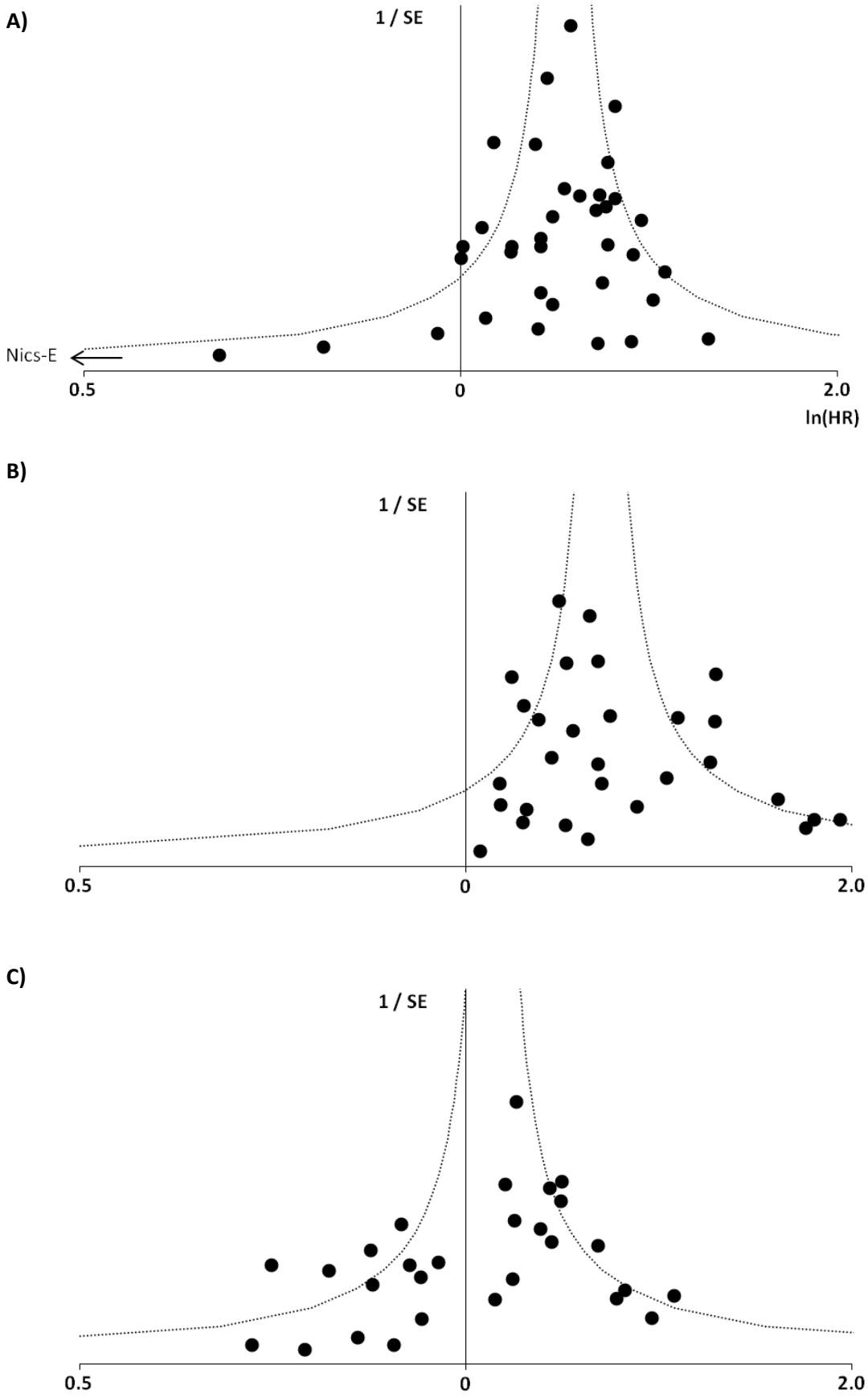

Figure 2.2 Funnel plots for adjusted hazard ratios for the risk of stroke (A), myocardial infarction (B) and cardiovascular death (C), per 1 SD increase in CV-SBP. Funnel limits represent confidence intervals.

2.4.2 Relationships between BP variability and Risk of Myocardial Infarction

The risk of myocardial infarction was also strongly associated with variability in both SBP and DBP, with a 27% increased risk per SD of CV-SBP and 19% increase per SD of CV-DBP (figure 2.3). There was significant heterogeneity between studies (p<0.001 I^2=74%p), with a number of smaller studies having greater than expected effect sizes resulting in a larger pooled effect size with random effects meta-analysis than fixed effect meta-analysis. Again the effect size was similar per SD of SD-SBP or SD of SD-DBP (SBP RE HR=1.26, 1.21-1.32, p<0.001, I^2=73%; DBP RE HR=1.32, 1.23-1.42, p<0.001, I^2=74%) and for trials in which the baseline SD of CV-SBP was known (RE HR=1.28, 1.22-1.34, p<0.001, I^2=74%). The effect size was greater in the single cohort study which reported MI as an outcome compared to randomised controlled trials (RE HR=1.36, 1.00-1.86, p=0.05).

Study	N	Events	HR	Cilow	Cihigh	p-value	p-het
NICS-EH	297	3	1.03	0.30	3.51	0.97	
PREVENT	760	32	1.06	0.85	1.33	0.59	
PART2	602	43	1.06	0.79	1.43	0.68	
MRC1	16368	395	1.09	0.99	1.20	0.09	
ELSA	1894	24	1.11	0.73	1.68	0.63	
CAPPP	10678	282	1.11	0.99	1.25	0.07	
MOSES	1191	33	1.12	0.81	1.54	0.5	
MRC2	4063	239	1.14	1.01	1.29	0.0407	
UKPDS	1035	143	1.17	0.99	1.38	0.07	
ALLHAT	29155	2072	1.18	1.13	1.23	<0.0001	
STOP2	6352	403	1.18	1.10	1.27	<0.0001	
TNT/IDEAL/CARDS	20952	1848	1.20	1.15	1.24	<0.0001	
JMIC-B	1341	18	1.20	0.76	1.88	0.43	
INVEST	16758	438	1.20	1.09	1.31	<0.0001	
PROGRESS	5907	177	1.21	1.06	1.39	0.0053	
BENEDICT	849	9	1.25	0.63	2.47	0.53	
EUROPA	11798	627	1.25	1.16	1.34	<0.0001	
UKTIA	2435	245	1.27	1.06	1.52	0.0094	
ADVANCE	10614	418	1.27	1.16	1.39	<0.0001	
SYST-EUR	4105	62	1.28	1.02	1.59	0.0305	
CONVINCE	14790	215	1.30	1.15	1.47	<0.0001	
Hata(2002)	419	139	1.36	1.00	1.86	0.05	
ABCD	848	62	1.44	1.17	1.77	0.0006	
HOT	17964	160	1.46	1.29	1.66	<0.0001	
DIABHYCA	4319	103	1.55	1.30	1.85	<0.0001	
ANBP2	5924	121	1.56	1.38	1.78	<0.0001	
NORDIL	10515	293	1.57	1.42	1.72	<0.0001	
PREVEND-IT	805	20	1.75	1.33	2.31	<0.0001	
VHAS	1098	8	1.84	1.14	2.97	0.0123	
HYVET	3286	16	1.87	1.26	2.77	0.0019	
SCAT	444	19	1.96	1.32	2.90	0.0008	
Fixed Effects	207566	7823	1.23	1.21	1.25	<0.0001	I'2 71.5%
Random Effects	207566	7823	1.27	1.22	1.33	<0.0001	<0.0001

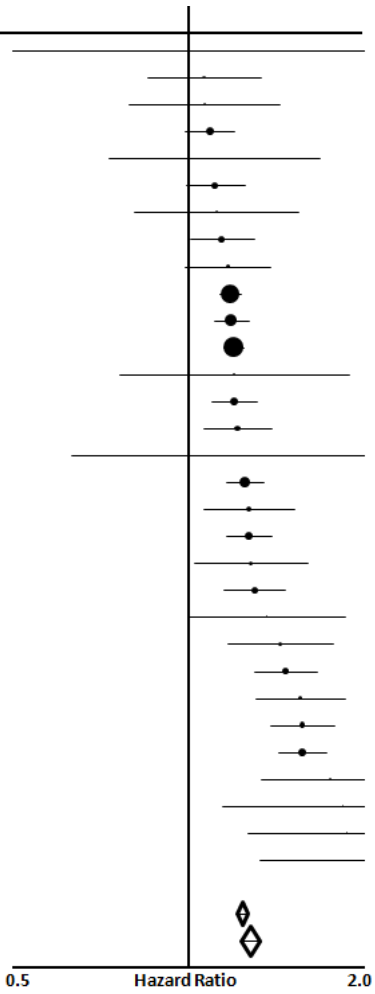

Figure 2.3 Forest plot of the relationship between CV-SBP and risk of myocardial infarction, adjusted for age, gender and mean SBP. Pooled estimates are presented as both fixed and random effects meta-analysis.

2.4.3 Relationships between BP variability and Risk of Cardiovascular Death

Compared to MI and stroke, the risk of cardiovascular death was less strongly related to CV-SBP, with a 7% increased risk per SD of CV-SBP (p=0.005), reducing to 5% after adjustment for age, gender and mean SBP. Although variability in SBP was still a significant predictor of risk of death (table 2.2), there was no significant relationship to CV-DBP (table 2.2). The effect size was similar per SD of SD-SBP or SD of SD-DBP (SBP RE HR=1.06, 1.00-1.12, p=0.03, I^2=69%; DBP RE HR=1.01, 0.93-1.10, p=0.84, I^2=70%) and for trials in which the baseline SD of CV-SBP was known (RE HR=1.04, 0.98-1.10, p=0.22, I^2=71%). The risk was also greater in the 3 observational cohorts that reported all-cause mortality as opposed to cardiovascular death (3 trials RE HR=1.23, 1.08-1.39, p=0.001, I^2=100%), although there was still a significant relationship with cardiovascular death after excluding these trials.

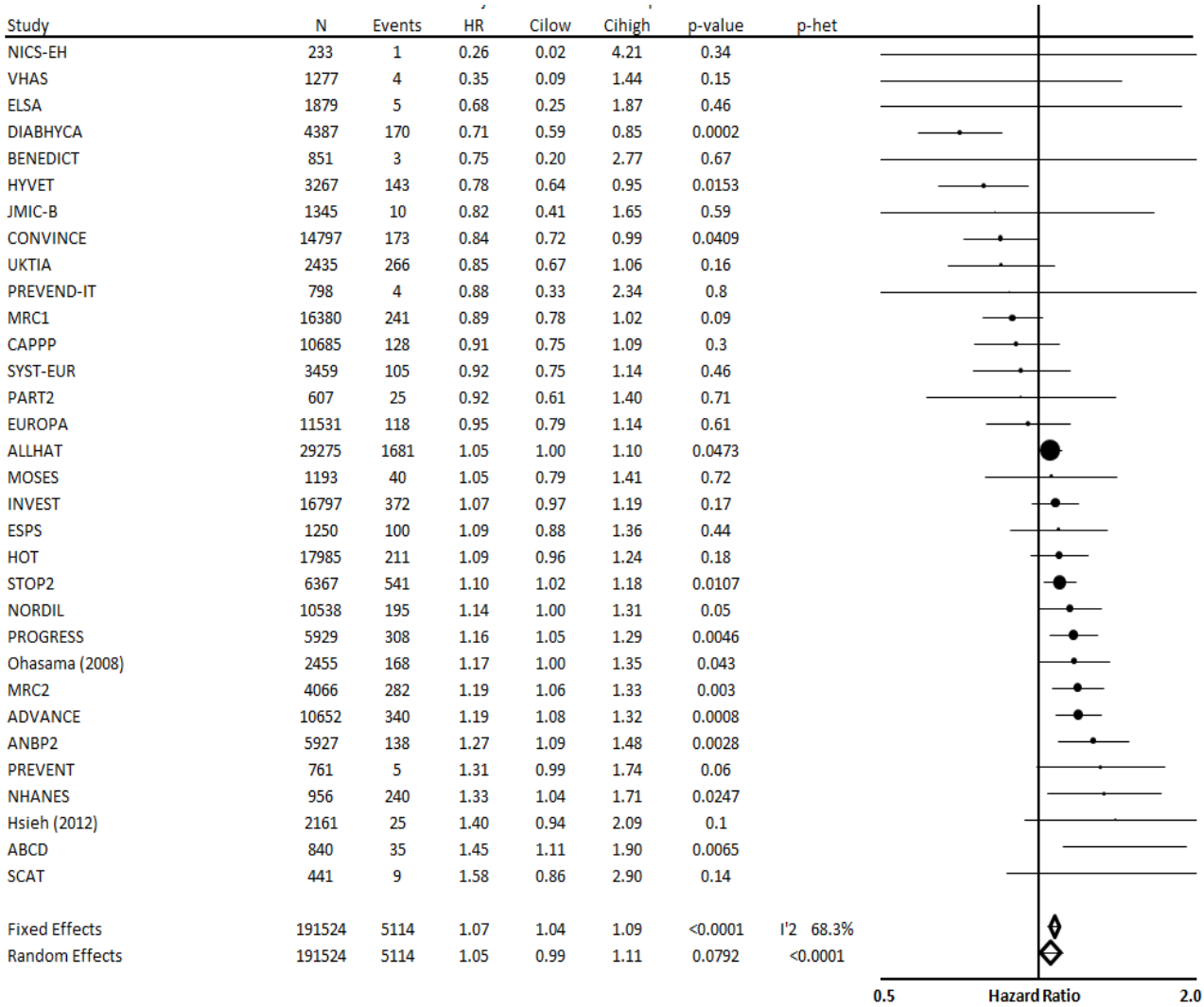

Figure 2.4 Forest plot of the relationship between CV-SBP and risk of cardiovascular death, adjusted for age, gender and mean SBP. Pooled estimates are presented as both fixed and random effects meta-analysis.

		Unadjusted						Adjusted					
		Trls	N / events	HR	95% CI		p-val	Het.	Trls	N / events	HR	95% CI		p-val	Het.
Stroke															
CV-SBP	FE	34	210200	**1.26**	**1.24**	**1.29**	<0.001	66.7%	37	234095	**1.22**	**1.19**	**1.24**	<0.001	58.9%
	RE		5733	**1.24**	**1.19**	**1.29**	<0.001	<0.001		6611	**1.21**	**1.17**	**1.25**	<0.001	<0.001
CV-DBP	FE	34	210240	**1.17**	**1.15**	**1.19**	<0.001	72.7%	34	230704	**1.17**	**1.14**	**1.19**	<0.001	59.5%
	RE		5660	**1.18**	**1.13**	**1.22**	<0.001	<0.001		6179	**1.17**	**1.13**	**1.21**	<0.001	<0.001
Myocardial Infarction															
CV-SBP	FE	29	186195	**1.26**	**1.23**	**1.28**	<0.001	72.7%	31	207566	**1.23**	**1.21**	**1.25**	<0.001	71.5%
	RE		5836	**1.29**	**1.23**	**1.35**	<0.001	<0.001		7823	**1.27**	**1.22**	**1.33**	<0.001	<0.001
CV-DBP	FE	29	186118	**1.18**	**1.16**	**1.20**	<0.001	77.9%	30	207070	**1.19**	**1.16**	**1.21**	<0.001	74%
	RE		5833	**1.20**	**1.14**	**1.26**	<0.001	<0.001		7681	**1.19**	**1.14**	**1.25**	<0.001	<0.001
Cardiovascular Death															
CV-SBP	FE	29	185952	**1.12**	**1.09**	**1.15**	<0.001	70.8%	32	191524	**1.07**	**1.04**	**1.09**	<0.001	68.3%
	RE		4681	**1.07**	**1.01**	**1.14**	0.0145	<0.001		5114	**1.05**	**0.99**	**1.11**	0.08	<0.001
CV-DBP	FE	29	185879	**1.05**	**1.02**	**1.07**	<0.001	73.8%	30	188040	**1.01**	**0.99**	**1.03**	0.41	62.7%
	RE		4677	**1.01**	**0.95**	**1.07**	0.8	<0.001		4702	**0.99**	**0.94**	**1.04**	0.67	<0.001

Table 2.2 Pooled estimates of the relationship between coefficient of variation of SBP and DBP and risk of stroke, myocardial infarction and cardiovascular death, with exposure and outcome periods temporally separated. Estimates are given per SD of CV-SBP or CV-DBP, by both fixed effects (FE) and random effects (RE) meta-analysis. Effect sizes are pooled between studies reporting unadjusted measures and reporting measures adjusted for age, gender and mean SBP, with or without adjustment for other cardiovascular risk factors.

2.4.4 Effect of temporal separation of exposure and outcome periods

The relationship between variability in SBP and the risk of stroke was slightly attenuated when the exposure and outcome periods were separated in time, particularly for the risk of myocardial infarction, to a 10% increase in risk per SD of CV-SBP or CV-DBP. However unlike stroke or MI, the relationship with cardiovascular death was stronger in trials separating the exposure and outcome periods (CV-SBP HR=1.16, 1.12-1.20, $p<0.0001$) (table 2.2).

2.4.5 Sources of heterogeneity

There was moderate heterogeneity between trials reporting the relationship between blood pressure variability and risk of stroke, MI or CV-death. For all outcomes this was partly explained by study type, with observational cohort studies demonstrating a stronger association with the risk of stroke than randomised controlled trials (HR=1.29, 1.14-1.46, $p<0.001$, 3 studies). However, differences in the clinical characteristics of the populations studied in each trial also explained some of the heterogeneity between trials. Stratifying studies by mean age of the population demonstrated no significant difference in the relationship between CV-SBP and risk of stroke or cardiovascular death (table 2.4), but there was an increased predictive value of CV-SBP for risk of MI with increasing age. In contrast, risk of stroke and MI were greatest in studies with mean baseline SBP >160 but there was a trend to a decreasing risk of CV death per SD increase in CV-SBP with increasing baseline SBP (figure 2.5).

Study	Trials	N	Events	HR	Cilow	Cihigh	p-value	p-het
Stratified by Age								
Stroke								
< 60 years	12	62650	1815	**1.22**	**1.14**	**1.31**	<0.001	0.015
60-70 years	15	141167	3613	**1.21**	**1.15**	**1.27**	<0.001	0.006
> 70 years	9	29028	999	**1.21**	**1.11**	**1.33**	<0.001	<0.001
Myocardial Infarction								
< 60 years	10	56873	2876	**1.21**	**1.12**	**1.3**	<0.001	0.016
60-70 years	13	121928	4326	**1.29**	**1.21**	**1.38**	<0.001	<0.001
> 70 years	8	28765	621	**1.35**	**1.2**	**1.53**	<0.001	<0.001
Cardiovascular Death								
< 60 years	10	38466	1087	**1.06**	**0.91**	**1.23**	0.45	<0.001
60-70 years	14	124102	3193	**1.08**	**1.02**	**1.14**	0.01	0.047
> 70 years	7	27706	734	**0.98**	**0.84**	**1.15**	0.81	<0.001
Stratified by Baseline SBP								
Stroke								
< 140 mmHg	9	54620	1281	**1.23**	**1.13**	**1.33**	<0.001	0.11
140 - 160 mmHg	16	102322	3399	**1.18**	**1.12**	**1.23**	<0.001	0.009
> 160 mmHg	12	77153	1931	**1.25**	**1.17**	**1.33**	<0.001	0.0013
Myocardial Infarction								
< 140 mmHg	7	51729	2933	**1.22**	**1.12**	**1.33**	<0.001	0.003
140 - 160 mmHg	14	97914	3955	**1.2**	**1.17**	**1.24**	<0.001	0.7
> 160 mmHg	10	57923	935	**1.42**	**1.27**	**1.58**	<0.001	<0.001
Cardiovascular Death								
< 140 mmHg	9	36090	821	**1.11**	**0.97**	**1.27**	0.13	0.015
140 - 160 mmHg	13	97928	3153	**1.05**	**0.98**	**1.13**	0.18	0.004
> 160 mmHg	10	57506	1140	**1.01**	**0.9**	**1.14**	0.83	<0.001

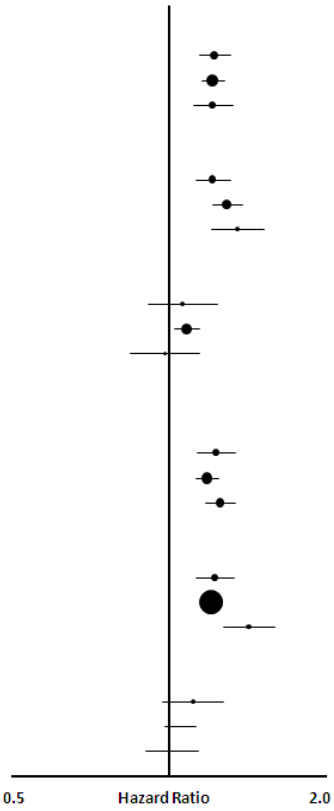

Figure 2.5 Estimates of the fully adjusted relationship between CV-SBP and risk of stroke, stratified by baseline age or SBP, pooled by random effects meta-analysis. HR=Hazard ratio; p-het = p value for heterogeneity

Heterogeneity also resulted from comorbidities in the populations studied. In limited studies with renal disease, the relationship between CV-SBP and stroke was less strong than the relationship in studies not requiring renal disease at baseline whilst renal disease increased the association with MI. However, BP variability was actually protective of the risk of CV death (table 2.3). Similarly, in studies in diabetes, there was a reduced relationship with stroke risk, an increased relationship with MI and no change with CV-death, whereas a premorbid history of stroke or other cardiovascular events had no impact on the strength of the relationship (table 2.3).

	Unadjusted								Adjusted							
	Trls	N	Events	HR	95% CI		p-val	Het.	Trls	N	Events	HR	95% CI		p-val	Het.
Stroke																
All Trials	34	210200	5733	**1.24**	**1.19**	**1.29**	<0.001	<0.001	37	234095	6611	**1.21**	**1.17**	**1.25**	<0.001	<0.001
Prior renal disease	4	6392	396	**1.15**	**0.99**	**1.33**	0.07	0.19	4	6392	396	**1.11**	**0.97**	**1.26**	0.13	0.25
Prior TIA or Stroke	5	13800	879	**1.22**	**1.12**	**1.33**	<0.001	0.005	5	13800	879	**1.18**	**1.09**	**1.27**	<0.001	0.03
Prior Diabetes	5	17721	569	**1.13**	**1.00**	**1.27**	0.041	0.19	5	17721	569	**1.12**	**1.01**	**1.25**	0.032	0.26
Myocardial Infarction																
All Trials	29	186195	5836	**1.29**	**1.23**	**1.35**	<0.001	<0.001	31	207566	7823	**1.27**	**1.22**	**1.33**	<0.001	<0.001
Prior renal disease	3	5973	132	**1.56**	**1.33**	**1.82**	<0.001	0.33	3	5973	132	**1.59**	**1.37**	**1.84**	<0.001	0.59
Prior TIA or Stroke	3	9533	278	**1.26**	**1.14**	**1.39**	<0.001	0.65	3	9533	278	**1.22**	**1.10**	**1.35**	<0.001	0.79
Prior Diabetes	5	17665	592	**1.31**	**1.22**	**1.40**	<0.001	0.39	5	17665	592	**1.33**	**1.20**	**1.47**	<0.001	0.16
Cardiovascular Death																
All Trials	29	185952	4681	**1.07**	**1.01**	**1.14**	0.0145	<0.001	32	191524	5114	**1.05**	**0.99**	**1.11**	0.08	<0.001
Prior renal disease	3	6036	177	**0.77**	**0.65**	**0.92**	0.0044	0.64	3	6036	177	**0.71**	**0.59**	**0.85**	<0.001	0.91
Prior TIA or Stroke	4	10807	406	**1.03**	**0.84**	**1.27**	0.75	0.0047	4	10807	406	**1.05**	**0.91**	**1.21**	0.47	0.11
Prior Diabetes	4	16730	548	**1.10**	**0.79**	**1.54**	0.56	<0.001	4	16730	548	**1.04**	**0.72**	**1.50**	0.84	<0.001

Table 2.3 Pooled estimates of the relationship between coefficient of variation of SBP and risk of stroke, myocardial infarction and cardiovascular death, for all trials and trials in patients with prior renal disease, cerebrovascular disease or diabetes. Estimates are given per SD of CV-SBP by random effects (RE) meta-analysis. Effect sizes are pooled between studies reporting unadjusted measures and reporting measures adjusted for age, gender and mean SBP, with or without adjustment for other cardiovascular risk factors.

2.4.5 Relevant studies not included in meta-analysis

In studies not fulfilling the inclusion criteria but reporting the risk of cardiovascular events, there was an increased risk of cardiovascular mortality, diabetes or stroke in male patients with a transient elevation of diastolic blood pressure compared to normotensive patients (CV mortality OR: 1.59 p=0.06; Stroke OR 15.9 p=0.03; diabetes OR=7.5 p=0.04).[54] In haemodialysis patients in the FOSIDIAL study, cardiovascular events were significantly associated with systolic BP variability (HR per 1% CV=1.49, 1.15-1.93, p<0.0001).[58] In contrast to these studies, a report from the ELSA study reported no significant association between visit-to-visit variability in SBP and cardiovascular events but did not report any numerical association.[8] However, data from the Blood Pressure Lowering Trialist's collaboration demonstrated that there was an association in this study, but that it failed to reach significance due to its small size (figure 2.1).

A number of studies reported relationships between blood pressure variability and markers of leukoaraiosis. In the Honolulu-Asia Aging study including 575 Japanese-American men, greater systolic blood pressure variability over three clinic visits between 1965 and 1974 was associated with an increased risk of white matter lesions on MRI between 1994 and 1996 comparing the top quintile of SBP variability with the bottom quintile (OR=2.2 95%CI 1.10-4.79), independent of mean SBP which was not associated with white matter disease (OR 1.01 0.9-1.02).[53] Chronic cerebrovascular disease was also increased in patients with increased variability in mean BP in a mixed ethnicity North American population, with an increase in white matter hyperterintensities (p=0.0017) and silent infarcts (p=0.004) across four groups with increasing mean MBP and SD.[56] Similarly, there was an increase in the incidence of cerebral microbleeds with increasing variability in blood pressure in a Chinese cohort (OR per 5mmHg SD-SBP: 1.34, 1.01-2.7, p=0.046), particularly in more hypertensive locations,[59] and an increase in cognitive impairment with increasing BP variability in a Japanese cohort of elderly patients with increased cardiovascular risk (MMSE <25 OR per 1% CV-SBP=1.60 p1.20-2.1).[57]

2.5 Discussion

Variability in systolic and diastolic BP was associated with the risk of stroke or myocardial infarction in 318700 patients in 43 cohorts, with a clinically significant >20% increased risk per SD increase in variability in SBP. There was a weaker but significant association with cardiovascular death, which was stronger in studies separating the BP measurement and outcome periods. These relationships were consistent across subgroups and study types, with or without adjustment for age, gender and mean BP. In addition, multiple reports identified a relationship between SBP variability and leukoaraiosis.

The validity of the relationship between BP variability and cardiovascular events has been questioned, partly due to negative findings in small studies[8] and studies with inappropriate methods of assessing within-individual variability in BP.[11] This is in contrast to large studies reporting significant associations in disparate populations,[5-7, 16] although these studies may be prone to residual confounding or reporting bias. This large meta-analysis of >300000 patients is prone to neither of these problems: it is well-powered; it incorporates a wide-range of patients in multiple settings; all studies used reliable measures of BP variability; there was no evidence of reporting or publication bias; it allowed for unadjusted analysis and adjustment for the most important confounders. In particular, effects were consistent between study type, patient characteristics and premorbid diseases.

Given the large number of studies, there was heterogeneity affecting most analyses. This heterogeneity was moderate for the primary analysis of stroke risk but was greater for pooled estimates of the relationship with cardiovascular death and myocardial infarction. However, it is apparent from the forest plots that this resulted primarily from a small number of events in small studies, with 11 strokes in NICS-E contributing more heterogeneity to the stroke meta-analysis than any other study. There was little heterogeneity amongst larger studies and similar results in sensitivity analyses, suggesting that this heterogeneity had little effect on the magnitude or reliability of the pooled effect sizes.

Although the heterogeneity is unlikely to affect the pooled estimates, it is still informative. Firstly, the relationships were stronger in observational cohorts than randomised controlled trials, possibly due to strict entry criteria for most RCTs that limit variability in blood pressure and so result in an underestimation of the pooled effect.[4] Importantly, the strong relationship in population based studies suggests that the relationship between BP variability and cardiovascular events is not restricted to patients already receiving antihypertensive medications but is present in largely untreated populations, and is therefore unlikely to be explained solely by drug half-life or compliance.[6, 13] Secondly, within-study adjustment for age, gender and mean SBP reduced heterogeneity between studies. Thirdly, there was a trend to stronger associations between BP variability and myocardial infarction in older individuals with higher baseline SBP, with the opposite pattern for cardiovascular death, although these differences were small. This may suggest a dissociation between the mechanism of death and myocardial infarction. Finally, renal disease appeared to reduce the strength of the association with stroke and increase it with MI. These discrepancies between studies were largely small, and except for renal disease and cardiovascular death, still resulted in significant associations between BP variability and outcome. However, they provide potential avenues of investigation to explain the mechanisms underlying the relationships between BP variability and cardiovascular events.

A greater than 20% increase in the risk of stroke or MI per SD of CV-SBP or DBP after adjustment for age, gender and mean SBP is clinically significant and is the most reliable current estimate of the relationship between BP variability and cardiovascular events. Across the entire population, the range of BP variability therefore reflects a significant burden of potentially preventable cardiovascular morbidity. Furthermore, as the relationship between blood pressure variability and stroke risk appears to be non-linear,[1] there is likely to be an even greater excess risk in the highest decile of the population. The association with cardiovascular death was weaker than stroke or MI, at least when BP variability was determined concurrently with outcomes. However, in studies in which

measurement of BP variability preceded the outcome period, the strength of association was significantly stronger, suggesting a longer-term causative relationship between BP variability and death.

Despite a large number of studies with extensive adjustment for potential confounders, this systematic review has some limitations. Firstly, most of the cohorts included were from randomised controlled trials, with strict entry criteria that may result in underestimation of associations between BP variability and cardiovascular events. Furthermore, most patients included in RCTs, even in the placebo arm, receive treatment with antihypertensive medications. However, if treatment reduced BP variability then the most likely effect of including patients would be to reduce the relationship with BP variability, potentially explaining the stronger relationship in observational studies. Secondly, despite the persistent relationship in studies separating the measurement and outcome periods, this study cannot definitively demonstrate causality due to the observational nature of the included studies. Causality would only be proven by interventions that solely reduced BP variability and then resulted in a reduction in cardiovascular events, consistent with our meta-analysis of antihypertensive medication effects on BP variability.[4] Finally, there was a large variation in the outcomes and measures of BP variability reported by different trials, limiting which trials could be combined in meta-analysis. However, there were adequate trials to combine relationships for each measure and outcome.

In conclusion, variability in systolic and diastolic blood pressure is significantly associated with stroke, myocardial infarction and cardiovascular death, independently of age and mean BP. The relationship is clinically significant with >20% increased risk per SD of BP variability, providing an opportunity to significantly reduce the risk of cardiovascular events through appropriate choice of antihypertensives.

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CHAPTER THREE

Effects of antihypertensive drug class on consistency of control of blood pressure and risk of stroke: analysis of over 2 million readings in 244,479 participants

3.1 Summary

Inconsistent control of BP, manifest as visit-to-visit variability and episodic hypertension, is a risk factor for stroke. I have previously shown that antihypertensive drug classes differ in effects on the group distribution of BP but effects on stability of BP within individuals and factors that alter the magnitude of these effects are poorly understood.

Using fixed and random-effects meta-analysis of individual patient data (IPD) from 32 trials (244,479 participants), I calculated antihypertensive effects on the consistency of control of group mean BP (M-VR), the stability of control of BP from visit-to-visit within individuals (I-VR), and updated analyses of effects on the group distribution of BP at follow-up visits (G-VR). Differences between class effects on G-VR and stroke risk due to treatment duration, half-life and patient characteristics were determined.

Effects of treatment on I-VR and M-VR (r^2=0.90) explained effects on G-VR SBP (p<0.00001). Compared with other classes, calcium channel blockers (CCB) reduced I-VR, M-VR and G-VR (I-VR=0.89, 95% CI=0.82-0.96, p=0.0001; M-VR 0.83, 0.77-0.89, p<0.001; G-VR 0.81, 0.75-0.87, p<0.001) and diuretics reduced I-VR (0.86, 0.76-0.97, p=0.02), whereas I-VR, M-VR and G-VR were increased by ACE-inhibitors (1.15, 1.07-1.23, p<0.0001; 1.16, 1.02-1.33, p=0.03; 1.12, 1.02-1.22, p=0.02) and beta-blockers (1.25, 1.08-1.44, p=0.002; 1.17, 1.03-1.32, p=0.02; 1.25, 1.17-1.33, p=0.0001). Drug-class effects on G-VR (309 trials; 292,883 participants) were independent of half-life and indication and were greatest in the first year of follow-up (prior to add-on drugs), coinciding with the largest differences in stroke risk (CCBs versus non-diuretic drugs: OR=0.74, 0.65-0.85, p<0.0001).

Antihypertensive drug-classes differ in stability of control of BP within individuals (I-VR) and in consistency of control of mean BP between individuals (M-VR). Effects were consistent for patient groups and drug half-life, but were attenuated with prolonged treatment, probably due to the effect of add-on medications.

3.2 Introduction

Hypertension is a powerful independent risk factor for stroke and other vascular events,[1] and antihypertensive drugs are highly effective in their prevention.[2, 3] If lowering of blood pressure (BP) explains the benefits of antihypertensive drugs, it is likely that the consistency of lowering within and between individuals will also be important. Indeed, inconsistent control of BP, manifest as increased visit-to-visit variability in BP, high maximum BP and episodic hypertension, has been shown to be an independent risk factor for stroke,[4, 5] even when control of mean SBP during follow-up is good.

Two recent reports suggested that antihypertensive drug classes differ in their effects on variability in SBP, which correlated with differences in their effectiveness in preventing stroke.[6, 7] However, although one report showed differences in effects on within-individual variability in BP using individual patient data from two large randomised controlled trials (RCTs),[7] the majority of the evidence was based on a meta-analysis of data on effects of drug-class on the cross-sectional group distributions of BP during follow-up rather than on temporal variation within individuals.[6] Although the cross-sectional distribution of BP may be a good measure of the overall consistency of control of BP at the group level, it is a composite of two parameters that can only be measured with individual patient data: within-individual visit-to-visit variability in BP and between-individual differences in mean BP. To understand how current antihypertensive drugs differ in their control of BP, and to design new drugs to improve control, it is important to understand the determinants of consistency of control in individuals.

First, using all available individual patient data from RCTs of antihypertensive drugs, I aimed to determine drug class effects on within-individual visit-to-visit variability (I-VR) in BP, between-individual variation in control of mean BP (M-VR), and the resulting effect on group variation in BP at specific follow-up visits (G-VR). Second, given that reporting of group cross-sectional distribution of BP in trials of antihypertensive drugs eligible for my previous meta-analysis was relatively poor,[6, 8] I also aimed to update estimates of drug-

class effects on G-VR by more complete inclusion of trials in order to exclude any bias due to selective reporting and to determine influences of drug half-life, indication for treatment, and trial design (cross-over versus parallel group) on G-VR. Third, there are very high-rates of protocol-driven use of add-on drugs of different classes during early follow-up visits in many trials and Prof Rothwell previously observed that drug-class effects on variability in BP (I-VR and G-VR) in the MRC trial based on the initial randomised comparison diminished during follow-up.[7] I therefore determined the time-course of effects on BP variability during follow-up and related this to the time-course of effects on risk of stroke and other vascular events.

3.3 Methods

3.3.1 Data collection

Given the limitations of de-novo searches of bibliographic databases in identifying all eligible studies,[9] I identified RCTs from published systematic reviews. I searched the MEDLINE and Cochrane databases (1950 to week 1, July 2011) using combinations of the following search terms: [*meta(-)analysis*] AND [*antihypertensive agents* OR *blood-pressure lowering*].[10] Non-English language papers were included. The reference lists of all identified reviews and corresponding webtables were subsequently searched. For every trial fulfilling the inclusion criteria (table 3.1), the main results paper was reviewed. If this report did not fulfil the inclusion criteria, sub-studies were checked. A search for trials randomising >100 patients per treatment group for >1 year for the analysis of cardiovascular outcomes was replicated by a second person (Urs Fischer).

No trial reported intra-individual variability in blood pressure except for the two trials initially reported by Prof Rothwell.[5] Prof Rothwell therefore contacted the principal investigators of trials via the Blood Pressure Lowering Trialists' Collaboration (BPLTC) or directly if they were not involved in the BPLTC.[11] The following data were requested for each participant randomised in these trials: baseline clinical characteristics, all measurements of systolic and diastolic blood pressure at baseline and at each follow-up

visit (based on either a single measurement at each visit, or the mean of more than one measurement, as per the original trial protocol); all major vascular events that occurred during follow-up, including stroke (ischaemic, haemorrhagic or unknown), myocardial infarction, heart failure and cardiovascular death. For trials included in the BPLTC, definitions of outcomes have been reported previously.

Table 3.1 – Characteristics of included trials.

Inclusion Criteria

- Controlled trials, group allocation by randomisation, minimisation or similar
- Reported in peer-reviewed journal available in the British Library.
- Groups differ only by class of agent given or drug versus control.
- >2 weeks of follow-up.
- Any language.
- Reports number of patients and mean and standard deviation at both baseline and follow-up of either systolic or diastolic blood pressure.

Exclusion Criteria

- Trials requiring a recent acute cardiovascular event (within 3 months of a stroke, myocardial infarction or chest pain requiring intervention), to limit confounding by acute causes of increased BP variability that may be differentially affected by antihypertensive medications.
- Trials requiring patients with: active left ventricular failure (symptomatic or ejection fraction <40%), portal hypertension, severe liver disease, pulmonary hypertension, dialysis dependent renal failure, major life-limiting disease or disease causing significant functional impairment (excluding stroke more than 3 months prior to randomisation).
- Trials requiring a hypertensive 'crisis' at initiation of treatment.

3.3.2 Statistical analysis

The distribution of SBP at any given follow-up visit (group SD SBP) is determined partly by differences between individuals in their mean SBP (averaged across all visits) and partly to variability in SBP within individuals from visit to visit, each contributing in roughly 50:50 proportion to group SD SBP in cohorts with hypertension or previous TIA and stroke (excluding a small third component due to inter-individual variance in intra-individual variability).[5] Effects on either of these parameters could therefore explain effects of BP-lowering drugs on group SD SBP. For example, about 60% of the reduction in group SD SBP in the amlodipine versus atenolol arms of the ASCOT-BPLA trial was due to reduced within-individual visit-to-visit variability and about 40% was due to between-individual

variation in mean SBP.[7] In this study, I determined the effects of randomised treatment on group distribution of SBP and its two main component variables as follows:

1. The group distribution of SBP was expressed as the variance (SD^2) of the distribution of measurements taken at the follow-up visit closest to one year, to minimise the effects of add-on drugs. For each trial, I determined the ratio of the variances (group variance ratio; G-VR) between the different treatment groups. The 95% confidence interval of VR was generated from the F-distribution, and then the standard error was estimated from the logarithm of VR, assuming an approximately normal distribution given the large and usually equal group sizes.[12]

2. Mean SBP within individuals was calculated from measurements at all follow-up visits from 6 months onwards. Measurements taken at earlier follow-up visits were excluded because of the systematic fall in BP in the early phases of the trials due to initiation of treatment and dose titration. The effect of randomised treatment on the distribution of mean BP was expressed as the ratio of the variances of the distributions in the different treatment groups (mean variance ratio; M-VR). The confidence interval of I-VR was calculated as for G-VR.

3. Within-individual visit-to-visit variability in BP was also calculated from measurements at all follow-up visits from 6 months onwards. The effect of randomised treatment on within-individual visit-to-visit variability in BP was calculated using the square of the mean SD-BP for each treatment group, which was taken as the average within-individual variance and compared between treatment groups as the natural logarithm of the ratio of the within-individual variances (individual variance ratio; I-VR). The confidence interval of I-VR was calculated as for G-VR.

Since the majority of trials randomised patients to an initial drug class but added other drugs of different classes during later follow-up if initial control of BP was not optimal, I-VR and M-VR were also determined for follow-up visits from 6-24 months only, in order to

reduce contamination by effects of other drug-classes. All analyses were done by randomized treatment allocation on an intention-to-treat basis. The associations across all trials between G-VR, I-VR and M-VR were explored by univariate correlation and by multiple linear regression weighted by the size of the trial.

3.3.3 Meta-analyses by drug-class

Eight main drug-classes were defined as: placebo; dihydropyridine calcium channel blockers (CCB); non-dihydropyridine calcium channel blockers (CCBND); thiazide and thiazide-like (i.e. indapamide, xipamide and chlorthalidone) diuretics (Diuretic); angiotensin converting enzyme inhibitors (ACE); beta-blockers (BB); angiotensin receptor blockers (ARB); alpha-1 antagonists (AA).

I used random-effects meta-analysis (weighted by the inverse variance of G-VR) to obtain pooled estimates of effects of drug-class on G-VR, I-VR, and M-VR SBP and DBP. Analyses were done based on parameters derived from follow-up visits from 6-24 months and from 6 months until the end of the trial. Sensitivity analyses were also done excluding all measurements taken at follow-up visits after a major vascular event.

3.3.4 Expanded meta-analysis of drug-class effects on group BP variability

Having measured drug-class effects on M-VR and I-VR in the trials in which it was available, and determined the degree to which G-VR is determined by these two measures and therefore represents a global measure of consistency of blood pressure control, I further explored drug-class effects by combining the unpublished data from the newly available trials with the data from my previous systematic review.

Effects of treatment on variation in group BP were also quantified as G-VR at the follow-up visit closest to one year and also as the difference in the percentage change in coefficient of variation (SD/mean) from baseline. Pooled estimates and confidence intervals of the difference between treatment groups in change in CV were obtained by bootstrap methods.[6] Parallel-group and crossover-design trials were analysed together.

To identify determinants of differences between antihypertensive drug classes on consistency of control of SBP, a number of stratified meta-analyses of G-VR were performed. Firstly, to assess the effect of duration of treatment, and therefore the impact of add-on drugs, meta-analyses of G-VR and the risk of cardiovascular events were performed for each year after randomisation, where this information was available. Secondly, as drug half-life has been postulated as a cause of drug-class differences, meta-analyses of G-VR were performed for studies including comparisons between each class with drugs from other classes with shorter half lives or drugs from other classes with longer half lives. Thirdly, meta-analyses of G-VR were performed stratified by age (<55, 55-65, >65 years), baseline SBP (<140, 140-160, >160) or comorbidities.

All analyses were performed in SPSS 20.0 or Microsoft Excel 2007.

3.4 Findings

3.4.1 Drug class effects on cardiovascular outcomes

I determined the effects of antihypertensive drugs class on risk of vascular events during trial follow-up in trials for which IPD was available (table 3.2). Meta-analysis of comparisons of CCBs or diuretics with other drug-classes showed a significant reduction in risk of stroke (pooled OR=0.88, 0.82-0.94, p=0.0002) despite only a small reduction in group mean SBP (-1.3/0.6 mmHg), with little heterogeneity (p=0.34) between trials. There was also a significant reduction in cardiovascular mortality. Stroke risk was reduced both in comparisons against ACE inhibitors or ARBs and against beta-blockers (table 3.2), but ACE inhibitors and ARBs tended to be more effective in preventing myocardial infarction and heart failure.

3.4.2 Within-individual variability in BP

Individual BP patient data at baseline and during follow-up were available from 32 large RCTs (244,479 patients, appendix 1), including 45 randomised treatment comparisons. Figure 3.1 shows the effect of treatment on the average within-individual visit-to-visit variability in BP (I-VR) in each trial for all follow-up visits from 6 months until the end of the trial. There was a strong correlation between the effects of randomized treatment on I-VR SBP (from 6 months onwards) and G-VR SBP (at follow-up closest to one year) (all comparisons r^2=0.67 p<0.0001, drug vs drug: r^2=0.77, p<0.0001), but no significant relationship between I-VR and difference in mean SBP (r^2=0.08, p=0.06). Drug class effects on I-VR SBP were similar to those on G-VR in comparisons of drug vs drug and drug vs placebo (figure 3.2). Compared with other classes, I-VR SBP at 6-24 months follow-up was reduced on calcium channel blockers (CCB) (OR=0.89, 95% CI=0.82-0.96, p=0.004) and diuretics (0.86, 0.78-0.96, p=0.005) and increased on ACE-inhibitors (1.15, 1.07-1.23, p<0.0001) and beta-blockers (1.25, 1.08-1.44, p=0.002).

	Events / Patients randomised			Fixed Effects				Random Effects			ΔBP	
	Trl	**Group 1**	**Group 2**	**OR**	**95% CI**	**p-Val**	**p-Het**	**OR**	**95% CI**	**p-Val**	**SBP**	**DBP**
CCBs or diuretics vs all other drugs												
Stroke	23	2798 / 90800	2289 / 69667	**0.87**	(0.82 – 0.92)	<0.001	0.34	**0.88**	(0.82 – 0.94)	0.0002	-1.3	-0.6
MI	26	4440 / 91447	2869 / 70323	**0.98**	(0.93 – 1.03)	0.47	0.14	**0.99**	(0.92 – 1.07)	0.87	-1.4	-0.7
Heart Failure	16	3323 / 83577	2209 / 62347	**0.92**	(0.87 – 0.98)	0.005	<0.001	**1.04**	(0.87 – 1.24)	0.70	-1.2	-0.6
CV Mortality	19	3576 / 83091	2543 / 62604	**0.93**	(0.88 – 0.99)	0.014	0.41	**0.93**	(0.88 – 0.99)	0.02	-1.3	-0.6
Total Mortality	25	8406 / 35357	2188 / 35594	**0.97**	(0.93 – 1.00)	0.09	0.99	**0.97**	(0.93 – 1.00)	0.09	-1.3	-0.6
CCBs or diuretics vs RAS inhibitors												
Stroke	13	1794 / 40175	1235 / 25006	**0.90**	(0.83 – 0.98)	0.01	0.45	**0.90**	(0.83 – 0.98)	0.016	-1.1	-1.0
MI	15	2915 / 40590	1493 / 25436	**1.03**	(0.96 – 1.10)	0.45	0.14	**1.13**	(0.98 – 1.30)	0.10	-1.0	-0.9
Heart Failure	11	2322 / 39756	1252 / 24609	**1.04**	(0.97 – 1.12)	0.26	0.02	**1.10**	(0.98 – 1.24)	0.12	-1.1	-1.0
CV Mortality	10	2135 / 35738	1189 / 21240	**0.98**	(0.90 – 1.06)	0.57	0.67	**0.98**	(0.90 - .1.06)	0.57	-0.9	-1.0
Total Mortality	15	5073 / 40855	2998 / 26371	**0.98**	(0.93 – 1.04)	0.54	0.99	**0.98**	(0.93 – 1.04)	0.54	-1.1	-0.9
CCBs or diuretics vs Beta-blockers												
Stroke	9	653 / 35357	810 / 35594	**0.82**	(0.74 – 0.91)	0.0002	0.26	**0.83**	(0.72 – 0.97)	0.017	-1.1	-0.7
MI	10	917 / 35589	1011 / 35820	**0.90**	(0.81 – 0.98)	0.02	0.76	**0.90**	(0.81 – 0.98)	0.02	-1.1	-0.7
Heart Failure	4	417 / 28553	411 / 28671	**1.02**	(0.89 – 1.17)	0.20	0.02	**1.02**	(0.77 – 1.36)	0.89	-0.8	-0.7
CV Mortality	9	890 / 32085	977 / 32297	**0.91**	(0.83 – 1.00)	0.046	0.33	**0.91**	(0.81 – 1.02)	0.10	-1.2	-0.8
Total Mortality	10	2075 / 35357	2188 / 35594	**0.94**	(0.89 – 1.01)	0.08	0.90	**0.94**	(0.89 – 1.01)	0.08	-1.1	-0.6

Table 3.2. Results of fixed and random effects meta-analyses comparing incidence of major cardiovascular outcomes in patients randomised to drug classes that reduce SBP variability compared to other drug classes. p-Val = p-value for effect size; p-Het = p-value for heterogeneity; Trl = trials; CV = cardiovascular. Differences in mean BP are weighted by study size.

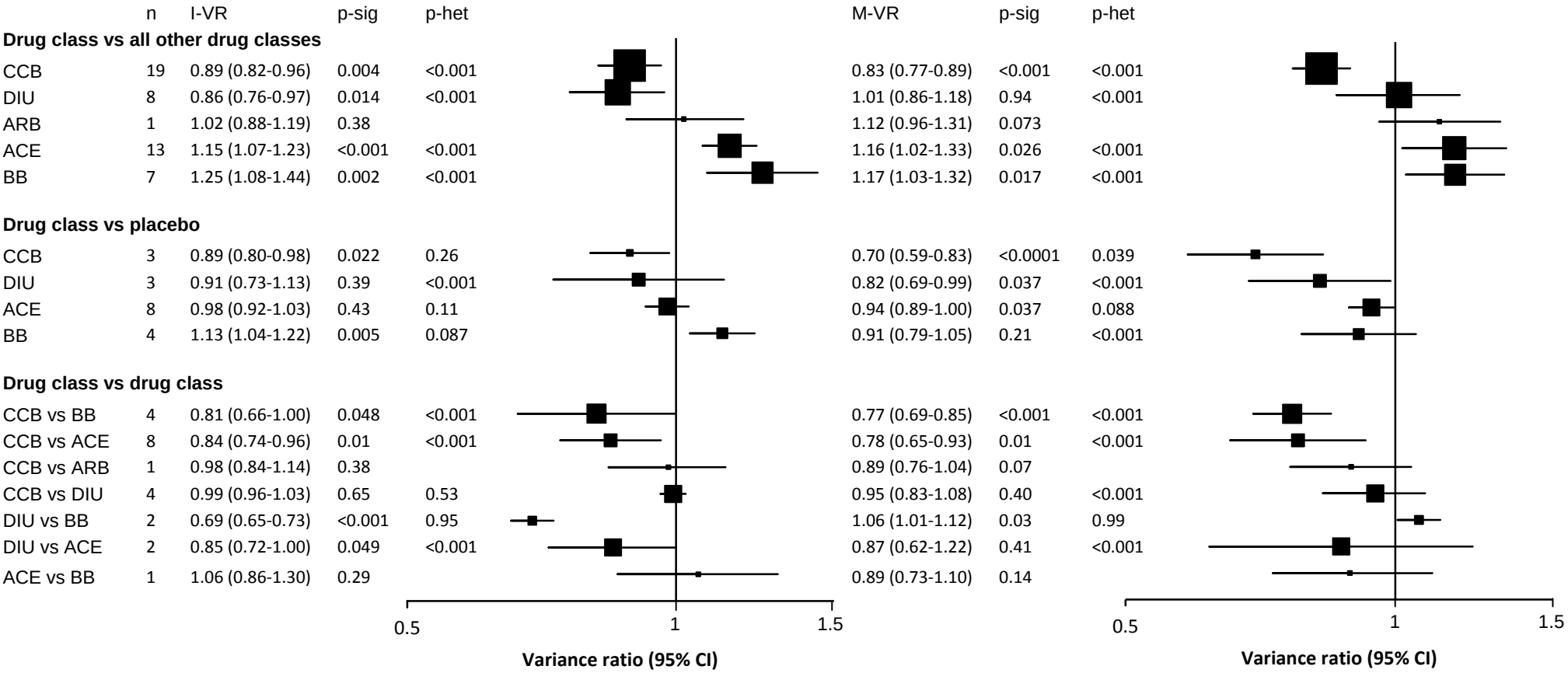


Figure 3.1. Effect of treatment allocation on within-individual variability of SBP (I-VR) and inter-individual variation in group mean SBP (M-VR) pooled by random-effects meta-analysis. Analyses are based on measurements from 6 to 24 months.

3.4.3 Between-individual variability in mean SBP

Figure 3.1 also shows the effect of treatment on the average between-individual variation in mean SBP (M-VR) in each trial. There was also a strong correlation between the effects of randomized treatment on M-VR SBP and G-VR SBP (r^2=0.80 p<0.0001, drug vs drug: r^2=0.78, p<0.0001), but no significant relationship between M-VR and difference in mean SBP (r^2=0.02, p=0.34). M-VR was reduced by CCBs (OR=0.83, 0.77-0.89, p<0.001) and increased on ACE-inhibitors (1.16, 1.02-1.33, p=0.03) and beta-blockers (1.17, 1.03-1.32, p=0.02), but was not reduced by diuretics.

Effects of randomised treatment on I-VR and M-VR were correlated (r^2=0.41 p<0.0001, drug vs drug: r^2=0.50, p<0.0001), reflecting the similarity in several drug-class effects. However, the effects of treatment were independently associated with G-VR in a combined model across all trials (I-VR - regression coefficients: I-VR = 0.411, p=0.004; M-VR =0.68, p<0.0001), the two variables accounting for almost of all of the heterogeneity in effect of randomised treatment on G-VR SBP (combined model: r^2=0.90, p<0.0001), with the small residual component being accounted for by between-individual variance in within-individual visit-to-visit variability.

3.4.4 Expanded meta-analysis of effects on group BP variability

Addition of data on G-VR in BP from 32 new trials increased inclusion in my systematic review from 32.1% to 63% of all patients randomised in eligible trials (Appendix 4). Meta-analysis of the effect of treatment showed clear drug-class effects on G-VR SBP (figure 3.2) and G-VR DBP (figure 3.3). Compared with other drugs, G-VR SBP was reduced by dihydropyridine or non-dihydropyridine CCBs and by diuretics but increased by beta-blockers, ACEI and ARBs. Equivalent analyses of group CV SBP rather than group SD SBP showed similar class effects (figure 3.2 and 3.3). The effects were similar in parallel group trials and cross-over trials, but the magnitude of the effect was greater in cross-over studies (figure 3.4), probably due to the lack of add-on medications.

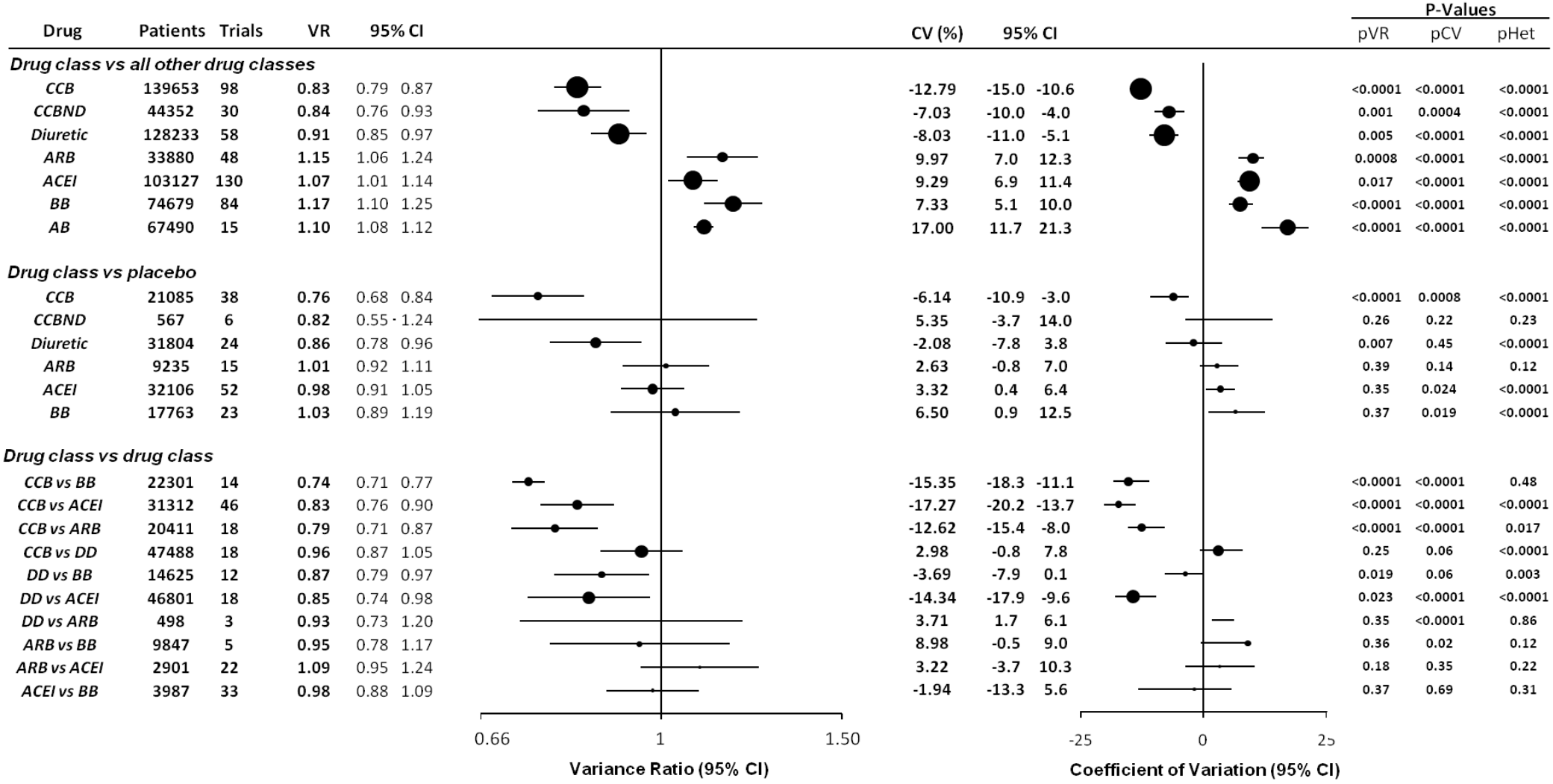


Figure 3.2 Pooled analyses of within-trial differences in group variation in SBP for each drug class versus either placebo, each other drug class, or all other drug classes combined. Comparisons are by either the ratio of variances (VR) between groups or the difference in percentage increase in coefficient of variation compared to baseline, with the VR comparisons pooled by random effects meta-analysis and the CV comparisons pooled by bootstrap methods. 'pHet' refers to heterogeneity as calculated in the random-effects meta-analysis.

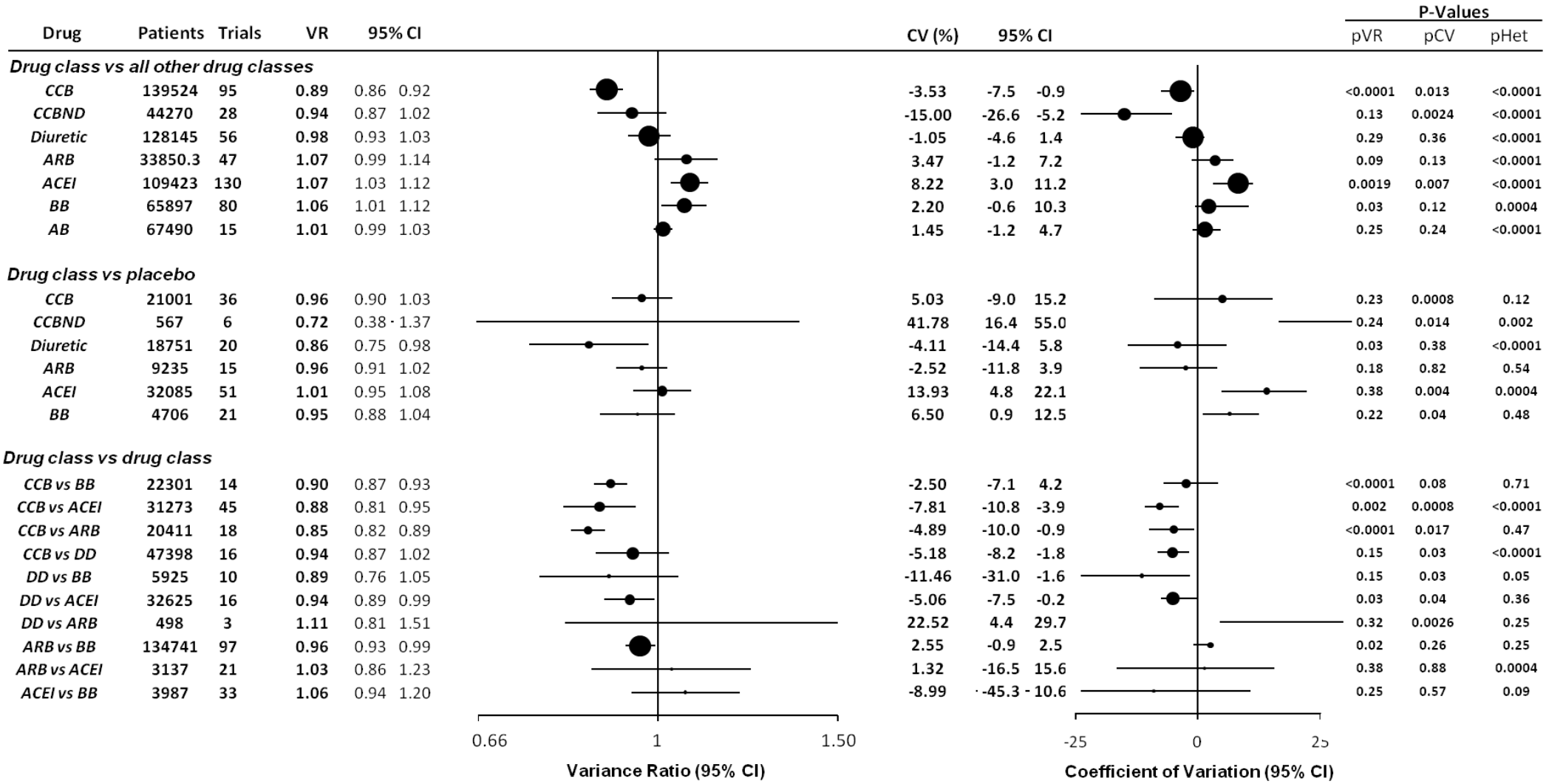
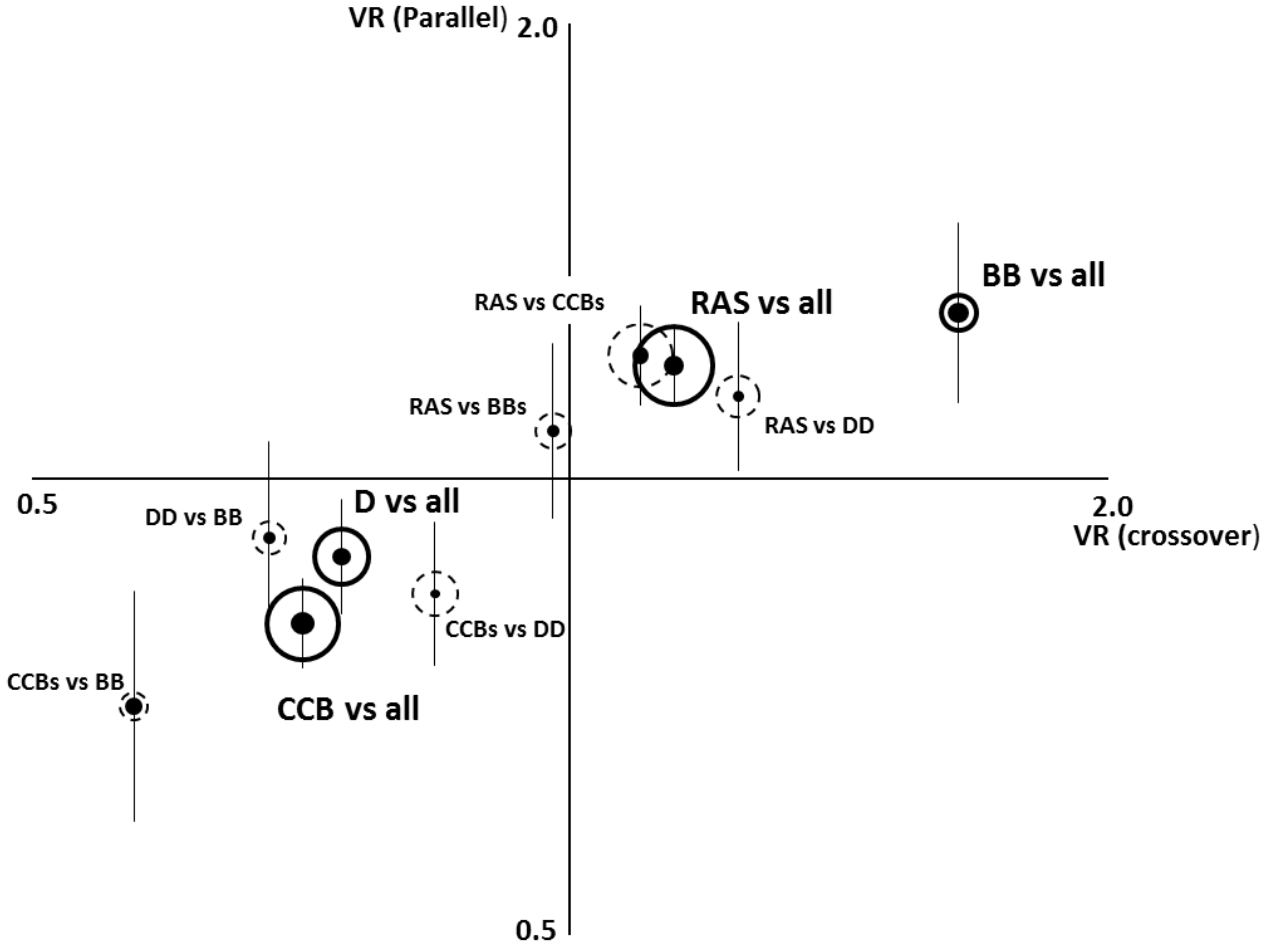


Figure 3.3 Pooled analyses of within-trial differences in group variation in DBP for each drug class versus either placebo, each other drug class, or all other drug classes combined. Comparisons are by either the ratio of variances (VR) between groups or the difference in percentage increase in coefficient of variation compared to baseline, with the VR comparisons pooled by random effects meta-analysis and the CV comparisons pooled by bootstrap methods. 'pHet' refers to heterogeneity as calculated in the random-effects meta-analysis

Figure 3.4 Relationship between meta-analyses of effect of randomised treatment allocation on G-VR (ratio of variances of group SBP on follow-up) from crossover-design trials versus parallel-group design trials. Dashed circles represent individual drug-class comparisons. Solid circles represent comparisons of each drug class with all other drug classes, excluding comparisons of CCBs with diuretics and beta-blockers with RAS inhibitors due to similar effects on variability. CCBs=calcium channel blockers; DD=diuretics; RAS=renin-angiotensin system inhibitors – ACEI and angiotensin receptor blockers; BB=beta-blockers.



3.4.5 Determinants of drug-class effects on group BP variability

Stratification of studies by whether the comparator drug had a longer or shorter half life demonstrated a similar magnitude of effect of drug class, independent of half-life (figure 3.5). Similarly, on stratifying studies by the characteristics of the population, there was no modification of drug-class effects on G-VR by year of publication, presence of renal disease, myocardial infarction or diabetes. Similarly, there was no significant effect of age or baseline SBP, despite a trend towards a greater reduction in G-VR with calcium channel blockers in young patients, and patients with higher baseline SBP (figure 3.6).

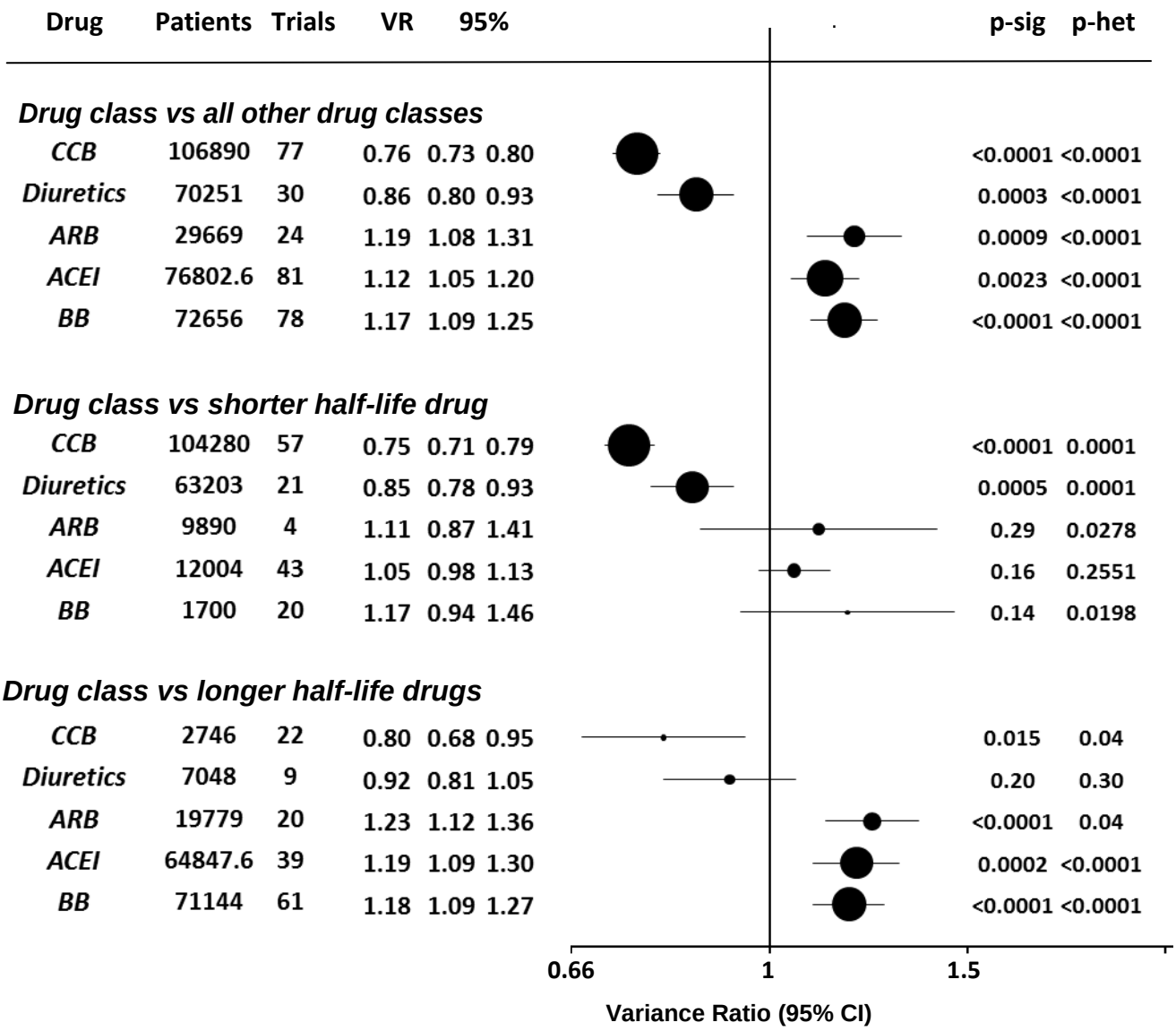


Figure 3.5 Random-effects meta-analysis of the effect of randomisation to each class of antihypertensive compared to all others on variability in SBP, stratified by the relative half-life of the drugs compared. Similar effects are seen for randomisation to each drug class compared to drugs of other classes with equal or longer half lives as for comparisons with drugs with equal or shorter half-lives. Comparisons of calcium channel blockers (CCBs) with diuretics and ACEI with angiotensin receptor blockers (ARBs) are excluded. BB= beta-blockers; pHet = p value for heterogeneity.

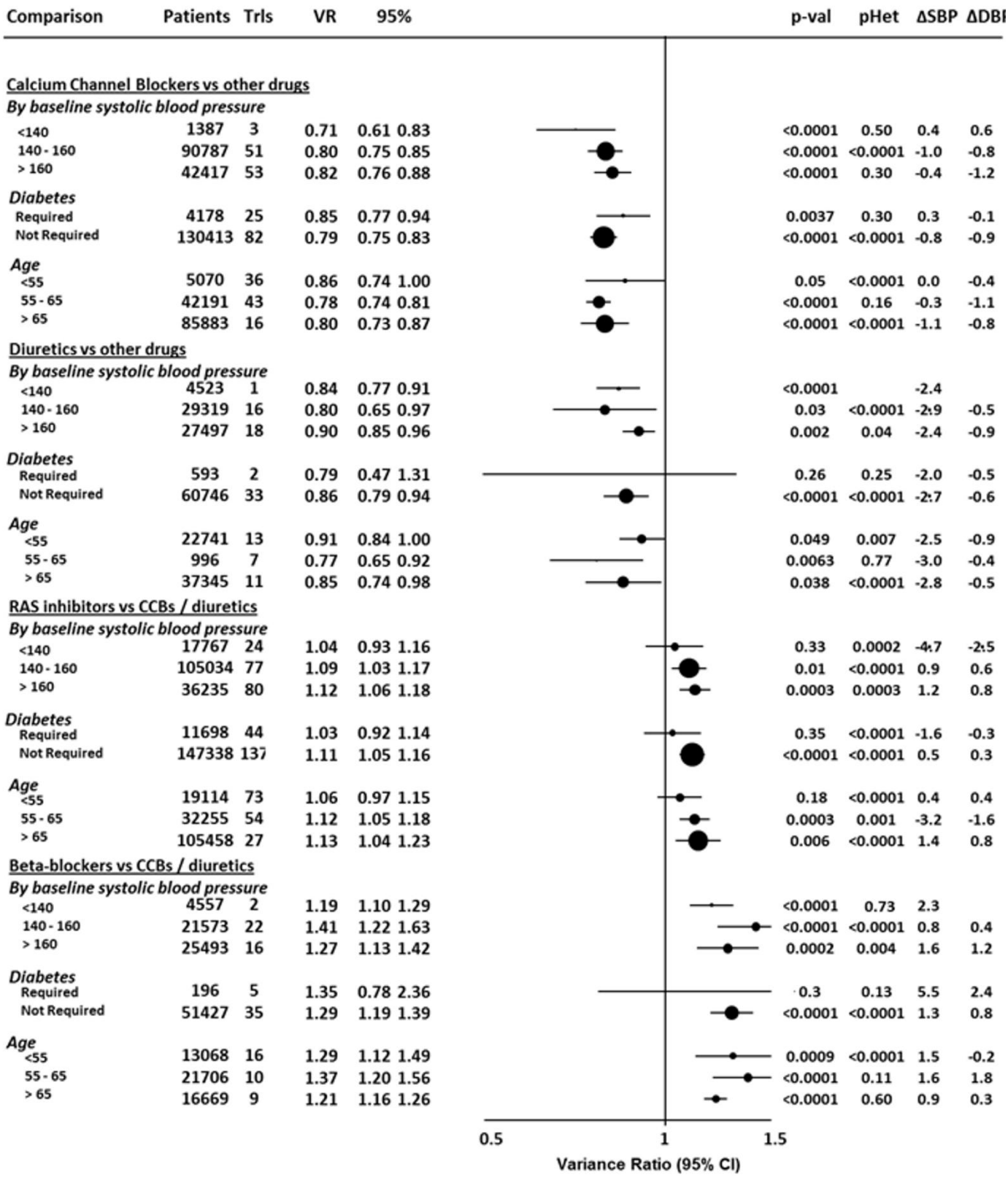


Figure 3.6 Random effects meta-analysis of the effect of randomisation to drug classes reducing variability in SBP compared to drug classes increasing variability in SBP, stratified by patient characteristics at baseline. Comparisons between CCBs and diuretics and between renin-angiotensin system (RAS) inhibitors and beta-blockers were excluded. P-val = p-value; pHet = p-value for heterogeneity; ΔSBP = difference between groups in mean SBP at follow-up; ΔDBP = difference between groups in mean DBP at follow-up; VRJ = variance ratio; Trls = trials

3.4.6 Effect of duration of treatment

Drug-class effects on G-VR SBP were greatest during the first year of follow-up (figure 3.7) compared to later years, prior to the initiation of multiple add-on drugs in most studies (Appendix 3), although effects were generally maintained until the end of the trials. Given that the effect of CCBs and diuretics on G-VR SBP was greatest during the first year of trial follow-up, I determined the effects on risk of stroke in year-one versus subsequent follow-up. For both classes of drugs independently and in combination, the reduction in stroke risk in direct comparisons with other classes was greater in year one than during later follow-up, with little heterogeneity across studies (table 3.3). Again, the reduction in stroke risk in year-one of direct comparisons of CCBs or diuretics versus other drug-classes was larger (OR=0.76, 0.68-0.84, p<0.0001) than expected on the basis of the 1.2/0.6 mmHg reduction in group mean BP.

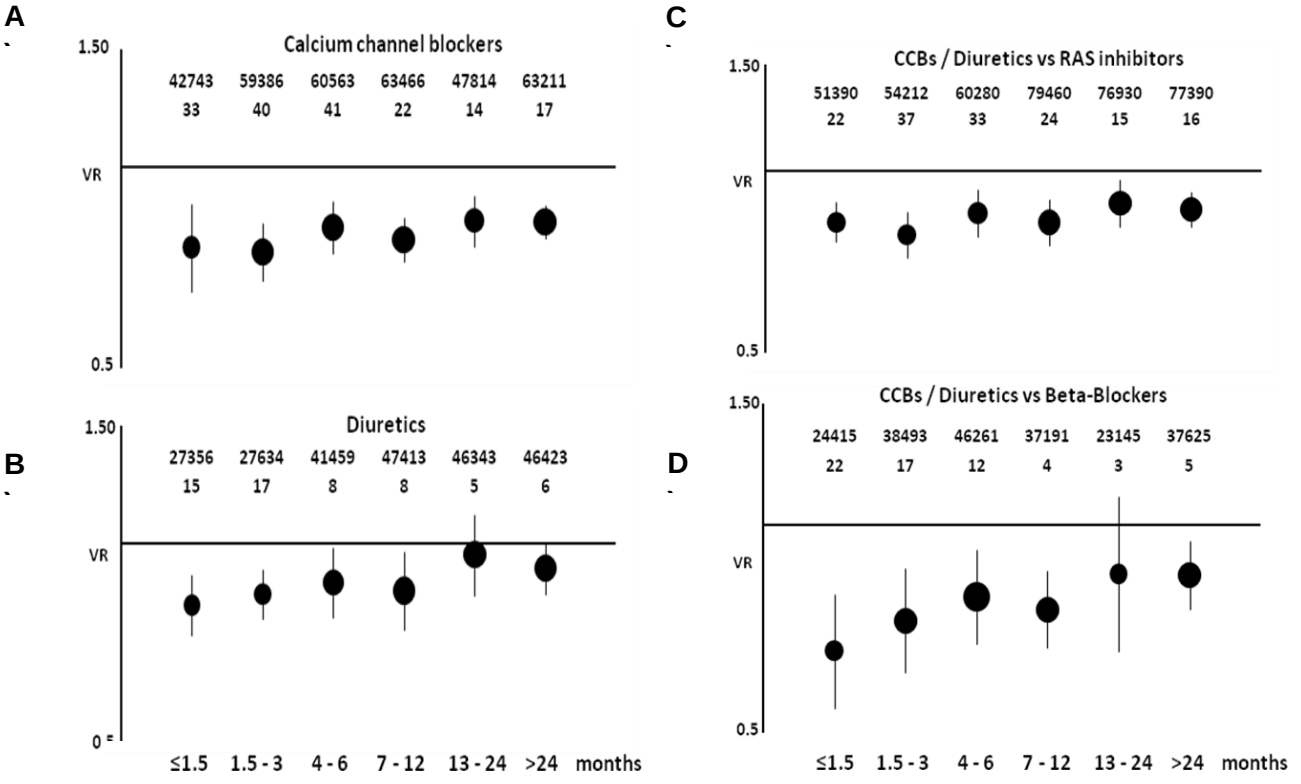


Figure 3.7. **Effect of randomisation to each class of antihypertensive on variability in SBP at different timepoints after randomisation.** In panels A and B, Calcium channel blockers (CCBs) and diuretics are compared to all other classes except each other respectively. In panels C and D, CCBs and diuretics combined are combined to RAS inhibitors and beta-blockers respectively. VR = variance ratio. Number of trials and number of patients at each timepoint are shown at the top of each panel.

	Events / Patient Yrs at risk			Fixed Effects Meta-Analysis					Random Effects Meta-Analysis				ΔBP	
	Trl	Group 1	Group 2	OR	95% CI	p-Val	p-Het	p-Int	OR	95% CI	p-Val	p-Int	SBP	DBP
CCBs or diuretics vs all other drugs														
Year 1	18	587 / 84452	728 / 77612	**0.76**	(0.68 – 0.84)	<0.001	0.63		**0.76**	(0.68 – 0.84)	<0.001		-1.23*	-0.56*
Years 2+	18	2210 / 290207	2350 / 266089	**0.91**	(0.85 – 0.96)	0.001	0.16	0.005	**0.92**	(0.85 – 0.99)	0.03	0.004	-0.43	-0.40*
All Years	18	2797 / 374658	3078 / 343701	**0.87**	(0.82 – 0.92)	<0.001	0.27		**0.88**	(0.82 – 0.93)	<0.001		-0.69	-0.45
CCBs vs all other drugs														
Year 1	13	359 / 55980	509 / 54644	**0.74**	(0.65 – 0.85)	<0.001	0.46		**0.74**	(0.65 – 0.85)	<0.001		-0.67	-0.69**
Years 2+	13	1405 / 179326	1695 / 179852	**0.90**	(0.84 – 0.97)	0.006	0.08	0.011	**0.94**	(0.84 – 1.04)	0.24	0.0097	0.11	-0.52*
All Years	13	1513 / 202831	1680 / 192274	**0.87**	(0.81 – 0.92)	<0.001	0.18		**0.88**	(0.81 – 0.96)	0.003		-0.12	-0.59*
Diuretics vs all other drugs														
Year 1	5	228 / 28472	219 / 22968	**0.78**	(0.64 – 0.94)	0.009	0.64		**0.78**	(0.64 – 0.94)	0.009		-2.75**	-0.58
Years 2+	5	805 / 110882	655 / 86238	**0.91**	(0.82 – 1.01)	0.08	0.51	0.15	**0.91**	(0.82 – 1.01)	0.075	0.15	-1.63*	-0.46
All Years	5	1033 / 139353	847 / 109206	**0.88**	(0.80 – 0.96)	0.005	0.43		**0.88**	(0.80 – 0.96)	0.005		-2.05**	-0.46
CCBs or diuretics vs RAS inhibitors														
Year 1	10	390 / 44398	319 / 29277	**0.77**	(0.66 – 0.89)	0.007	0.40		**0.77**	(0.65 – 0.91)	0.002		-1.28*	-0.75
Years 2+	10	1056 / 110301	1506 / 174036	**0.93**	(0.86 – 1.01)	0.07	0.59	0.03	**0.93**	(0.86 – 1.01)	0.07	0.047	-0.73	-0.49
All Years	10	1375 / 139578	1896 / 218434	**0.89**	(0.83 – 0.96)	0.0016	0.49		**0.89**	(0.83 – 0.96)	0.016		-0.90*	-0.59
CCBs or diuretics vs beta-blockers														
Year 1	5	137 / 31000	153 / 26763	**0.77**	(0.61 – 0.98)	0.03	0.28		**0.75**	(0.56 – 1.02)	0.07		-2.27*	-0.51
Years 2+	5	551 / 91973	598 / 83540	**0.85**	(0.75 – 0.95)	0.006	0.23	0.49	**0.87**	(0.74 – 1.03)	0.10	0.39	-0.60	-0.53
All Years	5	688 / 122973	751 / 110303	**0.83**	(0.74 – 0.92)	0.0004	0.34		**0.83**	(0.74 – 0.94)	0.002		-1.17	-0.49

Table 3.3 Results of fixed and random effects meta-analyses comparing drug class effects on incidence of stroke, stratified by effects during the first year of treatment compared to after the first year of treatment. p-Val = p-value for effect size; p-Het = p-value for heterogeneity; p-Int=p-value for interaction term between drug comparison and time period; difference in mean BP derived from random effects meta-analysis: * p<0.05 **p<0.001.

3.5 Discussion

If it is worth lowering BP, it is presumably worth doing it consistently, but there have been few studies of consistency of control of BP on antihypertensive drugs.[13] Indeed, until recently no trial had reported within-individual visit-to-visit variability in BP during follow-up by allocated treatment group. In Chapter 2, I showed that increased visit-to-visit variability in SBP is a powerful risk factor for stroke. Furthermore, in previous studies Prof Rothwell demonstrated that residual variability in SBP on treatment has a poor prognosis despite good control of mean SBP,[5] and I demonstrated that effects of antihypertensive drugs on risk of stroke appeared to be due partly to effects on variability in SBP.[6]

I have now substantially extended these previous observations of drug-class effects on variability in BP and risk of stroke. First, by adding new data on G-VR from 32 large trials (139,502 participants), I have increased inclusion from 32% to 64% of all patients randomised in eligible trials and thereby reduced any inclusion bias and increased statistical power. I have then shown that drug-class effects on G-VR were independent of drug half-life, indication for treatment, and baseline clinical characteristics.

Second, building on previous observations of drug-class effects on I-VR in two trials, I have confirmed that drug-classes differ in effects on consistency of control of BP within individuals (I-VR) using IPD from 32 trials (244,479 patients), and showed that they also differ in the consistency of control of mean BP (M-VR), resulting together in substantial differences between classes for group variability in SBP (G-VR).

Finally, I showed that drug-class effects on G-VR were greatest in short-term cross-over trials and that effects on consistency of control of BP and on stroke risk decreased in the same way during follow-up in larger parallel group trials, as was found previously in the VALUE study of CCBs versus ARBs, although the cause of this was not specifically addressed.[14] Indeed, drug-class effects on consistency of control of BP in large pragmatic parallel group design trials would be expected to be rapidly diluted in this way by the substantial protocol-driven use of add-on drugs of different classes during early follow-up. For example, in both INVEST[15] and ASCOT-BPLA,[16] an ACE inhibitor was added in the CCB arms and a diuretic was added to the beta-blocker arms. The frequent measurement of the BP-response to treatment during early follow-up and the low-threshold for

starting add-on drugs if any measurement is above target in many large trials does not necessarily reflect how hypertension is managed in routine clinical practice. Although it is possible that some of the observed diminution of the drug-class effects on consistency of control with increasing follow-up was due in part to physiological adaptation, the class effects in cross-over trials and in the first year of follow-up in the large parallel group trials are likely to provide the best estimates of effects of monotherapy for hypertension in routine practice. Nevertheless, drug-class effects on consistency of control of BP were still present at the end of trials and class-effects on stroke risk were present in analyses including all follow-up.

Although the most important barriers to effective control of BP are still the widespread under-diagnosis and under-treatment of hypertension,[17, 18] these findings have significant clinical implications. First, in relation to the choice of first-line BP-lowering drugs, I have shown that the consistency of control of BP is better, on average, on CCBs and diuretics than on ACE inhibitors, ARBs, or beta-blockers, and that this is associated with a reduced risk of stroke. CCBs and diuretics were also associated with a lower risk of cardiovascular death, although this effect was mainly driven by comparison with beta-blockers. ACE inhibitors and ARBs were less effective than CCBs and diuretics in preventing stroke, but were at least as good in preventing myocardial infarction and heart failure. It is likely therefore that the optimal first-line agent in treatment of hypertension will depend on the relative risk of stroke versus coronary events in the particular population (the relative risk varies several fold across the world)[19] or individual. Second, these findings show that the development of new BP-lowering drugs or new formulations should target consistency of control of BP as well as the reduction in group mean BP. Third, combination of drugs in routine practice and the formulation of fixed-dose combinations should also maximise consistency of control of BP. Fourth, contrary to some recent recommendations,[20] regular follow-up of patients on treatment for hypertension may be justified in order to identify and treat inconsistent control of BP. Finally, reporting of future randomised trials should include measures of within and between-individual consistency of control of BP as well as data on group mean BP.

Previous analyses and guidelines on choice of BP-lowering drugs have highlighted possible advantages of CCBs in preventing stroke, but have generally concluded that all classes of BP-

lowering drugs are similarly effective.[3, 21] However, most previous meta-analyses of trials comparing different drug-classes only determined effects of each drug-class versus all others combined (i.e. included trials randomising to CCBs versus diuretics). By grouping drug-classes in relation to their effects on consistency of control of BP, I have identified differences in effects on risk of stroke. For diuretics, the greater reduction in stroke risk than with other classes will also have been partly accounted for by the greater reduction in group mean BP, but this was not the case for CCBs. Moreover, if class effects were explained by effects on group mean BP then they would also be evident for heart failure and MI. Previous analyses have also not considered the possibility that drug-class effects might decrease over time due to substantial use of add-on drugs of different classes, obscuring specific drug class effects in previous meta-analyses.

These analyses do nevertheless have shortcomings. First, meta-analysis and interpretation of within-trial comparisons of variability in BP is not straightforward.[6] However, the previous finding that group SD SBP at follow-up visits was attributable in roughly 50:50 proportion to within-individual visit-to-visit variability (I-VR) and to between-individual variation in mean SBP (M-VR)[6] has been borne out. Second, the extent to which BP measured on clinic visits in clinical trials reflects overall day-to-day control is uncertain. However, the same limitation applies to both mean BP and to variability, and in chapter 2, within-individual variability in BP was a risk factor for stroke whether measured over a few days at home, or over several clinic visits. Moreover, the same drug-class effects on visit-to-visit variability in BP in the ASCOT-BPLA trial were also present for short-term variability on repeated measurements during single clinic visits and in the large substudy of 24-hour ABPM.[7] Third, more research is required to understand the drug-class effects on M-VR. Also, by using IPD from many trials I have been able to exclude potential artefacts, such as secondary changes in patterns of BP following non-fatal events during early follow-up. Furthermore, by stratifying the meta-analysis of drug-class effects on G-VR, I have demonstrated that effects are unlikely to significantly differ by disease status or age of the population. Fourth, data from some large trials are still unavailable for the meta-analysis of drug-class effects on G-VR. However, these are mainly trials of ACE inhibitors or ARBs and inclusion of large trials of CCBs and diuretics is more complete. Finally, although the effect of drug-class on consistency of control of BP was again correlated with effectiveness in prevention of

stroke, this is not proof of a causal link. However, if reducing mean BP reduces risk of stroke then it is likely that reducing BP consistently will also be beneficial.

Chapters 2 and 3 present post hoc analyses of observational cohorts and randomised controlled trials rather than prospective tests of the hypothesis that BP variability is related to the risk of stroke and that its reduction by some antihypertensive drug classes results in a reduction in the subsequent risk of stroke. This hypothesis would ideally be tested in new randomised trials but these would require very large samples with >10,000 patients with prolonged follow-up. Even if these can be carried out, such studies would primarily test the efficacy of different antihypertensive classes in preventing cardiovascular events, with BP variability measured as a secondary measure, as no intervention specifically reduces BP variability without other physiological effects. However, previous studies have already compared the relative efficacy of antihypertensives in a wide-range of populations, albeit without reference to BP varaibility. Therefore, given the large number of patients included, the wide variety of studies and the fact that no study recognised BP variability as a potentially important outcome at the beginning, these analyses are as reliable as can reasonably be achieved to base management decisions upon, and the best evidence available in the absence of new prospective studies. Therefore, in patients with increased BP variability or an increased risk of stroke, and where there is no compelling indication for an alternative medication, then an antihypertensive regimen containing a calcium channel blocker or a diuretic should be preferred to reduce stroke risk.

In conclusion, antihypertensive drug-classes differ in consistency of control of BP within and between individuals. In prevention of stroke in people with hypertension, we should aim for stabilisation of BP as well as lowering of mean BP.

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CHAPTER FOUR

Effects of antihypertensive treatment on headache and blood pressure variability

4.1 Summary

Antihypertensive drugs reduce headache but it is unclear whether there are differences between drug-classes. Calcium channel blockers (CCBs) decrease variability in systolic blood pressure (SBP) and stroke risk more than other classes, possibly due to decreased vascular tone. If so, there might be a correlation between drug class effects on variability in SBP and on headache. I determined antihypertensive class effects on variability in SBP and headache during follow-up in a systematic review of randomised controlled trials. I determined pooled estimates of treatment effect on group variability in BP and on the odds ratio for headache (OR) by random-effects meta-analysis.

Antihypertensive drugs reduced the incidence of headache compared to placebo (OR=0.75, 95%CI 0.69-0.82, p<0.0001, 198 comparisons, 43672 patients), but there was significant heterogeneity between drug classes (p=0.0007) with a greater effect of beta-blockers compared to placebo (VR=0.49, 0.33-0.68, p<0.0001, 16 trials) or all other drug classes (OR=0.73, 0.62-0.85, p=0.0002, 49 trials) and a lack of effectiveness of CCBs (vs placebo-OR=0.95, 0.79-1.15, 65 trials; vs other drugs-OR=1.19, 1.05-1.35, p=0.009, 101 trials). Drug class effects on headache were opposite to effects on variability in SBP (vs other drugs: CCB-VR=0.81, 0.71-0.85, p<0.0001; beta-blocker VR=1.17, 1.07-1.28, p<0.0001), but were unrelated to differences in mean SBP.

Antihypertensive drugs reduce headache but the effect differs between classes, corresponding to their effects on variability in SBP and the risk of stroke. This may partly be explained by consistent antihypertensive class effects on vascular tone in the peripheral (variability) and cerebrovascular circulations (headache).

4.2 Introduction

As shown in chapters 2 and 3, patients' with episodic hypertension have a high risk of stroke,[1,2] residual visit-to-visit variability in blood pressure (BP) on treatment has a poor prognosis despite good control of mean BP,[1,2] and benefits of some antihypertensive drugs in the prevention of stroke are strongly associated with reduced variability in SBP.[3,4] Variability in SBP is reduced by calcium channel blockers (CCBs) and by diuretics and increased by beta-blockers (BB), explaining class differences in effects on risk of stroke in randomized controlled trials (RCTs).[3,4] Furthermore, variability in SBP and risk of stroke is increased more by non-selective beta-blockers such as propranolol than by β1-selective beta-blockers.[5] The strength of these associations, the dose-response relationships[6] and the temporal relationship suggests that variability in SBP may be a causative risk factor for stroke. However, an alternative hypothesis is that mean SBP-independent effects of antihypertensive agents on the risk of stroke may reflect strongly correlated effects on other physiological parameters, particularly effects on cerebrovascular tone. Unfortunately, there are very few studies of the effects of antihypertensive drugs on the cerebrovascular circulation and these are mostly non-randomised studies in acute stroke, which are insufficient to draw conclusions regarding class effects.[7] However, effects of antihypertensive drug classes on incidence of headache are commonly reported in RCTs and differences in headache incidence in these studies may reflect effects on the cerebrovascular circulation, given that headaches are caused by cerebral vasodilating drugs such as nitrates and reduced by drugs known to cause vasoconstriction such as triptans.

A meta-analysis of only 4 classes of antihypertensive agents demonstrated that all of these classes reduced the incidence of headache compared to placebo in randomised controlled trials.[8] However, there were no significant differences between antihypertensive classes in the magnitude of effect on headache, leading the authors to conclude that blood-pressure lowering alone was the cause of the reduction in headache. The authors therefore

suggested that hypertension might cause headache, although this was not consistent with large observational studies.[9] Furthermore, antihypertensive classes were not directly compared with each other, the size of effect was only very weakly related to the degree of blood pressure reduction and the authors did not examine the effect of calcium channel blockers. Differences between antihypertensive classes on the incidence of headache independent of the effect on mean SBP would challenge the conclusion that blood-pressure lowering alone reduced the incidence of headache. Furthermore, if incidence of headache was correlated with variability in SBP, drug-class effects on headache, variability in SBP and risk of stroke might be partly explained by consistent effects on vascular tone in the peripheral (variability) and cerebrovascular circulations (headache).

Therefore, I did a systematic review to determine the effect of all major classes of antihypertensive drugs on the risk of headache compared to placebo and other drug classes and to assess how these effects relate to effects on mean and variability in SBP.

4.3 Methods

4.3.1 Search Strategy

I searched the MEDLINE and Cochrane databases (1950 to week 1, July 2009) using combinations of the following search terms: (“*meta(-)analysis”)* AND (“*antihypertensive”* OR “*blood(-) pressure lowering”)* as described in chapter 3. Non-English language papers were included. The reference lists of all identified reviews and corresponding webtables were subsequently searched for trials randomising patients to one antihypertensive drug compared to placebo or another antihypertensive class. In addition, a secondary search was performed to identify trials comparing non-selective and selective beta-blockers with the terms (Trial) AND ("blood-pressure lowering" OR "antihypertensive" OR "blood pressure lowering") AND ("*specific beta-blocker name*"), where each beta-blocker was searched for in turn. For every trial fulfilling the inclusion criteria the main results paper was reviewed. The definition and frequency of headache and mean (SD) BP at baseline and at all follow-up visits were extracted where reported for all patient groups.

4.3.2 Analysis

Within-trial differences between treatment groups in the incidence of headache were compared by odds ratios (OR) whilst inter-individual variance (SD^2) in SBP and DBP was expressed as the ratio of the variances (VR). Pooled estimates were obtained by random effects meta-analysis using Mantel-Haenszel methods weighted by the inverse variance. All analyses were based upon the group allocated to the highest dose of each drug within each trial, and the mean (SD) BP at the visit closest to 1 year of follow-up was used in all VR analyses. Sensitivity analyses were performed for trials lasting 26 weeks or less, and for trials reporting either new-onset or 'possibly drug-related' headaches. Trials reporting the number of patients withdrawn due to headache without the total number of patients experiencing headache were excluded.

Pooled analyses were performed for each drug class compared to either placebo or to all other drug classes combined. The drug classes included were calcium channel blockers (CCBs), ACE inhibitors (ACEI), angiotensin-receptor blockers (ARBs), beta-blockers (BB) and diuretics (thiazide and thiazide-like). In further analyses, BBs were subdivided into non-selective and β1-selective classes and CCBs were subdivided into dihydropyridine and non-dihydropyridine classes. For each comparison, pooled estimates were calculated by random effects meta-analysis of OR for headache, VR for SBP and DBP and difference in mean SBP and DBP for all trials in which sufficient information was presented. In addition, the difference in mean SBP and DBP weighted by trial size was calculated.

4.4 Findings

4.4.1 Data collection

Trial reports were identified from the same 255 meta-analyses as described in chapter 3, which generated 1858 citations to independent trials, resulting in 1372 eligible trials after review of all abstracts and papers. Of these 1372 trials, there were 355

comparisons reporting the incidence of headache for patients randomised to one drug class versus either placebo or another class, from 242 trial reports. In addition, there were 6 comparisons between non-selective and β1-selective beta-blockers from the additional search. Of these 361 comparisons, 229 reported SBP at follow-up by treatment group and 77 reported SD-SBP, allowing meta-analysis of VR-SBP and difference in SBP. Across all 1372 trials, there were 361 within-trial comparisons between treatment groups from 293 trial reports reporting SBP and SD-SBP at follow-up.

4.4.2 Effect of drug class on the incidence of headache versus placebo

Randomisation to any drug class compared to placebo was associated with a decreased risk of headache during follow up in all studies (OR=0.75, 95% CI 0.69-0.82, p<0.0001, p-heterogeneity=0.003, 198 comparisons, 36651 patients), including studies only reporting new-onset or 'drug-related' headache (OR=0.79, 0.66-0.96, p=0.02, 55 comps, 11628 pts). There was significant heterogeneity across the five drug classes (χ^2=21.3, df=5, p=0.0007). Beta-blockers reduced the incidence of headache the most (OR=0.47, 0.33-0.68, 16 comparisons, 1916 patients, p=0.0001) whilst CCBs did not significantly reduce the incidence of headache (OR=0.95, 0.79-1.15, 65 comparisons, 9291 patients, p=0.35). The other drug classes reduced headache to an intermediate degree (see figure 5.1) in spite of similar reductions in mean SBP compared to CCBs and beta-blockers.

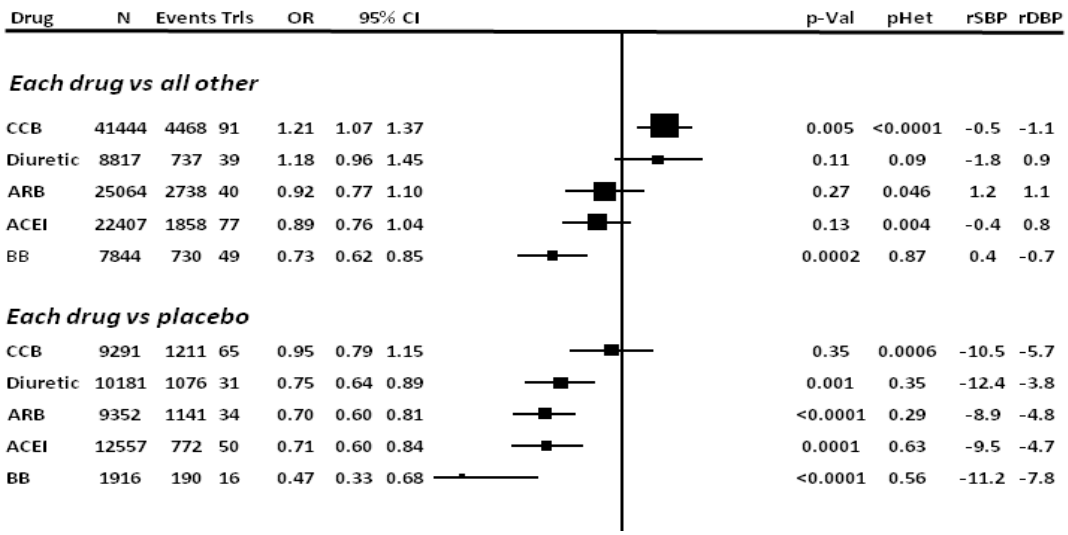

Figure 4.1 Effect of class of antihypertensive agent on incidence of headache compared to other antihypertensive classes or placebo. OR and reduction in mean SBP are pooled by random-effects meta-analysis, with 95% confidence intervals. *Trls* – trials; *rSBP/rDBP* - reduction in systolic or diastolic mean blood pressure.

4.4.2 Effect of drug class on the incidence of headache versus other drugs

There was significant heterogeneity in comparisons of drug class versus drug class (χ^2=475, df=313, p<0.0001). Baseline SBP, average age, proportion of men and year of publication explained only 9% of this heterogeneity whilst allocated drug class explained 24% of the remaining heterogeneity. The pattern of effect of drug class on incidence of headache in comparison to all other classes was the same as comparisons with placebo (figure 4.1). Beta-blockers reduced the incidence of headache compared to other classes whilst CCBs increased the incidence of headache, despite only minimal differences in mean BP. The pattern of effect was unchanged when limiting the analysis to trials of 26 weeks or less and in trials reporting the incidence of new-onset or possibly treatment-related headache. There were insufficient cross-over design studies to allow for within-patient comparisons by drug class.

There was no significant difference between non-selective and selective beta-blockers in direct comparisons with each other (OR=1.13, 0.83-1.54, 6 trials, 1810 patients, p=0.19) or in comparison to all other drugs (non-selective OR=0.68, 0.46-1.00, 9 trials, 1228 pts, p=0.06; selective OR=0.74, 0.61-0.88, 40 trials, 6616 pts, p=0.001). There was a slightly greater incidence of headache with non-dihydropyridine CCBs (verapamil or diltiazem) compared to other drugs than with dihydropyridine CCBs, and there was heterogeneity amongst non-dihydropyridine CCBs compared to other drugs (p<0.0001) and compared to placebo (p=0.001). This heterogeneity was due to a reduction in incidence of headache with amlodipine compared both to other drug classes (OR=0.82, 0.75-0.89, 24 trials, 19488 patients, p<0.0001) and compared to placebo (OR=0.61, 0.48-0.78, 13 trials, 2750 patients, p=0.0001), whilst there was a consistent increase in headache with other non-dihydropyridine CCBs (figure 5.2). However, excluding amlodipine from all comparisons did not significantly affect the results.

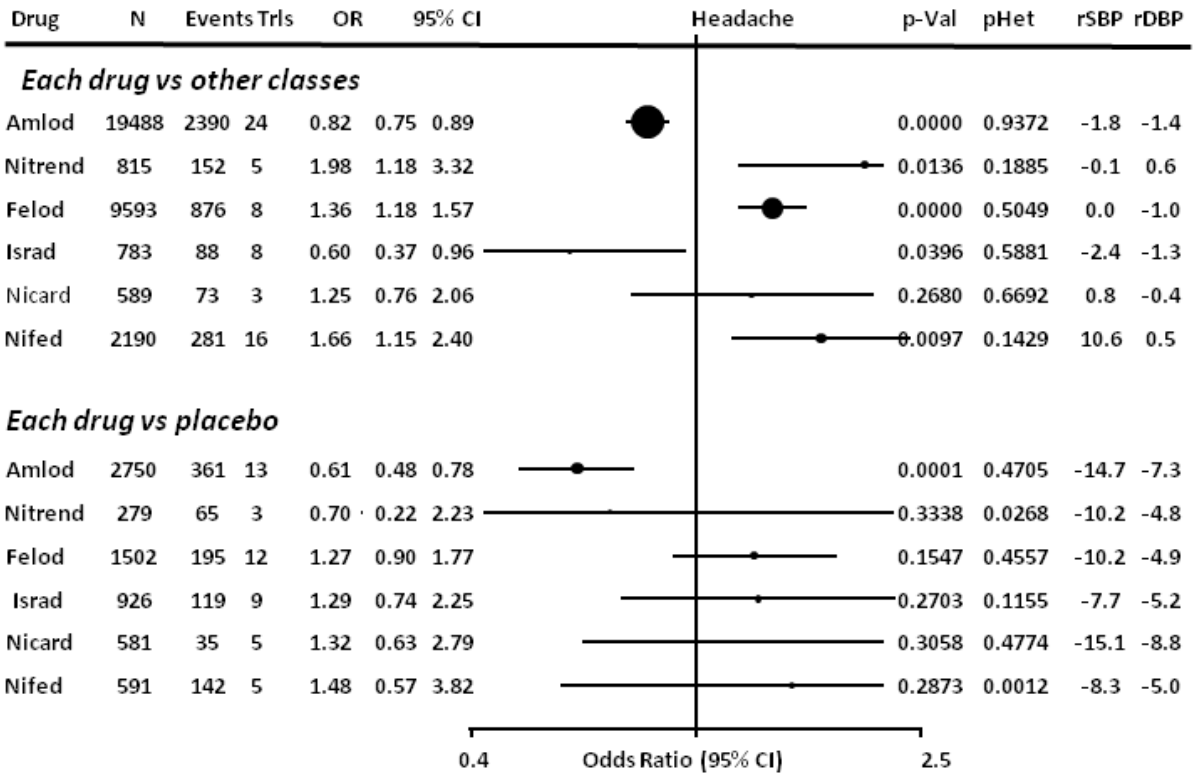

Figure 4.2 Effect of each dihydropyridine calcium channel blocker on incidence of headache compared to other antihypertensive classes or placebo. Each drug is abbreviated by removal of '-ipine.' OR and reduction in mean SBP are pooled by random-effects meta-analysis, with 95% confidence intervals. *Trls* – trials; *rSBP/rDBP* - reduction in systolic or diastolic mean blood pressure.

4.4.4 Effect of drug class on blood pressure variability

As reported in chapter 3, there were significant differences between drug classes in effects on variability in SBP compared to either placebo or all other drug classes (figure 3.1) across 361 trials comparisons, but in the opposite direction to the effect on headache. Variability in SBP was reduced most by CCBs, reduced less by diuretics, and increased by randomisation to a beta-blocker, compared to all other drugs or placebo. These effects were not explicable on the basis of differences in mean SBP. Despite the differential effect of amlodipine on headache compared to other CCBs, amlodipine still reduced variability in SBP compared to other drugs (VR=0.76, 0.72-0.82, p<0.0001) or placebo (VR=0.75, 0.66-0.84, p<0.0001) and excluding amlodipine from all comparisons did not significantly affect the results. The same pattern of effect was seen in the 77 comparisons for which both

incidence of headache and variability in SBP were reported. In these comparisons, CCBs reduced variability in SBP compared to all other drugs (VR=0.77, 0.74-0.80, p<0.0001, change in SBP=+3.54mmHg, 33 comparisons, 4698 patients) and in comparison to placebo (VR=0.66, 0.47-0.81, p=0.0273, change in SBP=-9.79mmHg, 10 comparisons, 1211 patients) whilst beta-blockers increased variability in SBP compared to other drugs, although this did not reach statistical significance due to the smaller number of patients (VR=1.25, 0.89-1.28, change in SBP=+0.91mmHg, 18 comparisons, 730 patients). There was no significant difference between drug classes in effects on mean SBP but there was a consistent relationship between effects on variability in SBP and incidence of headache in the meta-analyses versus placebo compared to the meta-analyses versus other drug classes (figure 4.3).

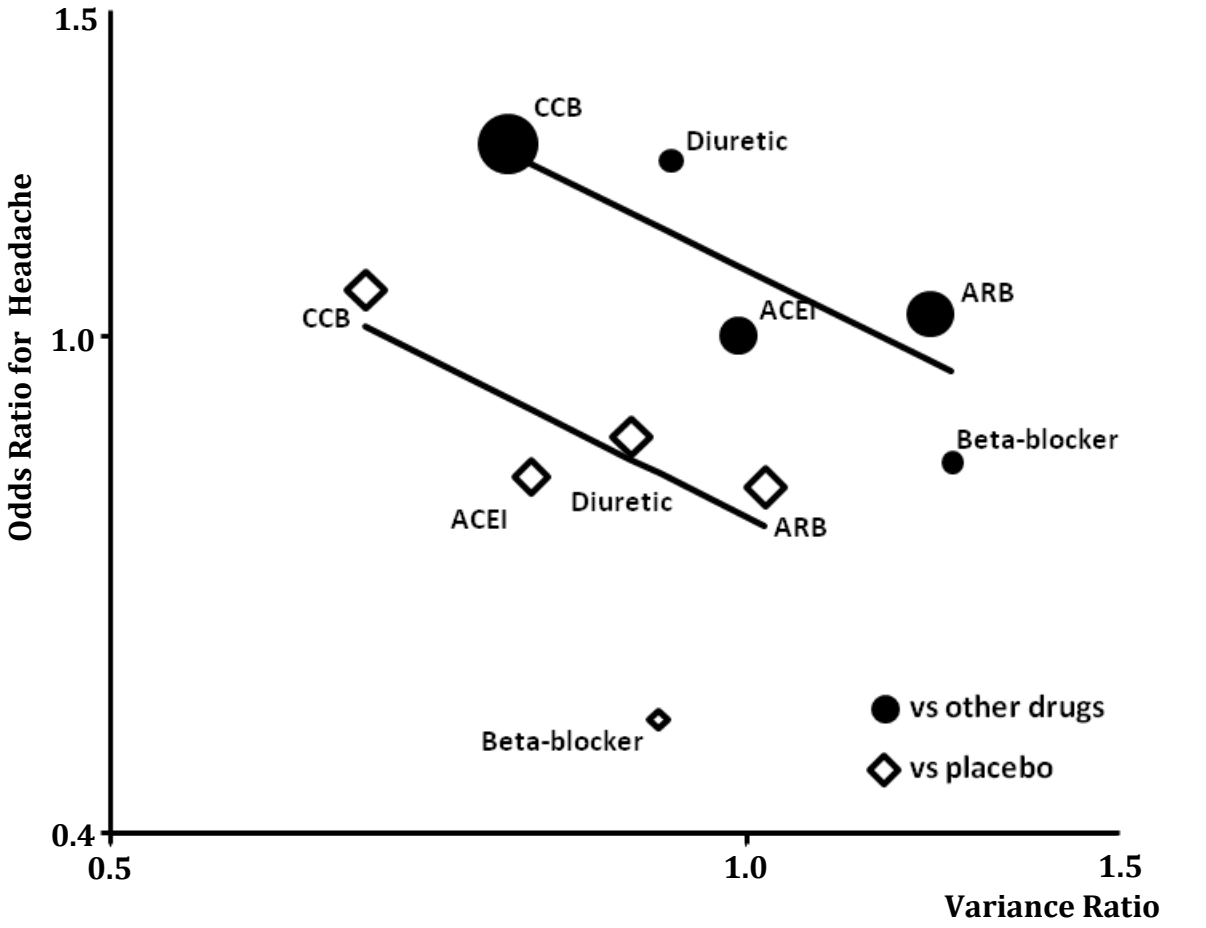

Figure 4.3 Relationship between variability in systolic blood pressure and incidence of headache in all trials reporting both measures, according to drug class. Each point is a plot of random effects meta-analyses for variance ratio for systolic blood pressure against odds ratio for headache comparing each drug class against either placebo or against all other drug classes. Illustrative linear regressions for each of these types of comparison are shown, weighted by the inverse variance of the odds ratio. CCB=calcium channel blocker; ARB=angiotensin receptor

4.5 Discussion

This is the largest meta-analysis of the occurrence of headache in RCTs of antihypertensive medications, including 248 trials compared to only 94 trials in the largest previous meta-analysis,[8] and is the first meta-analysis to compare all antihypertensive drug classes with each other. I showed that randomisation to antihypertensive medication reduced the incidence of headache compared to placebo but there were significant differences in the magnitude of effect between drug classes, independent of effects on mean SBP. Beta-blockers reduced headache more than other classes both in comparison to placebo and in comparisons with other classes, whilst CCBs did not reduce headache compared to placebo and increased headache compared to other drug classes. These drug class effects were not related to effects on mean SBP or DBP, but were opposite to the effect of each drug class on inter-individual variability in SBP.

The existence of a causal relationship between hypertension and headache is controversial, with observational studies producing conflicting results.[9-12] It is clear that some antihypertensive drugs are effective prophylactic agents in migraine, including beta-blockers,[13] non-dihydropyridine calcium channel blockers[14] and angiotensin receptor blockers.[15] A recent meta-analysis demonstrated that four of the main antihypertensive classes reduced the incidence of non-specific headache to a similar degree and concluded that the reduction in systemic blood pressure was likely to be the primary mechanism.[8] However, this study demonstrated significant heterogeneity between drug classes in their effects on headache which could not be explained by differences in mean BP. Therefore, although the effect of any antihypertensive drug compared to placebo suggests that the lowering of blood pressure reduces headache, this study shows that the differences between classes are equally important and correspond to effects on variability in SBP. Headache is most frequent and variability in SBP is lowest with calcium channel blockers whilst the opposite effect is seen wtih beta-blockers. This is consistent with a separate publication of the effect of CCBs on headache from the previous meta-analysis reporting

the effect of the other four main drug classes.[16] One possible explanation is that differences in variability in SBP reflect effects on peripheral vascular tone and correlate with changes in the cerebral circulation that may partly explain the resulting differences in incidence of headache.

A change in cerebral perfusion due to alterations in cerebrovascular tone with beta-blockers or calcium channel blockers might explain the relationship between the effects of these drug classes on both blood pressure variability and the risk of stroke. A reduction in cerebral perfusion with beta-blockers could convert subclinical ischaemia into a TIA or ischaemia into infarction. However, cerebral perfusion is not a static entity, as suggested by the episodic nature of both headache and cerebral ischaemia. The clinically significant effects of these drugs on the risk of stroke are likely to occur at the extremes of the cerebral autoregulation curve where cerebral perfusion is threatened by wide fluctuations in cerebral activity and systemic blood pressure. Therefore, the systemic and cerebral actions of calcium channel blockers may act synergistically by reducing both the occurrence of acute hypertensive episodes and by reducing the resulting cerebral vasoconstriction during severe hypertension which can cause distal ischaemia.[17] However, effects of drug classes on risk of stroke are unlikely to be solely explained by effects on cerebral perfusion, as indicated by the primary relationship between blood pressure variability and risk of stroke, independent of antihypertensive treatment.[1,2]

Unfortunately, the few small studies of the effects of antihypertensive medications on the cerebral circulation have been of variable quality, used a wide variety of imaging techniques or indices of cerebrovascular function and have included a wide range of patient groups. As a result, it is impossible to draw firm conclusions about class effects, although in most studies all drugs maintain cerebral perfusion whilst lowering blood pressure, including studies with beta-blockers,[18,19] CCBs,[20,21] and especially ACEI[19,22-23] and ARBs.[20,24-25] However, there is some evidence that CCBs reduce cerebrovascular resistance more than diuretics[21] or ACEI[27] but might occasionally cause excessive falls in cerebral blood flow,[27,28]

whilst beta-blockers are less effective than ACEI in maintaining cerebral perfusion reserve.[19] These findings would be consistent with the results of this meta-analysis but there are insufficient studies to fully elucidate the effects of any specific class, or the overall pattern of effects of these drugs on cerebrovascular haemodynamics.

This meta-analysis suggests that there are effects on headache that are not entirely class specific. In particular, amlodipine reduced the incidence of headache, unlike other CCBs, despite similar reductions in both mean SBP, variability in SBP and stroke risk.[3] This reduction in headache despite clear evidence of vasodilatation has been demonstrated in earlier reports[29] and is unlikely to reflect a lack of cerebral vasodilatation but may be due to the much longer time to peak concentration with amlodipine than with other CCBs, allowing sufficient time for autoregulation to prevent an excess of cerebrovascular dilatation.[30] This suggests that relatively rapid cerebral vasodilatation is required for the precipitation of headache, which is consistent with it's episodic nature, whilst the speed of onset of a drug may be less relevant for the prevention of headache from other causes.

However, there are a number of limitations to this systematic review. Firstly, the trials included in this meta-analysis did not address the effect of antihypertensive agents on the incidence of headache in known headache sufferers. Secondly, no paper defined the aetiology of the reported headaches or the frequency of headaches and too few papers reported the relative severity of headache to allow for a meaningful analysis. Most commonly, headache was defined as a side-effect, but the reduced incidence compared to placebo suggests that antihypertensive drugs actually reduced the occurrence of primary headaches. As such it is impossible to define whether the effects are specific to any particular headache type, and it is feasible that the drug class specific effects on headache are acting on a non-haemodynamic mechanism in specific headache types, for example beta-blockers reducing cortical spreading depression, although the lack of a protective effect of non-dihydropyridine CCBs suggests that the majority of the effect was on non-migrainous headaches and the close correlation with BP variability does suggest a

haemodynamic process. Nonetheless, it is likely that some drug classes have both haemodynamic effects on some headache types via effects on BP and cerebral perfusion and non-haemodynamic effects on other headache types, such as migraine. Thirdly, there were limited trials of longer duration reporting the incidence of headache. Therefore it is possible that antihypertensive treatment has a relatively acute effect on headache which is not sustained. Fourthly, I was unable to directly assess the effect of treatment on intra-individual variability in SBP in trials also reporting headache incidence as it was not available for any of these trials, but drug class effects on interindividual variability are the same as drug class effects on intraindividual variability.[3,5]

One major implication of this finding is that any study that seeks to determine the physiological determinants of blood pressure variability and how blood pressure variability may result in an increased risk of stroke, also needs to determine any covariation in changes in the cerebral circulation. For interventional tests, the effect of any intervention on blood pressure variability also needs to determine the effect on the cerebral circulation. As a result, extensive assessment of baseline cerebral perfusion, cerebral autoregulation and cerebral reactivity to carbon dioxide are included in the Physiological Cohort study described in chapters 9-10.

In conclusion, antihypertensive treatment reduces the incidence of headache compared to placebo, but the magnitude of effect differs between drug-classes independently of the magnitude of blood pressure reduction. These drug-class differences correspond to their effects on variability in SBP, suggesting that some of the relationship between antihypertensive drug-class effects on variability in SBP and effects on stroke risk may be due to associated effects on the cerebral circulation.

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CHAPTER FIVE

Frequency, validity and prognostic value of residual hypertension: home versus ambulatory blood pressure after TIA or non-disabling stroke

5.1 Summary

Diagnosis of hypertension on the basis of BP measurements in clinic has been questioned and most guidelines now recommend confirmation by ambulatory (ABPM) or home (HBPM) monitoring, but recent NICE guidelines preferentially recommend ABPM. However, there are no valid direct comparisons of HBPM and ABPM, and it is unclear which method provides a more accurate measure of BP, a prerequisite for measuring blood pressure variability. To validate HBPM versus ABPM, I compared residual hypertension on HBPM and ABPM with 10 markers of hypertensive disease, including markers of hypertensive arteriopathy, premorbid hypertension and cardiovascular events or death.

Among 500 consecutive patients recruited from a dedicated TIA/stroke clinic, mean SBP on HBPM (3 readings, 3 times daily for 7 days) was more strongly associated than on ABPM (difference p=0.016) with all markers of hypertensive arteriopathy (OR per 10mmHg SBP: HBPM 1.47, 95% CI 1.28-1.68, p<0.001 vs ABPM OR 1.18, 1.02-1.36, p=0.03), and individually with leukoaraiosis (1.34, 1.16-1.56, p<0.001 vs 1.03, 0.86-1.23, p=0.80), aortic stiffness (r=0.21, p=0.01 vs r=0.04, p=0.67), creatinine (r=0.24, p<0.001 vs r=0.11, p=0.012), stroke vs TIA (OR=1.34 , 1.15-1.56, p<0.001 vs 1.12 , 0.96-1.31, p=0.16) and cognitive impairment (OR=1.41, 1.21-1.65, p<0.001 vs 1.12, 0.96-1.31, p=0.15), particularly in patients >65 years. HBPM also better identified premorbid hypertension (area under ROC curve: 0.73, 0.68-0.78 vs 0.60, 0.54-0.65, p-diff=0.0002), again mainly in patients >65 years (0.70, 0.62-0.77 vs 0.55, 0.47-0.63, p-diff=0.002). BP>135/85 predicted the risk of recurrent events on HBPM but not on ABPM: stroke (OR=2.46, 1.01-6.02, p=0.049 vs 1.09, 0.42-2.83, p=0.86); all cardiovascular events (2.62, 1.25-5.48, p=0.011 vs 1.51, 0.69-3.30, p=0.30); all cause death (2.65, 1.28-5.46, p=0.008 vs 1.67, 0.80-3.49, p=0.18).

In patients with TIA or non-disabling stroke, HBPM was more accurate than ABPM at identifying hypertensive arteriopathy, premorbid hypertension and cardiovascular events or death, probably due to the limitations of ABPM in patients >65 years, demonstrating its greater validity in measurement of blood pressure and blood pressure variability.

5.2 Introduction

In chapters 1-3, I demonstrated that variability in clinic blood pressures was strongly associated with the risk of recurrent cardiovascular events. However, repeated clinic measures are an impractical method of assessing blood pressure variability. Home blood pressure monitoring (HBPM) is an alternative, but there is little evidence for the prognostic significance of variability on HBPM. Prior to using it to assess variability in blood pressure, it is important to demonstrate that it is a reliable method of blood pressure measurement in comparison to the currently accepted gold-standard.

In primary prevention, validity of diagnosis of hypertension on the basis of BP measurements in clinic has been questioned and most guidelines now recommend independent confirmation, ideally by awake ambulatory (ABPM) rather than home (HBPM) monitoring, although 7 days of HBPM is recommended for screening and when ABPM is not available.[1-3] Recent cost-effectiveness analyses[4] (and hence the new NICE guideline[1]) also recommended ABPM during usual waking hours, but in the absence of comparative studies based on hard clinical outcomes these were based on the assumption that ABPM was an absolute gold standard, with 100% sensitivity and specificity for the identification of clinically relevant hypertension.[5] Irrespective of the validity of this assumption, reliability of prediction of cardiovascular events would arguably be a better measure of clinical utility, and the only two direct comparisons of ABPM versus HBPM[6-7] in predicting the risk of cardiovascular events did not demonstrate significant differences, even with HBPM limited to three measurements of BP on one day. Moreover, the median age of participants in previous studies comparing ABPM and HBPM was only about 50 years,[6-10] whereas half of new diagnoses of hypertension are now made over the age of 65 in developed countries.[11]

As well as the dearth of comparative studies of the utility of ABPM versus HBPM in identifying hypertension at older ages, there are also no studies in a secondary prevention setting. Given the very high absolute risks of recurrent vascular events in secondary prevention, the older age, and the larger absolute benefits of antihypertensive treatment,[12-

[13] reliable diagnosis of hypertension is particularly important. In the case of TIA and stroke, guidelines recommend BP-lowering in all patients with clinic BP>130/80[14-16] but under-treatment is substantial in all countries in which studies have been done[18-24] and missed hypertension is common, partly due to considerable visit-to-visit variability in BP.[17] Indeed, the high day-to-day variability in BP in this group of patients[25] could reduce the reliability of single-day assessment with ABPM. Current guidelines recommend a one-off clinic review of patients one month after TIA or stroke in order to assess initial risk factor control, but do not address how best to gauge BP control.[26] I therefore studied mean SBP and DBP on awake ABPM versus 7-day HBPM, as recommended by hypertension guidelines,[1-3] one month after TIA and stroke, and compared their pathological validity by correlation with fivemarkers of physiological dysfunction associated with hypertensive end-organ damage "hypertensive arteriopathy" (renal dysfunction,[27] arterial stiffness,[28] leukoaraiosis,[29] diagnosis of stroke versus TIA and cognitive impairment[30]). We compared their clinical validity by association with pre-existing hypertension (a prior diagnosis or mean BP>140/90 on last 20 primary care readings) and prediction of the risk of vascular events on follow-up, stratifying analyses by age.

5.3 Methods

5.3.1 Study Population

Consecutive patients were recruited between April 2008 and January 2012 from the Oxford Vascular Study (OXVASC)[31] TIA and minor stroke clinic.[32] The OXVASC population consists of 92,728 individuals registered with 100 primary-care physicians in nine practices in Oxfordshire, UK.[31] All consenting patients with TIA or stroke underwent a standardised medical history and examination, ECG and routine blood tests. Patients underwent a stroke protocol MRI brain and contrast-enhanced MRA of the extracranial brain-supplying arteries (or CT-brain and either a carotid Doppler ultrasound or CT-angiogram when MR imaging was contraindicated), an echocardiogram and 5 days of ambulatory cardiac monitoring. All patients were reviewed by a study physician, the diagnosis verified by the senior study

neurologist (Prof Peter Rothwell), and aetiology determined by a panel of stroke neurologists. A subgroup of 150 patients underwent measurement of aortic stiffness by applanation tonometry to determine carotid-femoral pulse wave velocity (Sphygmocor, AtCor Medical, Sydney, Australia), either at the first assessment or at one month, taking the average of two acceptable measures, as described in chapter 9.[33] Such measures of aortic stiffness are one of the strongest physiological markers of future cardiovascular risk associated with hypertension.[28]

Patients were followed-up face-to-face at 1, 3, 6, 12, 24 and 60 months. The Montreal Cognitive Assessment was administered by standardised protocol at the 6 month follow-up appointment[34] by trained study nurses. Cognitive impairment was defined as a score <25, in line with previous validation studies.[34] Recurrent cardiovascular events were ascertained at each follow-up and by multiple overlapping methods of ascertainment in the over-arching OXVASC study. Premorbid cognitive function was not formally assessed.

5.3.2 Procedures

Clinic BP was measured at ascertainment and the one month follow-up visit in the non-dominant arm, by trained personnel, in the sitting position after five minutes of rest, with two measurements made 5 minutes apart. The lifetime medical record held by the primary care physician was manually reviewed and all premorbid BPs recorded.

From the first clinic visit, all patients started home BP monitoring (HBPM) after appropriate training. They were asked to perform three home BP readings over 10 minutes, three times daily (after waking, mid-morning and evening) with a Bluetooth-enabled, regularly-calibrated, telemetric BP monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT. Patients were instructed to relax in a chair for 5 minutes before performing readings in the non-dominant arm, or the arm with the higher reading if the mean SBP differed by >20mmHg between arms. Anonymised measures were transmitted by Bluetooth radio to a mobile phone, for secure transmission to a server hosting a password-protected website for review and download (t+ Medical, Abingdon, UK).

The day before the one month follow-up visit, ambulatory BP monitoring (ABPM) was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by a trained study nurse. BP was measured at 30 minute intervals during the day and 60 minute intervals at night. During a reading, patients were asked to sit down and refrain from excessive activity and were asked to keep a diary of the day.

Patients continued home monitoring until at least the one month follow-up appointment. Hypertension was treated as per current guidelines. Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a combination of perindopril arginine 5mg and indapamide 1.25mg, followed by amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion.

Leukoaraiosis on brain imaging was assessed on axial T2 MRI scans during routine clinical review by a neuroradiologist (the Oxford scale), and categorised into none, mild, moderate or severe. Scans were subsequently scored by trained observers according to a modified version of the Blennow and Fazekas scales[35] on CT and MRI, with scores concatenated into the same 4 categories, as reported in previous OXVASC publications.[36] These rapid and well validated assessment methods provide good statistical power and accuracy with large datasets, such that the added precision of volumetric measurement is not required, but are significantly more efficient to calculate than volumetric measures.

5.3.3 Analysis

Mean SBP and DBP for 7-day HBPM were derived from the 7 days prior to the one month ABPM as recommended by guidelines,[1-3] using the average of the last two readings from each of the three daily sets. Equivalent values for one-day HBPM were derived on the day prior to the ABPM. Mean awake SBP and DBP on ABPM were derived after automated and manual exclusion of artefactual measurements according to predefined criteria.[37] Mean premorbid SBP and DBP were derived from the last 20 readings recorded in primary care, with sensitivity analyses limited to the last 10 readings or all readings in the last five years.

Premorbid hypertension was defined as known hypertension reported by the patient, treatment with antihypertensives to lower BP, a diagnosis of hypertension on the primary care list of diagnoses or a mean premorbid SBP >140 or mean DBP >90.[1] Sensitivity analyses were performed with premorbid hypertension defined only by a mean premorbid BP >140/90.

Mean SBP or DBP on ABPM and HBPM were correlated with the five measures of hypertensive arteriopathy, using general linear models for continuous variables and by logarithmic or ordinal regression for categorical variables, including all patients with available data for each form of monitoring in all regressions estimating associations. Arteriopathy was defined as: aortic pulse wave velocity >12m/s;[3] creatinine >120mmol/dl; MoCA score <25; stroke versus TIA; or moderate or severe leukoaraiosis. A composite measure for hypertensive arteriopathy was also calculated based on the number of markers present, excluding pulse wave velocity due to the smaller sub-population. All analyses were stratified by age above or below 65 years. Accuracy of mean SBP on ABPM versus HBPM was validated by receiver operator characteristic (ROC) curve analysis for identification of premorbid hypertension (as defined above), stratified by age above or below 65 years.

The risks of stroke, cardiovascular events (TIA, stroke, myocardial infarction, other acute vascular events or cardiovascular death) and all-cause mortality were determined by Kaplan-Meier curves and Cox Regression for residual hypertension (defined as above) on ABPM versus HBPM, or a 10mmHg increase in mean SBP, with and without adjustment for age, gender, diabetes, smoking, family history, hyperlipidaemia and atrial fibrillation. Due to the small number of outcome events, stroke was not subdivided into haemorrhagic versus ischaemic stroke, or into subtypes of ischaemic stroke. Associations with hypertensive arteriopathy were determined in all patients with available data for each type of monitoring whilst analyses identifying a limited number of events (premorbid hypertension or cardiovascular events) were only performed in patients undergoing both ABPM and HBPM.

5.4 Findings

5.4.1 Study Population

Of 520 consecutive patients consenting to BP monitoring, 500 (96%) complied with the protocol (2 died and 18 had poor compliance or withdrew consent) and had adequate 7-day readings prior to the one month follow-up. 459 (92%) also had ABPM (2 moved out of the study area before 1 month, 7 were too unwell or died, 8 had inadequate readings and 32 refused ABPM). Consistent with previous reports,[38] mean BP on clinic measurements at one month was 4 / 1 mmHg higher than on ABPM and was 8 / 1 mmHg higher than on HBPM (table 5.1). However, the SBP distribution was wider on HBPM than ABPM or clinic BP, resulting in similar numbers of patients with residual hypertension (BP>135/85): 107 (20%) patients on HBPM and 124 (23%) patients with ABPM, with 148 (28%) identified by HBPM when using a lower threshold (BP >130/85). There was only moderate correlation between mean SBP and DBP on ABPM with 1 day or 7 days of HBPM (figure 5.1), and relatively weak agreement for the diagnosis of residual hypertension at one month in all patients (kappa=0.40, 0.30-0.50), in patients previously known to be hypertensive (kappa=0.41, 0.29-0.52) and in patients aged ≥65 years (kappa=0.43, 0.31-0.55).

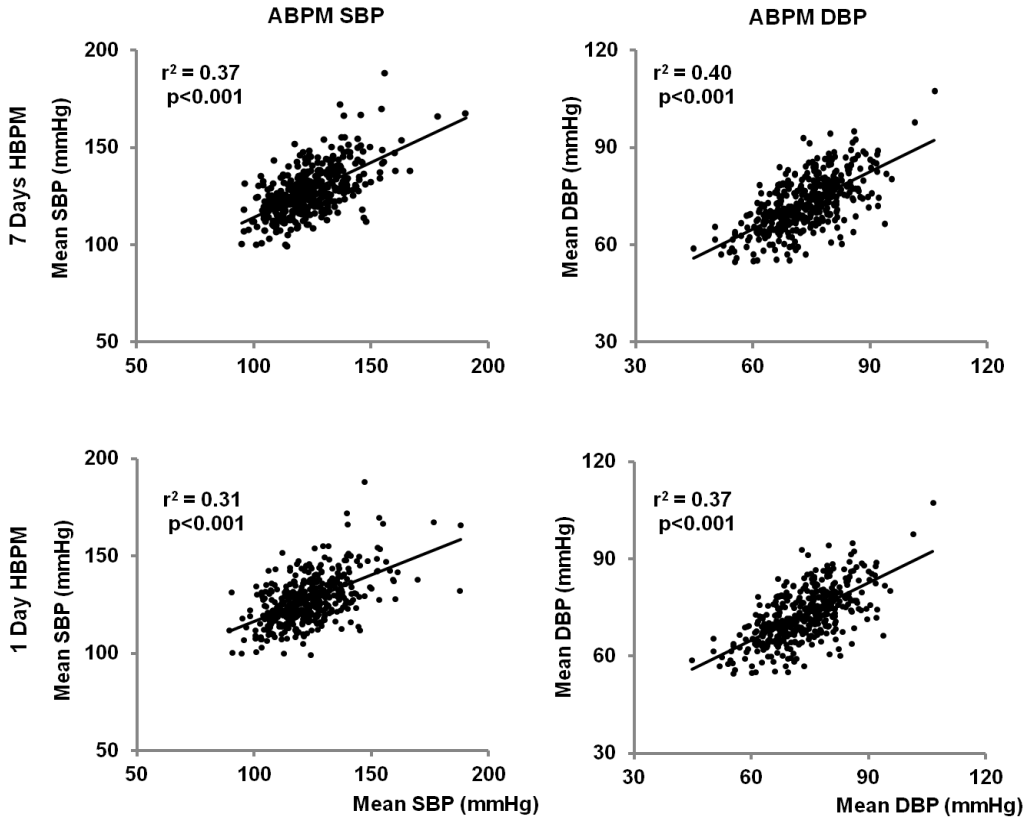


Figure 5.1. Relationship between systolic and diastolic blood pressure on ambulatory (ABPM) and either 1 day or 7 days of home (HBPM) blood pressure monitoring. r^2 and p values are derived from linear regression.

Characteristic	HBPM (500)	ABPM (451)
Age	69.3 (16.2)	69.2 (12.9)
Female	246 (49)	215 (48)
Risk Factors		
Hypertension	280 (56)	249 (56)
Hyperlipidaemia	199 (40)	182 (41)
Diabetes	76 (15)	66 (15)
Family history of stroke	136 (27)	125 (28)
Previous Stroke or TIA	117 (23)	104 (23)
Atrial Fibrillation	70 (14)	65 (15)
Heart Failure	31 (6)	30 (7)
Migraine	155 (31)	143 (32)
Smoker	72 (15)	66 (15)
Alcohol Excess	50 (10)	46 (10)
Height (cm)	167.9 (10.1)	168.9 (9.6)
Weight (Kg)	77.2 (21.2)	76.7 (16.1)
BMI	27.2 (6.2)	26.8 (4.9)
Blood Pressure (mmHg)		
One month clinic SBP	131.1 (17.3)	131.4 (17.2)
One month clinic DBP	74.9 (10.6)	74.2 (10/8)
Morning HBPM SBP	123.4 (13.1)	123.5 (13.1)
Morning HBPM DBP	73.5 (8.9)	73.4 (8.9)
Awake ABPM SBP	127.3 (12.3)	127.4 (12.3)
Awake ABPM DBP	72.8 (8.1)	72.8 (8.2)
Blood Tests		
Creatinine (mmol/L)	91.2 (30)	90.6 (28)
Total Cholesterol (mmol/L)	5.3 (1.8)	5.3 (1.9)
LDL Cholesterol (mmol/L)	3.0 (1.1)	3.0 (1.1)
HDL Cholesterol (mmol/L)	1.5 (0.5)	1.5 (0.5)
TSH (mu/L)	2.2 (1.8)	2.2 (1.7)
Event Type		
TIA	274 (57)	256 (58)
Stroke	205 (43)	182 (42)
Event Aetiology*		
Large Artery Disease	44 (9)	38 (9)
Cardioembolic	70 (14)	67 (15)
Lacunar	70 (14)	62 (14)
Other	16 (3)	15 (3)
Undetermined / multiple	300 (60)	269 (59)
Event Territory		
Carotid	214 (45)	201 (46)
Vertebrobasilar	224 (47)	207 (47)
Unknown / both	43 (9)	34 (8)

Table 5.1 Population characteristics in patients undergoing home blood pressure monitoring (HBPM) and undergoing ambulatory monitoring (ABPM). Frequencies are given as number (%) whilst continuous variables are expressed as mean (SD).

*Event classified by panel of neurologists according to the Trial of Org 10172 classification into large artery (artherosclerosis), cardioembolic (predominantly AF) and lacunar (small vessel disease).

There was a stronger association between mean SBP on HBPM versus ABPM with the total number of markers of excessive hypertensive arteriopathy including moderate/severe leukoaraiosis, cognitive impairment, stroke vs TIA and creatinine (per 10mmHg mean SBP: HBPM 1.47, 95% CI 1.28-1.68, p<0.001 vs ABPM OR 1.18, 1.02-1.36, p=0.03, difference p=0.016). The associations were similar in patients <65 years old (HBPM 1.67, 1.28-2.20, p<0.001 vs ABPM 1.47, 1.13-1.92, p=0.002, difference p=0.75), but were significantly stronger for HBPM in patients >65 years (HBPM 1.34, 1.14-1.58, p<0.001 vs ABPM 1.02, 0.86-1.21, p=0.78, difference p=0.011).

5.4.2 Leukoaraiosis

Of the 500 patients undergoing home monitoring, 490 had brain imaging available (10 patients refused or imaging was performed at other centres), of whom 420 had no contraindications and tolerated MRI. Among 490 patients with brain imaging, mean SBP on 7 days of HBPM predicted the presence of any vs no leukoaraiosis or none/mild vs moderate/severe leukoaraiosis more strongly than awake SBP on ABPM (table 5.2). This difference persisted after excluding those cases with only CT-imaging (home OR=1.31, p=0.038; ABPM OR=0.91, p=0.56). Similarly, severity of leukoaraiosis on the Fazekas scale was associated with mean SBP on HBPM but not on ABPM (table 5.2). There was no association with DBP (table 5.3). The stronger association with HBPM was largely explained by a stronger association with HBPM than ABPM in patients >65 years old, compared to a similarly strong association in patients <65 years old (table 5.4), but was also explained by the time period of monitoring with a stronger association on 7 days of HBPM than 1 day of HBPM (table 5.2). On ROC curves only home SBP significantly discriminated the presence of moderate or severe leukoaraiosis (home SBP AUC=0.60, 0.54-0.67; ABPM SBP AUC=0.49, 0.42-0.56; p-diff=0.0002), excessive leukoaraiosis for age (home SBP AUC=0.58, 0.50-0.66; ABPM SBP AUC=0.54, 0.46-0.62), and any leukoaraiosis (home SBP AUC=0.61, 0.55-0.67; ABPM SBP AUC=0.55, 0.49-0.61).

	Clinic		ABPM		1 Day HBPM		7 Days HBPM	
	R or OR	P	R or OR	P	R or OR	p	R or OR	p
Premorbid SBP (mmHg)	**0.49**	<0.001	**0.33**	<0.001	**0.41**	<0.001	**0.45**	<0.001
Creatinine (mmol/L)	**0.13**	0.005	**0.11**	0.012	**0.20**	<0.001	**0.24**	<0.001
Aortic PWV (m/s)	**0.21**	0.012	**0.04**	0.67	**0.20**	<0.001	**0.21**	0.012
Cognition (MoCA <25)	**1.17** (1.04 – 1.31)	0.004	**1.12** (0.96 – 1.31)	0.15	**1.34** (1.16 – 1.55)	<0.001	**1.41** (1.21 – 1.65)	<0.001
Stroke vs TIA	**1.13** (1.01 – 1.26)	0.029	**1.12** (0.96 – 1.31)	0.16	**1.30** (1.14 – 1.49)	<0.001	**1.34** (1.15 – 1.56)	<0.001
Leukoaraiosis								
Moderate or Severe	**1.25** (1.09 – 1.42)	0.001	**1.03** (0.86 – 1.23)	0.80	**1.26** (1.10 – 1.45)	0.001	**1.34** (1.16 – 1.56)	<0.001
Fazekas score severity								
Total Fazekas score	**1.28** (1.15 – 1.43)	<0.001	**1.09** (0.94 – 1.27)	0.24	**1.29** (1.13 – 1.46)	<0.001	**1.38** (1.20 – 1.58)	<0.001
Periventricular	**1.28** (1.15 – 1.43)	<0.001	**1.05** (0.90 – 1.22)	0.55	**1.30** (1.14 – 1.49)	<0.001	**1.37** (1.19 – 1.59)	<0.001
Deep White Matter	**1.26** (1.10 – 1.44)	<0.001	**1.13** (0.97 – 1.32)	0.12	**1.25** (1.10 – 1.43)	<0.001	**1.34** (1.16 – 1.55)	<0.001

Table 5.2 Relationships between mean SBP on 7 days of Home (HBPM) monitoring vs 24-hour ambulatory (ABPM) monitoring with premorbid SBP, markers of hypertensive arteriopathy and cerebral leukoaraiosis. Associations with continuous measures are given as univariate R and p-values. Categorical associations are presented as odds ratios from binary logistic or ordinal regression per 10mmHg increase in SBP. MoCA = Montreal Cognitive Assessment score.

	Clinic		ABPM		1 Day HBPM		7 Days HBPM	
	R or OR	p	R or OR	P	R or OR	p	R or OR	p
Premorbid DBP	**0.45**	<0.001	**0.39**	<0.001	**0.39**	<0.001	**0.42**	<0.001
Creatinine	**-0.05**	0.31	**0.04**	0.36	**-0.03**	0.49	**0.03**	0.55
Aortic PWV	**-0.19**	0.029	**0.25**	0.003	**-0.13**	0.12	**0.10**	0.23
MoCA <25	**0.94** (0.79 – 1.12)	0.48	**0.81 (**0.64 – 1.03)	0.09	**0.96** (0.78 – 1.18)	0.69	**0.97 (**0.78 – 1.20)	0.78
Stroke vs TIA	**1.13** (0.95 – 1.33)	0.17	**1.12** (0.96 – 1.31)	0.16	**1.32** (1.08 – 1.61)	0.006	**1.32** (1.07 – 1.62)	0.009
Leukoaraiosis								
Moderate or Severe	**0.80** (0.66 – 0.96)	0.015	**0.68** (0.52 – 0.89)	0.004	**0.89** (0.72 – 1.10)	0.29	**0.93** (0.75 – 1.16)	0.52
Fazekas score severity								
Total Fazekas score	**0.87 (**0.70 – 0.97)	0.02	**0.76** (0.60 – 0.96)	0.02	**0.84** (0.69 – 1.01)	0.07	**0.84** (0.67 – 1.01)	0.06
Periventricular	**0.82** (0.69 – 0.98)	0.025	**0.66** (0.56 – 0.82)	<0.001	**0.85** (0.69 – 1.02)	0.07	**0.79** (0.64 – 0.97)	0.03
Deep White Matter	**0.82** (0.69 – 0.98)	0.025	**0.62** (0.48 – 0.79)	<0.001	**0.86** (0.70 – 1.04)	0.07	**0.87** (0.70 – 1.07)	0.20

Table 5.3 Relationships between mean diastolic BP on 7 days of Home (HBPM) monitoring vs 24-hour ambulatory (ABPM) monitoring with premorbid DBP, markers of hypertensive arteriopathy and cerebral leukoaraiosis. Associations with continuous measures are given as univariate R and p-values. Categorical associations are presented as odds ratios from binary logistic or ordinal regression per 10mmHg increase in DBP. MoCA = Montreal Cognitive Assessment score

5.4.3 Aortic stiffness

In patients undergoing measurement of aortic stiffness, mean SBP on HBPM was significantly associated with PWV but mean SBP on ABPM was not (table 5.2), with similar relationships for mean DBP (table 5.3). HBPM was more accurate at identifying excessive aortic stiffness (PWV >12 m/s: HBPM OR=1.61, 1.04-2.65, p=0.03; ABPM OR=1.40, 0.91-2.15 p=0.13). This relationship was partly determined by age, with a greater reduction of the association between ABPM SBP and PWV in patients >65 years compared to <65 years than with the association between HBPM SBP and PWV (table 5.4).

5.4.4 Renal function

Mean SBP on HBPM was more strongly associated with creatinine than mean SBP on ABPM (table 5.2), and was more accurate at identifying an excessive creatinine level (HBPM OR =1.40, 1.12-1.76, p=0.004; ABPM OR=1.10, 0.84-1.44 p=0.48), with a significant interaction between mean SBP on HBPM and gender (p=0.008) due to a greater creatinine in men with high mean SBP than women. Mean DBP was not significantly related to creatinine with either form of monitoring. The stronger association between creatinine and HBPM compared to ABPM was due to a weaker relationship with ABPM in patients >65 years and the longer duration of monitoring with 7 days of HBPM compared to 1 day of HBPM (table 5.4).

5.4.5 Diagnosis of stroke

Mean SBP on HBPM was associated with a diagnosis of stroke versus TIA but ABPM was not (table 5.2). Mean DBP on HBPM vs ABPM was also more strongly associated with a diagnosis of stroke (table 5.3). Again, there was no relationship with mean SBP on ABPM in patients >65 years, with a significant relationship on ABPM at <65 years or on HBPM at all ages.

	Clinic		ABPM		1 Day HBPM		7 Days HBPM	
	R or OR	P	R or OR	P	R or OR	P	R or OR	p
Premorbid SBP (mmHg)								
< 65 years	**0.62**	<0.001	**0.59**	<0.001	**0.33**	0.014	**0.54**	<0.001
> 65 years	**0.44**	<0.001	**0.23**	<0.001	**0.32**	<0.001	**0.37**	<0.001
Creatinine (mmol/L)								
< 65 years	**0.14**	0.08	**0.16**	0.043	**0.14**	0.065	**0.17**	0.024
> 65 years	**0.09**	0.10	**0.11**	0.07	**0.18**	0.001	**0.21**	<0.001
Aortic PWV (m/s)								
< 65 years	**0.31**	0.02	**0.17**	0.20	**0.33**	0.014	**0.35**	0.007
> 65 years	**0.17**	0.12	**0.04**	0.71	**0.15**	0.17	**0.17**	0.13
Cognition (MoCA <25)								
< 65 years	**1.62** (1.24 – 2.11)	<0.001	**1.48** (1.07 – 2.06)	0.017	**1.29** (0.97 – 1.71)	0.08	**1.36** (1.00 – 1.86)	0.05
> 65 years	**1.02** (0.90 – 1.16)	0.76	**1.04** (0.86 – 1.24)	0.71	**1.27** (1.07 – 1.52)	0.006	**1.34** (1.11 – 1.61)	0.002
Stroke vs TIA								
< 65 years	**1.24** (1.00 – 1.53)	0.049	**1.37** (1.02 – 1.83)	0.037	**1.47** (1.13 – 1.92)	0.004	**1.56** (1.16 – 2.08)	0.003
> 65 years	**1.10** (0.97 – 1.25)	0.16	**1.02** (0.85 – 1.23)	0.82	**1.25** (1.07 – 1.47)	0.006	**1.28** (1.08 – 1.53)	0.005
Mod/Sev Leukoaraiosis								
< 65 years	**1.38** (0.98 – 1.95)	0.07	**0.95** (0.60 – 1.50)	0.82	**1.43** (0.99 – 2.07)	0.56	**1.62** (1.04 – 2.53)	0.031
> 65 years	**1.15** (0.99 – 1.34)	0.07	**1.10** (0.88 – 1.36)	0.41	**1.14** (0.97 – 1.33)	0.10	**1.17** (0.97 – 1.42)	0.11
Fazekas Score								
< 65 years	**1.39** (1.12 – 1.72)	<0.001	**1.11** (0.85 – 1.44)	0.46	**1.21** (0.94 – 1.54)	0.14	**1.25** (0.95 – 1.64)	0.11
> 65 years	**1.16** (1.02 – 1.33)	0.023	**1.20** (1.00 – 1.45)	0.76	**1.21** (1.03 – 1.41)	0.017	**1.30** (1.10 – 1.54)	0.002

Table 5.4 Relationships between mean SBP on 7 days of Home (HBPM) monitoring vs 24-hour ambulatory (ABPM) monitoring with premorbid SBP, markers of hypertensive arteriopathy and cerebral leukoaraiosis, in patients over versus under 65 years of age. Associations with continuous measures are given as univariate R and p-values. Categorical associations are presented as odds ratios from binary logistic or ordinal regression per 10mmHg increase in SBP. MoCA = Montreal Cognitive Assessment score.

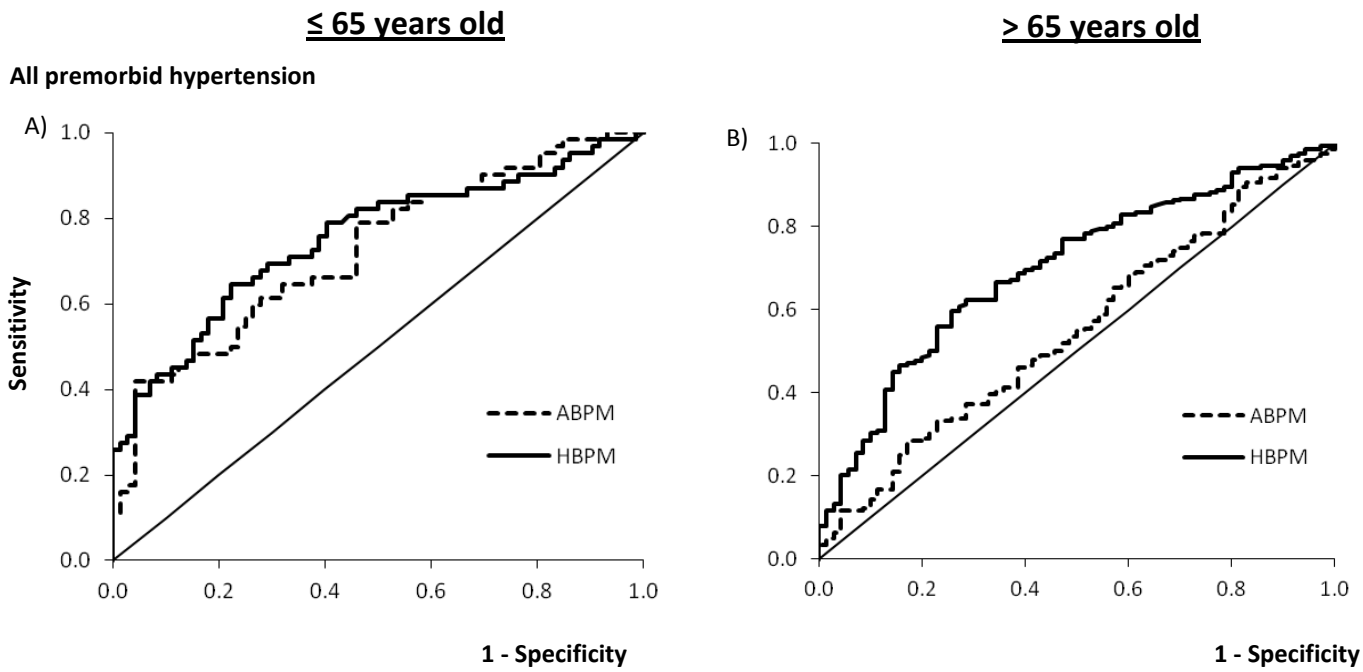
5.4.6 Cognitive impairment

The presence of cognitive impairment (MoCA <25 at 6 months) was significantly associated with a 10mmHg increase in SBP on HBPM but not ABPM (table 5.2), although there was no relationship with DBP. Similarly, the risk of a greater severity of cognitive impairment was more strongly associated with a 10mmHg increase in mean SBP on HBPM than ABPM (HBPM OR=1.44, 1.25–1.66 p<0.001; ABPM OR=1.17, 1.01-1.35, p=0.04). There was no relationship between cognitive impairment and mean SBP on ABPM in patients >65 years old, but significant relationships with ABPM in patients <65 years old.

5.4.7 Premorbid hypertension

Residual hypertension on HBPM at one month was significantly more accurate than ABPM (p=0.0002) in identifying premorbid hypertension in all patients (figure 5.2) and in 205 patients with a premorbid BP >140/90 but no formal diagnosis of hypertension (missed premorbidly, table 5.2). This difference persisted for patients with masked premorbid hypertension, for patients who required no change in treatment during follow-up (table 5.2) and when using only the last 10 readings or the last 5 years of readings. Accuracy of HBPM was improved when using morning and evening readings, as recommended by current guidelines[1] (All patients SBP AUC = 0.76 0.72 – 0.81 p<0.0001; missed premorbidly AUC = 0.76, 0.68-0.85 p<0.0001)***.*** The strength of the relationship was strongly related to age, with a similar accuracy for ABPM and HBPM in patients <65 years, but a significantly greater accuracy of HBPM in patients >65 years compared to ABPM in this age group (figure 5.2). Residual hypertension on HBPM had similar sensitivity with improved specificity compared to ABPM for diagnosis of hypertension for premorbid hypertension in all individuals (HBPM: sensitivity 0.29, specificity 0.92; ABPM: sensitivity 0.35, specificity 0.84) but was significantly more sensitive and specific at a revised threshold for HBPM of 130/85[28] (HBPM sensitivity 0.40, specificity 0.89)***.*** Relationships with premorbid SBP were stronger with mean SBP on HBPM at one month than with ABPM (table 5.2), with a stronger relationship when using all HBPM readings (premorbid all readings: r^2=0.227 p<0.001; 5 years: 0.194 p<0.001).

Figure 5.2. Receiver operator characteristic curves for identification of premorbid hypertension by mean SBP on HBPM vs ABPM, stratified by age. Premorbid hypertension is defined as hypertension reported by the patient or listed in the primary care record, on treatment for hypertension or mean premorbid SBP >140 or DBP >90. Results are stratified by age above or below 65 years old.



	Home BP		ABPM		
	AUC (95%CI)	p-value	AUC (95%CI)	p-value	p-diff
Any hypertension					
All definitions	**0.732** (0.68 - 0.78)	<0.0001	**0.595** (0.54 - 0.65)	0.002	0.0002
Prior diagnosis	**0.681** (0.63 - 0.73)	<0.0001	**0.583** (0.53 - 0.64)	0.002	0.008
By premorbid BP	**0.698** (0.65 - 0.755)	<0.0001	**0.632** (0.58 - 0.69)	<0.0001	0.04
Missed hypertension					
Missed premorbidly	**0.754** (0.66 - 0.85)	<0.0001	**0.586** (0.48 - 0.69)	0.12	0.01
Missed in clinic	**0.921** (0.85 – 0.99)	<0.0001	**0.603** (0.39 - 0.82)	0.49	0.003
Masked Hypertension	**0.798** (0.66 - 0.93)	<0.0001	**0.741** (0.61 - 0.88)	0.001	0.28
No change in treatment	**0.639** (0.51 - 0.77)	0.04	**0.549** (0.41 - 0.69)	0.46	0.18

Table 5.5. Accuracy of home versus ambulatory blood pressure monitoring for identification of premorbid hypertension. Area under the receiver operating characteristic curve is reported for the presence of premorbid hypertension, defined by the most recent 20 readings before their cerebrovascular event. Missed hypertension refers to an elevated premorbid mean BP which had not resulted in a diagnosis or treatment for hypertension, either premorbidly or after the initial clinic assessment. Masked hypertension refers to all patients with an elevated mean BP premorbidly who were normotensive in clinic.

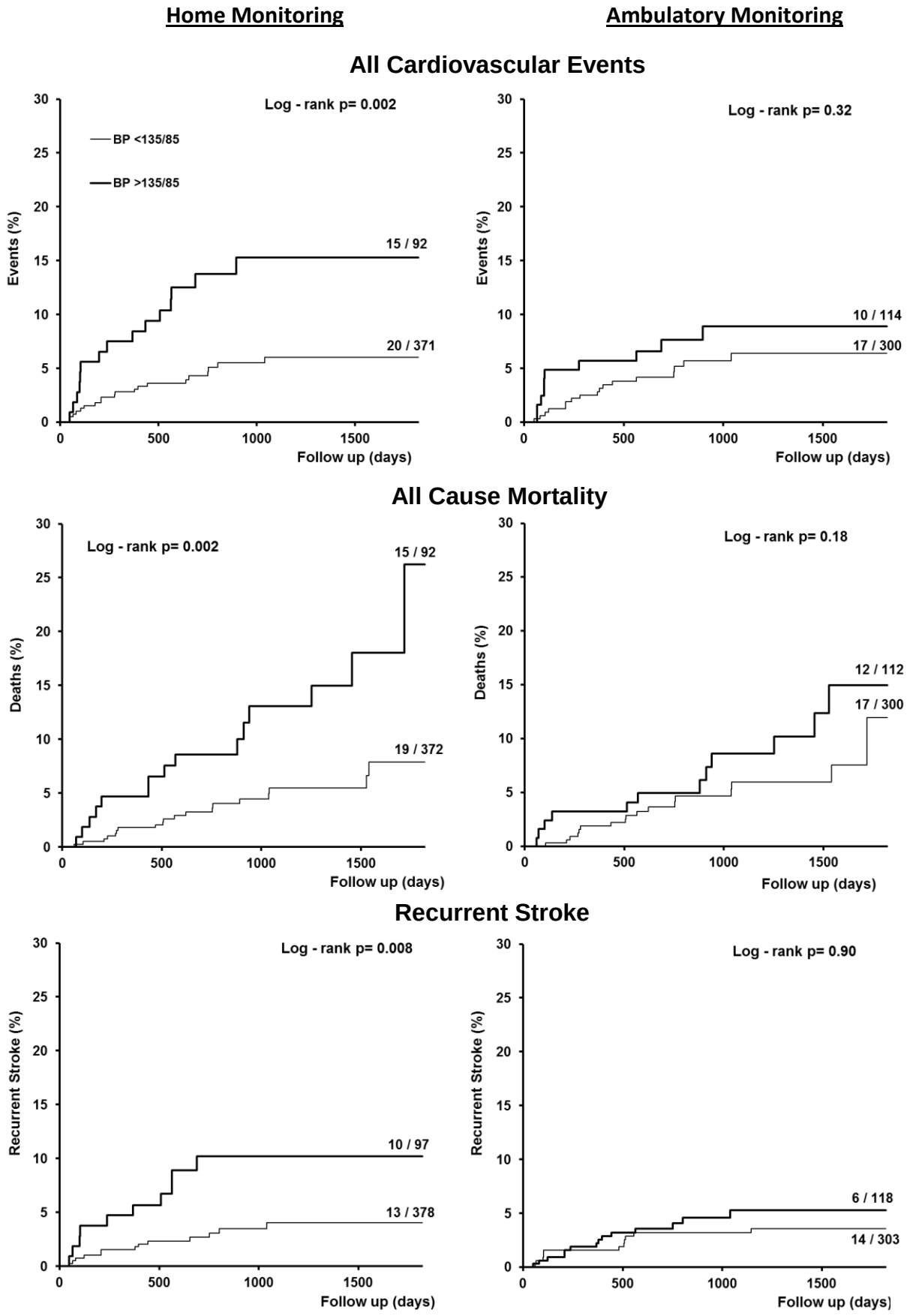


Figure 5.3 Kaplan-Meier curves of cardiovascular events occurring after blood pressure monitoring, by hypertensive status defined by either HBPM or ABPM. For each monitoring method, the risk of each event is compared for normotensive versus hypertensive patients by log-rank tests. 'All cardiovascular events' includes recurrent stroke, MI, acute peripheral vascular events and cardiovascular death. Hypertension was defined as mean SBP >135 or mean DBP >85.

Model	Ev	HBPM HR	HBPM 95% CI	HBPM p-value	ABPM HR	ABPM 95% CI	ABPM p-value
BP > 135 / 85							
Unadjusted Model							
Cardiovascular Mortality							
+ Stroke, MI, PVD	29	**2.62**	(1.25 – 5.48)	0.011*	**1.51**	(0.69 – 3.30)	0.30
+ TIA, stroke, MI, PVD	51	**2.04**	(1.15 – 3.62)	0.015*	**1.23**	(0.68 – 2.23)	0.50
All cause death	30	**2.65**	(1.28 – 5.46)	0.008*	**1.67**	(0..80 – 3.49)	0.18
Cardiovascular death	13	**3.13**	(1.05 – 9.32)	0.04*	**1.77**	(0.56 – 5.60)	0.33
Stroke	20	**2.46**	(1.01 – 6.02)	0.049*	**1.09**	(0.42 – 2.83)	0.86
Adjusted Model							
Cardiovascular Mortality							
+ Stroke, MI, PVD	29	**2.42**	(1.13 – 5.15)	0.022*	**1.51**	(0.68 – 3.34)	0.32
+TIA, stroke, MI, PVD	51	**2.03**	(1.13 – 3.64)	0.018*	**1.26**	(0.69 – 2.31)	0.45
All cause death	30	**2.26**	(1.06 – 4.78)	0.034*	**1.77**	(0.84 – 3.77)	0.14
Cardiovascular death	13	**3.24**	(1.05 – 10.0)	0.041*	**2.14**	(0.66 – 7.00)	0.21
Stroke	20	**2.17**	(0.86 – 5.49)	0.10	**1.07**	(0.41 – 2.84)	0.89
Per 10mmHg SBP							
Unadjusted Model							
Cardiovascular Mortality							
+ Stroke, MI, PVD	29	**1.28**	(1.02 – 1.60)	0.034*	**1.04**	(0.78 – 1.39)	0.79
+ TIA, stroke, MI, PVD	51	**1.13**	(0.94 – 1.37)	0.19	**098**	(0.78 – 1.23)	0.85
All cause death	30	**1.40**	(1.14 – 1.71)	0.001*	**1.06**	(0.79 – 1.41)	0.72
Cardiovascular death	13	**1.26**	(0.89 – 1.78)	0.19	**0.81**	(0.50 – 1.31)	0.40
Stroke	20	**1.22**	(0.92 – 1.62)	0.18	**0.92**	(0.64 – 1.34)	0.67
Adjusted Model							
Cardiovascular Mortality							
+ Stroke, MI, PVD	29	**1.19**	(0.93 – 1.52)	0.17	**1.05**	(0.79 – 1.40)	0.74
+TIA, stroke, MI, PVD	51	**1.09**	(0.89 – 1.33)	0.41	**1.00**	(0.80 – 1.25)	0.99
All cause death	30	**1.20**	(0.96 – 1.49)	0.11	**1.08**	(0.82 – 1.42)	0.60
Cardiovascular death	13	**1.09**	(0.75 – 1.58)	0.68	**0.90**	(0.57 – 1.41)	0.64
Stroke	20	**1.11**	(0.82 – 1.52)	0.50	**0.91**	(0.63 – 1.31)	0.61

Table 5.6 Hazard ratios for the risk of each event for either hypertensive versus normotensive patients or per 10mmHg increase in SBP, defined by either home or ambulatory blood pressure monitoring. Hazard ratios (HR) are generated from unadjusted Cox Proportional Hazards regression models and following adjustment for age, gender, smoking, family history of stroke, diabetes, dyslipidaemia and atrial fibrillation. Hypertension is defined as a mean SBP >135 or a mean DBP >85. N=number of events; HBPM=home blood pressure monitoring; ABPM=awake ambulatory blood pressure monitoring; MI=myocardial infarction; PVD=acute peripheral vascular disease; TIA=transient ischaemic attack. * p<0.05

5.5.8 Risk of Recurrent Events

Hypertension (BP >135/85) defined by HBPM vs ABPM was significantly more predictive of a composite of cardiovascular events and cardiovascular death (figure 5.3 and table 5.5). Specifically, a diagnosis of hypertension on HBPM or a 10mmHg increase in SBP was more predictive of the risk of each of all cardiovascular events, stroke, cardiovascular death and all-cause death than the equivalent measures on ABPM. Although the predictive value of a diagnosis of hypertension on ABPM was not significant, it was still more predictive than a diagnosis of hypertension on clinic blood pressure at 1 month (risk of stroke, MI, PVD or CV death: ABPM HR=1.48, 0.68-3.62 vs clinic HR=1.27, 0.56 – 2.92). Again, accuracy of home SBP in predicting risk of stroke was related to duration of monitoring (risk of stroke, MI, PVD or CV death: 1 day HBPM HR=1.27, 1.05-1.54; 7 days HBPM OR=1.32, 1.08-1.61; all measures 1.40, 1.14-1.72).

5.6 Discussion

Mean SBP on 7 days of HBPM was more strongly related than mean awake SBP on ABPM with five markers of hypertensive arteriopathy, premorbid hypertension, and risk of recurrent events, due mainly to weak associations for ABPM in patients aged ≥65 years of age, although the superiority of HBPM over ABPM was also partly explained by the longer time-period of monitoring. Despite an active treatment policy, approximately 20% of patients still had residual hypertension on 7-day HBPM, with 43% of all recurrent cardiovascular events occurring in this group.

Although the large difference in predictive value between ABPM and HBPM in this population is in contrast to previous studies,[6-7] the only previous large study directly comparing prognostic value of HBPM and ABPM was carried out in a primary prevention setting in participants with a mean age of 50 years and using only a single day of HBPM.[6] The different findings may reflect the difference in age of the study populations and the fact that I used 7 days of monitoring, as is now recommended in current guidelines,[1,3] but the

physiological validity of HBPM compared to ABPM is supported by the stronger association with cardiovascular risk factors (creatinine, aortic stiffness) and functionally important sequelae of hypertension (leukoaraiosis, more prolonged neurological deficit and cognitive impairment). The greater accuracy of longer duration of monitoring may reflect both correction for day-to-day variability in blood pressure,[17,39] which increases substantially with age,[17] and may allow for greater habituation to testing, reducing both artefactual readings and limiting the pressor response to BP monitoring which can affect up to the first 10 hours of ABPM measurements.[40-41]

This study used a number of methods to validate SBP on HBPM and ABPM including a practical gold standard (future cardiovascular risk) and historic hypertension, providing a diagnosis of hypertension independently of this study. It also used five markers of "hypertensive arteriopathy," physiological and clinical disease markers known to be associated with a history of hypertension. However, all five markers are complex phenotypes with a number of potential causes not necessarily related to hypertension. For example, leukoaraiosis was historically defined by pathological changes in arterioles and capillaries in the brain including lipohyalinosis, vessel rarefraction and fibrinoid necrosis.[42] However, it is now defined by a heterogeneous pattern of T2 hyperintensities on MRI scans which are associated with hypertension at the population level,[29] but can be seen in conditions that are not associated with hypertension, such as cerebral amyloid angiopathy, which has a prevalence between 7-70% in different cohorts, increasing with age.[43-44] All five markers of hypertensive arteriopathy have multifactorial causes, but replicating the epidemiological associations with hypertension still provides a validation of ABPM and HBPM SBP, as any association reproduced should reflect hypertension-dependent disease rather than be confounded by alternative causes of each marker of hypertensive arteriopathy.

These findings have a number of clinical implications. First, HBPM appears to be more accurate than clinic BP (the current standard after TIA and stroke)[14-16] in identifying

clinically relevant residual hypertension after initial assessment, investigation and treatment in patients with recent minor cerebrovascular events. Furthermore, it is likely that HBPM would be a more cost-effective option after TIA and stroke, as a recent cost-effectiveness analysis estimated that the cost of diagnosis per patient for HBPM and ABPM were £39 and £53 respectively. This analysis found ABPM to be more cost-effective than HBPM only because it assumed that ABPM was more accurate, however sensitivity analyses demonstrated a greater cost-effectiveness of HBPM when it was assumed to have at least equivalent accuracy, as in our study. Second, residual hypertension on HBPM was common despite intensive monitoring and optimised treatment, identifying a large subgroup who are at-risk yet potentially treatable. Incidence of residual hypertension was not greater on HBPM than on ABPM but HBPM classified patients more accurately into at risk groups. Nonetheless, ABPM still had an equal or greater prognostic value compared to clinic BP. Third, these results cast doubt on recent cost-effectiveness analyses[5] and associated guidelines.[1] In contrast to my findings, these had to assume that differences between HBPM and ABPM simply reflected inaccuracy of HBPM, due to the dearth of direct comparisons of the prognostic value of ABPM versus HBPM in the primary prevention setting. As well as being cheaper,[4] HBPM probably increases patient awareness of their condition and the factors that exacerbate it, although it doesn't provide information about nocturnal BP. It may therefore be prudent to do similar studies to this in the primary prevention setting to validate recent guidelines. Fourth, since the vast majority of new diagnoses of hypertension are now made in patients >50 years old and current guidelines recommend ABPM-based diagnosis at all ages, limited accuracy of ABPM in older age groups is likely to have important clinical and public health implications.

This study does have limitations. Firstly, it was carried out in a high-risk, cerebrovascular disease population which clearly limits generalizability. However, in the absence of similar data in other clinical settings, my findings may be of some more general use. Secondly, I studied HBPM and ABPM performed after 1 month of active treatment,

which may limit applicability to newly presenting patients. However, clinical guidelines in patients with TIA and stroke specifically recommend assessment of risk factor control one month after initiation of treatment.[25] Thirdly, there were significant differences in mean BP level on HBPM versus ABPM. However, this is consistent with previous studies[38] and a similar number of patients had residual hypertension on HBPM and ABPM, demonstrating the improved re-classification of patients through the use of HBPM. Fourthly, despite the significant predictive value of residual hypertension on HBPM, there were a relatively small number of clinical outcome events (n=51). However, the stronger associations with hypertensive arteriopathy on HBPM versus ABPM were reliably demonstrated in all 500 patients, consistent with differences in prognostic value. In addition, for associations with specific outcomes (cardiovascular events or premorbid hypertension), analyses were limited to patients undergoing both ABPM and HBPM to prevent confounding due to the small numbers of events. Finally, the longer duration of HBPM may result in greater habituation to HBPM compared to ABPM, with fewer artefactual elevations in BP due to a reduced startle or anxiety-related pressor response. It is possible that 7-day ABPM would perform as well as HBPM, even if a single awake ABPM is based on BP readings made approximately the same number of times as our 7-day HBPM.

In summary, in this chapter I have demonstrated that residual hypertension on HBPM at one month after a TIA or minor stroke was more strongly associated with premorbid hypertensive disease and was the best predictor of the risk of recurrent cardiovascular events compared to currently recommended methods including awake ABPM or clinic BP, due probably to greater validity in older patients and to the longer duration of monitoring, although further research is required to determine the relative predictive value of nocturnal ABPM. These results suggest that greater use of HBPM in secondary prevention of cerebrovascular disease will have significant efficacy and cost-effective benefits in reducing cardiovascular events, and highlight the need for more research to validate recent guidelines on diagnosis of hypertension in primary prevention.[1-3]

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CHAPTER SIX

Validity of day-to-day variability and maximum systolic blood pressure on multi-day home versus single-day ambulatory monitoring: frequency versus duration?

6.1 Summary

Blood pressure variability and maximum BP predict stroke independently of mean BP on clinic visit-to-visit and home day-to-day monitoring (HBPM), but not on 24-hr ambulatory monitoring (ABPM), but their physiological and clinical validity are questioned. Therefore I determined the validity of variability and maximum SBP on HBPM versus ABPM.

Among 500 consecutive patients with TIA or minor stroke (Oxford Vascular Study), the coefficient of variation (CV=standard deviation / mean) and maximum SBP on 1 month home monitoring (3 readings, 3 times daily) versus awake ABPM at 1 month were more strongly associated with clinical characteristics (CV: r^2=0.201 p<0.001 vs 0.07 p=0.001; max: 0.167 p<0.001 vs 0.03 p=0.47), 20 pre-event BP readings (CV: r=0.14 p=0.003 vs 0.06 p=0.24; max: 0.43 p<0.001 vs 0.12 p=0.02), and hypertensive arteriopathy (leukoaraiosis: CV OR=1.32 p<0.001 vs 1.04 p=0.12; Max: 1.27 p<0.001 vs 1.02 p=0.58). Max and CV SBP on HBPM versus ABPM were stronger predictors of all-cause mortality (per 10mmHg: 1.22, 1.04-1.43 vs 1.04, 0.87-1.25; per 1%CV: 1.22, 1.02-1.46 vs 0.99, 0.92-1.12), and cardiovascular events (max: 1.21, 1.03-1.43 vs 1.12, 0.95-1.32). Associations were stronger for All-days vs 7-day vs 1-day HBPM (CV-SBP: risk factors r^2: 0.20 vs 0.13 vs 0.09; leukoaraiosis: 1.32 vs 1.20 vs 1.10; cardiovascular events: 1.14 vs 1.11 vs 0.97). CV and max SBP were stronger predictors than mean SBP (mortality: CV 1.71 p=0.001; max 1.78 p<0.001; mean 1.53 p=0.003; CV events: CV 1.39 p=0.045; Max 1.61 p=0.002; Mean 1.47 p=0.009).

The validity of day-to-day variability and maximum SBP on HBPM compared to ABPM was demonstrated by stronger associations with clinical characteristics, hypertensive arteriopathy and cardiovascular events, due in part to duration of monitoring.

6.2 Introduction

Awake systolic blood pressure (SBP) variability on ABPM predicts the future risk of cardiovascular events,[1, 2] is associated with clinical characteristics[3, 4] and identifies physiologically-determined blood pressure pathology such as the 'morning surge'.[5] Unfortunately, despite the greater predictive value of mean BP on ABPM compared to clinic readings, awake SBP variability on ABPM has a relatively weak predictive value[1] and a lack of variability-specific treatment options has limited its translation into clinical practice. Furthermore, maximum blood pressure attained on ABPM has not been specifically investigated in a large prospective study.

In contrast to variability and maximum BP on ABPM, episodic hypertension, maximum SBP and visit-to-visit variability in SBP in clinic[6, 7] were strong predictors of incident and recurrent cardiovascular events in 5 large cohorts.[8] Compared to atenolol-based regimens, treatment with an amlodipine-based regimen in ASCOT-BPLA or a thiazide diuretic in the MRC-2 study[8] reduced variability and maximum SBP and hence stroke risk, with similar drug effects in meta-analyses of all published studies.[9-11] The prognostic significance of visit-to-visit variability in SBP has subsequently been independently confirmed[2,12,13] but only one report has demonstrated a strong relationship between maximum SBP and end-organ damage compared to mean SBP,[14] and no reports have addressed the relationship with cardiovascular events.

Recent guidelines have not identified variability and maximum SBP as treatment targets,[15-17] partly because their validity as a marker of physiologically determined pathology is doubted, with poor medication adherence and measurement artefact cited as likely explanations for their clinical effects.[18] ABPM remains the recommended method of assessing blood pressure, despite a lack of comparative evidence as described in chapter 5,[15] and the assumed physiological precision of ABPM in charting an individual's diurnal BP variation results in its continued use to assess SBP variability.[19] However, single-day ABPM has limitations: it cannot assess day-to-day SBP variability, which may have an independent physiological basis; short-term sampling with ABPM is more likely to miss

significant episodic peaks occurring less frequently than daily; and ABPM may be more prone to measurement artefacts due to less time to habituate to readings.[20, 21]

Therefore, in a high-risk population with TIA or minor stroke I compared the clinical and physiological validity of variability in SBP and maximum SBP on 1 month of day-to-day home versus single-day ABPM readings by comparison with clinical characteristics, premorbid readings, markers of hypertensive arteriopathy and the risk of clinical events and determined to what extent these relationships depended on duration of monitoring.

6.3 Methods

6.3.1 Procedures

This analysis was carried out in the same population as that studied in Chapter 5, with consecutive patients recruited between April 2008 and January 2012 from the Oxford Vascular Study's (OXVASC)[22] TIA and minor stroke clinic, usually within twenty-four hours of referral.[23] Again, clinic BP was measured at ascertainment and the one month follow-up visit in the non-dominant arm, by trained personnel, in the sitting position after five minutes of rest, with two measurements made 5 minutes apart. From the ascertainment visit, or the earliest opportunity after discharge, all patients performed sets of three home BP readings (HBPM), three times daily (on waking, mid-morning at ~10-11am and before sleep) with a Bluetooth-enabled, regularly-calibrated, telemetric BP monitor. At the 1 month follow-up visit, awake ambulatory measurements (ABPM) were performed with an A&D TM-2430 monitor in the non-dominant arm, fitted by a trained study nurse, at 30 minute intervals during the day and 60 minute intervals at night.

Patients were asked to continue home monitoring until at least the one month follow-up appointment. Mean BP was treated to a target of <130/80 on home monitoring or mean ABPM, except in the minority of patients with haemodynamically significant stenosis (bilateral carotid stenosis >70% or end-artery stenosis >70%) when targets were determined on an individual basis. Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a combination of perindopril arginine

5mg and indapamide 1.25mg, followed by amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion.

For this analysis, markers of hypertensive arteriopathy included creatinine (mmol/L), a diagnosis of stroke vs TIA, aortic stiffness (PWV=pulse wave velocity, m/s) and cerebral white matter disease (leukoaraiosis). Associations between BP variability and cognitive impairment are complex and prone to effects of reverse causation, and therefore were not assessed. Carotid-femoral PWV was assessed in a subgroup of 150 patients by applanation tonometry (Sphygmocor, AtCor Medical, Sydney, Australia), either at the acute assessment or at one month, taking the average of two acceptable measures (SD<2). Leukoaraiosis was assessed on axial T2 scans, scored according to a modified version of the Fazekas scale[24] by experienced observers (M Simoni/L Li) and on the simple 4 point Oxford scale: 'None', 'Mild,' 'Moderate' or 'Severe' (see chapter 5). This score was then dichotomised into either the presence or absence of advanced leukoaraiosis (moderate or severe versus mild or none).

Recurrent cardiovascular events were identified by multiple overlapping methods of ascertainment,[22] including face-to-face interviews to identify symptoms consistent with either a TIA, stroke, myocardial infarction or acute peripheral vascular event at each follow-up. Where possible, all patients with potential recurrent events were reviewed by a study physician and subsequently discussed with the principal investigator (PR) and a panel of stroke neurologists and physicians for verification of diagnosis and aetiological classification.

6.3.2 Analysis

In contrast to chapter 5, which aimed to compare the validity of HBPM and ABPM as recommended by current guidelines, in this analysis the aim was to derive the best available estimates of BP variability and maximum SBP. Therefore, home SBP and DBP were derived from all readings acquired from 7 days after the recruitment visit (to reduce acute treatment effects) until readings were not performed on at least 3 days of the week,

the monitor was returned or 90 days had elapsed, with the average of the last two readings of each BP cluster used to derive BP indices. Analyses were performed using all readings, or the 7 days or 1 day of readings just prior to the ABPM. As in chapter 5, SBP and DBP on ABPM were derived for awake readings following automated and manual exclusion of artefactual measurements according to predefined criteria,[25] whilst premorbid SBP and DBP were derived from up to the last 20 readings recorded in the lifetime primary care record. For each method of measurement, mean, minimum and maximum SBP and DBP were derived, whilst variability in SBP and DBP was determined as the coefficient of variation (CV =standard deviation / mean). On HBPM, CV was calculated as the residual CV (rCV) about a 9 day moving average rather than the global mean to remove slow variations in blood pressure due to changes in treatment. Finally, the frequency-dependent variation in BP was measured from the power spectrum of all clusters, interpolated by a cubic spline to a continuous sampling rate, for greater than weekly (<0.12 cycles / day), weekly (0.12-0.25 cyc/day), day-to-day (0.25-0.75 cyc/day) and diurnal (0.75-1.2 cyc/day) periods.

6.3.3 Statistical analysis

Gender differences in demographic characteristics were identified by chi-squared tests for discrete variables and t-tests for continuous variables. Unadjusted differences in BP indices between discrete patient groups were assessed by t-tests or ANOVA, whilst univariate correlations with continuous demographic indices were measured by linear regression. The overall strength of association between BP indices and all clinical characteristics were determined by general linear models (GLM, SPSS sum of squares type IV) including age, gender, BMI, atrial fibrillation (premorbid or diagnosed within 6 weeks of the event), current smoking and history of myocardial infarction, diabetes, hyperlipidaemia, cardiac failure or family history of stroke, with or without an interaction term between age and gender. Secondly, the distribution of BP indices across the population was determined by stratification into gender and 5 quintiles of age. Finally, relationships with premorbid

hypertension and markers of hypertensive arteriopathy were determined by linear regression for continuous estimates, by binary logistic regression for dichotomous measures (stroke vs TIA, advanced leukoaraiosis) and by ordinal regression (Fazekas score, total markers of hypertensive arteriopathy).

The risk of recurrent cardiovascular events per 10mmHg increase in maximum SBP or 1% increase in CV-SBP on ABPM or HBPM was assessed by Cox Proportional Hazards Regression to determine Hazard Ratios (HR), unadjusted and adjusted for age, gender, diabetes, smoking, family history and hyperlipidaemia. Recurrent events identified included probable or definite stroke, myocardial infarction, acute peripheral vascular events (ruptured abdominal aortic aneurysm or acute limb ischaemia), cardiovascular death or death of any cause. A composite outcome measure included TIA, stroke, myocardial infarction, acute peripheral vascular events and cardiovascular death.

6.4 Findings

6.4.1 Study population

This analysis was performed in the same 500 patients investigated in chapter 5. Patient characteristics are shown in table 5.1. As expected, there were strong associations between mean, minimum and maximum SBP within each BP measurement method and significant associations for these measures between BP measurement methods, but CV SBP was not correlated with mean SBP, whilst maximum SBP was correlated with both CV-SBP and mean SBP (table 6.1).

Table 6.1 Associations between variability and maximum SBP and DBP on premorbid, home (HBPM) and ambulatory (ABPM) blood pressure monitoring. Each cell contains the direction of effect, p-value and r^2 from a linear regression. Shaded areas demonstrate statistically significant associations. CV=coefficient of variation (standard deviation / mean).

	PMD Mean SBP	PMD Min SBP	PMD Max SBP	PMD SBP CV	Awake Mean SBP	Awake Min SBP	Awake Max SBP	Awake SBP CV	HBPM Mean SBP	HBPM Min SBP	HBPM Max SBP	HBPM SBP CV
PMD Min SBP	positive 0.000 0.333											
PMD Max SBP	positive 0.000 0.723	positive 0.000 0.049										
PMD SBP CV	positive 0.000 0.072	negative 0.000 0.144	positive 0.000 0.347									
Awake Mean SBP	positive 0.000 0.107	positive 0.000 0.064	positive 0.000 0.048	0.332 0.002								
Awake Min SBP	positive 0.000 0.042	positive 0.001 0.028	positive 0.005 0.020	0.561 0.000	positive 0.000 0.339							
Awake Max SBP	positive 0.001 0.028	0.084 0.006	positive 0.008 0.017	0.263 0.003	positive 0.000 0.365	positive 0.000 0.028						
Awake SBP CV	0.930 0.000	0.095 0.000	0.609 0.000	0.111 0.006	0.455 0.001	negative 0.000 0.230	positive 0.000 0.433					
HBPM Mean SBP	positive 0.000 0.227	positive 0.000 0.099	positive 0.000 0.155	positive 0.006 0.017	positive 0.000 0.365	positive 0.000 0.118	positive 0.000 0.096	0.944 0.000				
HBPM Min SBP	positive 0.000 0.057	positive 0.000 0.068	positive 0.002 0.022	0.888 0.000	positive 0.000 0.166	positive 0.000 0.112	positive 0.001 0.024	negative 0.005 0.017	positive 0.000 0.526			
HBPM Max SBP	positive 0.000 0.209	positive 0.000 0.072	positive 0.000 0.165	positive 0.000 0.035	positive 0.000 0.280	positive 0.000 0.063	positive 0.000 0.099	0.083 0.006	positive 0.000 0.615	positive 0.000 0.103		
HBPM SBP CV	positive 0.000 0.044	0.308 0.002	positive 0.000 0.050	positive 0.000 0.033	0.060 0.008	negative 0.011 0.014	positive 0.017 0.013	positive 0.000 0.061	positive 0.019 0.011	negative 0.000 0.203	positive 0.000 0.288	
HBPM SBP rCV	positive 0.001 0.023	0.753 0.000	positive 0.000 0.040	positive 0.000 0.035	0.828 0.000	negative 0.001 0.026	0.213 0.004	positive 0.000 0.059	0.248 0.003	negative 0.000 0.221	positive 0.000 0.184	positive 0.000 0.789

6.4.2 *Association between variability and maximum BP with clinical characteristics*

Age, gender and cardiovascular risk factors were more strongly associated with maximum SBP, mean SBP and CV of SBP on HBPM than on ABPM, with stronger associations with clinical characteristics with increasing duration of HBPM (table 6.2). Comparing different BP indices, clinical characteristics were most strongly associated with variability in SBP, followed by maximum SBP, with a weaker association for mean SBP. The strong association with variability in SBP on HBPM reflected associations with day-to-

day SBP variability at each time of day and with variability in SBP within each day, with the strongest influence on day-to-day and diurnal variability rather than longer time periods in frequency based analysis (table 6.2).

Blood Pressure Models		**r^2**	**p-value**	**Independent clinical predictors**
Systolic Blood Pressure				
Mean	ABPM	0.043	0.019	Male* AF LVF* -MI
	1d HBPM	0.129	<0.0001	Age*** Male** LVF** DM lipid* -MI*
	7d HBPM	0.136	<0.0001	Age*** Male** LVF** DM lipid* -MI* smoke* BMI*
	All HBPM	0.129	<0.0001	Age*** Male** LVF* DM lipid* -MI* smoke* BMI*
	Premorbid	0.270	<0.0001	Age*** -MI** BMI***
Maximum	ABPM	0.025	0.47	*LVF**
	1d HBPM	0.125	<0.0001	Age*** Male** DM lipid* LVF** -MI
	7d HBPM	0.146	<0.0001	Age*** Male* lipid* LVF*
	All HBPM	0.167	<0.0001	Age*** lipid** smoke LVF** -MI
	Premorbid	0.290	<0.0001	Age*** -MI** BMI*** DM
Total Variability (CV)	ABPM	0.070	0.001	Age** Female** EtOH**
	1d HBPM	0.087	<0.0001	Age** LVF** AF
	7d HBPM	0.133	<0.0001	Age*** Female** AF** BMI*
	All HBPM	0.201	<0.0001	Age*** Female*** FHx AF** -MI EtOH BMI
	Premorbid	0.049	0.025	Age* Female* EtOH
Day-to-day Variability (CV)	Morning	0.072	<0.0001	Age** Female*** FHx* smoke* AF
	Mid-morning	0.138	<0.0001	Age*** Female** AF* BMI*
	Evening	0.120	<0.0001	Age*** Female** AF* LVF EtOH
Short-term Variability (CV)	Diurnal	0.228	<0.0001	Age*** Female** AF* MI* BMI
	Within Visit	0.127	<0.0001	Age* Female*** LVF BMI**
Spectral Analysis	*> weekly*	0.042	0.13	*(smoke* BMI*)*
	Weekly	0.052	0.044	Age* LVF* EtOH
	Day-to-day	0.108	<0.0001	Age*** Female smoke* LVF*
	Diurnal	0.142	<0.0001	Age*** Female**

Table 6.2 Relationships between clinical characteristics and all blood pressure indices in multivariate general linear models. * p<0.05; **p<0.01; ***p<0.001

6.4.3 Clinical determinants of variability and maximum SBP

Age was the strongest determinant of both maximum SBP and DBP and variability in SBP and DBP on home and premorbid readings in univariate analyses (table 6.3) and in multivariate models (table 6.2). However, although age was associated with variability in SBP on ABPM, it was not associated with mean or maximum SBP on ABPM. Gender was the next strongest predictor of all BP indices, but male gender was associated with a greater mean and maximum SBP, whilst female gender predicted greater variability in SBP. In addition to age and gender, AF determined day-to-day variability in SBP, whilst heart failure was a strong predictor of maximum SBP.

6.4.4 Distribution of variability and maximum SBP by age and gender

Given the strong relationship with age and gender, BP indices were determined stratified by gender and quintiles of age (figure 6.1). For HBPM and premorbid visit-to-visit readings, this demonstrated a well defined increase with age for maximum SBP and variability in SBP for both genders, but with greater variability in SBP in women at every age. This was predominantly due to a greater age-associated increase in maximum SBP compared to the increase in mean and minimum SBP, although with a greater increase in women than men. However, the relationship between age and variability in SBP or maximum SBP was less well defined on ABPM, especially for women, with an excess variability in younger women compared to men (figure 6.1). Mean, minimum and maximum DBP fell with increasing age with no significant difference between genders (figure 6.1). In contrast, variability in DBP increased with age as for SBP but this trend was better defined on HBPM and premorbid visit-to-visit variability than ABPM, again with a non-significant increase in variability in the youngest women compared to men on both ABPM and HBPM. Day-to-day readings after waking, mid-morning and in the evening demonstrated variations in maximum blood pressure that were similar to analyses using all timepoints (figure 6.2).

Characteristics	Premorbid						HBPM						Awake					
	Mean			CV			Mean			rCV			Mean			CV		
Age	0.45	<0.001	***	0.241	<0.001	***	0.218	<0.001	***	0.368	<0.001	***	0	0.302		0.132	0.005	**
Male vs Female	139.5 (13)	138.5 (15)		9.3 (3)	10.2 (3)		125.4 (12)	121.8 (13)		5.5 (2)	6 (2)		128.5 (13)	126.2 (12)		11.3 (3)	12.3 (4)	
	0.44			0.008		**	0.001		**	0.002		**	0.046		*	0.003		**
Hypertension	127.7 (10)	145.7 (11)		8.4 (4)	10.5 (3)		117.6 (10)	127.4 (13)		5.5 (2)	5.9 (2)		124.6 (10)	129.2 (13)		12.1 (4)	11.6 (4)	
	<0.001		***	<0.001		***	<0.001		***	0.025		*	<0.001		***	0.198		
Family History CVA	139.1 (14)	138.6 (14)		9.7 (3)	9.7 (3)		124.1 (13)	122.4 (12)		5.8 (2)	5.6 (2)		127.8 (12)	126.5 (12)		11.9 (3)	11.5 (4)	
	0.736			0.994			0.164			0.2			0.308			0.377		
Hyperlipidaemia	138.1 (14)	140.1 (13)		9.5 (3)	10 (3)		122.2 (12)	125.7 (13)		5.7 (2)	5.9 (2)		126.6 (12)	128.5 (13)		11.8 (3)	11.8 (4)	
	0.12			0.094			0.003		**	0.264			0.107			0.976		
Diabetes	138.7 (14)	140.8 (13)		9.6 (3)	10.7 (3)		122.9 (12)	127.5 (14)		5.7 (2)	6 (2)		127.1 (12)	128.9 (13)		11.8 (4)	11.8 (3)	
	0.2			0.004		**	0.006		**	0.169			0.303			0.992		
Heart Failure	138.6 (14)	143.2 (14)		9.6 (3)	11 (3)		123.1 (13)	129.9 (13)		5.7 (2)	6.9 (2)		127.2 (12)	130.4 (13)		11.7 (4)	12.5 (3)	
	0.092			0.034		*	0.007		**	<0.001		***	0.193			0.139		
Smoker	139.7 (13)	134.3 (16)		9.8 (3)	9.5 (4)		123.5 (13)	124.8 (13)		5.8 (2)	5.3 (2)		127 (12)	129.7 (13)		11.8 (4)	11.7 (3)	
	0.01		*	0.564			0.43			0.012		*	0.118			0.783		
Atrial Fibrillation	138.4 (14)	142.3 (12)		9.6 (3)	10.4 (3)		123.4 (13)	124.8 (13)		5.6 (2)	6.7 (2)		127.7 (12)	125.7 (12)		11.7 (4)	12.1 (3)	
	0.013		*	0.042		*	0.398			<0.001		***	0.207			0.417		
Previous stroke	139.3 (13)	138.9 (14)		10 (3)	9.7 (3)		123 (11)	123.8 (13)		5.9 (2)	5.7 (2)		126.2 (11)	127.8 (13)		11.7 (3)	11.8 (4)	
	0.758			0.351			0.454			0.213			0.194			0.675		
Stroke vs TIA	137.6 (13)	140.7 (14)		9.7 (3)	9.8 (3)		121.8 (11)	126.3 (14)		5.9 (2)	5.6 (2)		126.8 (11)	128.5 (14)		11.9 (4)	11.6 (3)	
	0.019		*	0.694			<0.001		***	0.082			0.173			0.298		
Myocardial Infarction	139.3 (14)	134.1 (11)		9.7 (3)	10.7 (3)		123.6 (13)	123.6 (9)		5.7 (2)	6.8 (2)		127.6 (12)	124.8 (10)		11.7 (4)	12.5 (3)	
	0.029		*	0.104			0.999			0.017		*	0.179			0.261		
BMI	0.164	<0.001	***	0	0.82		0.114	0.013	*	-0.1	0.019	*	0.08	0.091		0.02	0.604	
Weight	0.09	0.137		0	0.713		0.1	0.107		0.1	0.104		0.1	0.113		0	0.673	
Waist : hip ratio	0.04	0.291		0.06	0.178		-0.1	0.02	*	0.139	0.002	**	0	0.057		0.02	0.544	
Creatinine	0.183	<0.001	***	0.07	0.1		0.231	<0.001	***	0.131	0.003	**	0.109	0.021	*	0.05	0.205	
Cholesterol	0	0.063		0	0.13		-0.1	0.015	*	0	0.1		0.02	0.636		0	0.562	
TSH	0.119	0.012	*	0.06	0.162		0.117	0.011	*	0.08	0.08		0.03	0.446		0	0.921	
GFR	-0.19	<0.001	***	-0.16	<0.001	***	0	0.439		-0.37	<0.001	***	0.08	0.108		-0.1	0.04	*
Alcohol intake	0	0.272		0	0.633		0.01	0.824		0	0.58		0	0.879		0.04	0.346	

Table 6.3. Unadjusted relationships between clinical characteristics and systolic blood pressure variability on premorbid, home and ambulatory blood pressure readings. Dichotomous variables are given as mean (SD) with p-values from t-tests for absence vs presence of each characteristic. Correlations between continuous variables are given as r and p-values. * p<0.05, ** p<0.01, ***p<0.001

Characteristics	Premorbid						HBPM						Awake ABPM					
	Minimum			Maximum			Minimum			Maximum			Minimum			Maximum		
Age	0.173	<0.001	***	0.467	<0.001	***	0	0.821		0.345	<0.001	***	-0.11	0.014	*	0.01	0.832	
Male vs Female	119.4 (12)	114.9 (12)		163.5 (25)	166 (27)		103.6 (12)	98.1 (13)		152.6 (19)	150.1 (20)		101.3 (13)	98.2 (12)		163 (21)	161.8 (20)	
	<0.001		***	0.286			<0.001		***	0.156			0.01		*	0.536		
Hypertension	113.7 (11)	119.4 (13)		143.4 (16)	177.4 (22)		97.7 (10)	103 (13)		142.8 (18)	156.7 (19)		97.5 (11)	101.2 (14)		160.9 (21)	163.4 (20)	
	<0.001		***	<0.001		***	<0.001		***	<0.001		***	0.001		**	0.2		
Family History CVA	117.5 (13)	116.7 (12)		165.1 (26)	163.8 (25)		101.2 (13)	100.1 (12)		152.3 (20)	148.7 (19)		99.7 (13)	99.9 (12)		163.5 (20)	159.7 (21)	
	0.522			0.614			0.334			0.061			0.898			0.08		
Hyperlipidaemia	117.6 (13)	116.8 (11)		162.4 (26)	167.8 (25)		100.2 (12)	102 (13)		148.7 (18)	155.1 (21)		98.9 (13)	101.2 (13)		161.6 (19)	163.6 (22)	
	0.446			0.026		*	0.124			<0.001		***	0.062			0.304		
Diabetes	117.8 (13)	114.6 (12)		163.1 (25)	173.2 (26)		100.5 (13)	103.1 (13)		150.6 (19)	155.8 (21)		99.6 (13)	100.8 (13)		162.1 (20)	164.4 (22)	
	0.034		*	0.002		**	0.101			0.048		*	0.461			0.42		
Heart Failure	117.4 (12)	115.4 (15)		163.8 (26)	175.8 (23)		100.8 (13)	101.3 (11)		150.4 (19)	164.6 (24)		99.9 (13)	98.3 (12)		161.9 (21)	168.5 (17)	
	0.464			0.011		*	0.811			0.003		**	0.471			0.049		*
Migraine	117.9 (13)	115.8 (12)		164.9 (25)	164 (26)		101.8 (13)	98.9 (12)		152.2 (19)	149.3 (20)		99.7 (13)	100.1 (12)		163.1 (22)	160.8 (17)	
	0.087			0.73			0.015		*	0.134			0.782			0.231		
Smoker	117.4 (13)	116.4 (11)		166.1 (25)	154.8 (29)		100.4 (12)	103.6 (13)		151.6 (19)	150.2 (22)		99.7 (13)	100.3 (14)		162.4 (20)	162.5 (20)	
	0.512			0.003		**	0.065			0.611			0.738			0.967		
Atrial Fibrillation	117.3 (12)	117.2 (14)		163.4 (26)	172.1 (22)		101.3 (13)	98.5 (12)		150.6 (19)	155.9 (21)		100.2 (13)	97.1 (10)		162.6 (21)	161.4 (19)	
	0.963			0.003		**	0.081			0.052			0.033		*	0.645		
Previous stroke	116.9 (11)	117.4 (13)		165.5 (26)	164.5 (26)		100.3 (10)	101.1 (13)		150.9 (18)	151.5 (20)		98.7 (11)	100.1 (13)		159.5 (20)	163.3 (20)	
	0.707			0.735			0.465			0.75			0.27			0.095		
Stroke vs TIA	116.5 (12)	118.4 (13)		163.2 (26)	166.4 (26)		99.1 (12)	103.8 (13)		149.6 (19)	153.7 (20)		99.1 (11)	100.7 (14)		162.6 (21)	162.4 (20)	
	0.109			0.193			<0.001		***	0.025		*	0.218			0.939		
Myocardial Infarction	117.7 (12)	110.8 (11)		165 (26)	160.8 (15)		101.1 (13)	98.2 (11)		151.3 (20)	152.7 (16)		100 (13)	95.6 (12)		162.5 (21)	161.8 (18)	
	0.002		**	0.193			0.165			0.661			0.079			0.845		
BMI	0.08	0.054		0.129	0.005	**	0.123	0.008	**	0	0.845		0	0.778		0.02	0.581	
Weight	0.09	0.144		0.05	0.436		0	0.898		0.137	0.031	*	0	0.464		0.13	0.107	
Waist : hip ratio	0	0.71		0.06	0.155		-0.17	<0.001	***	0	0.919		0	0.436		0	0.158	
Creatinine	0.095	0.038	*	0.202	<0.001	***	0.119	0.007	**	0.241	<0.001	***	0.04	0.295		0.133	0.005	**
Cholesterol	0	0.617		-0.12	0.008	**	0	0.713		-0.09	0.036	*	0	0.97		0	0.971	
TSH	0.05	0.215		0.106	0.026	*	0.01	0.806		0.146	0.002	**	0	0.97		0.03	0.439	
GFR	0	0.375		-0.27	<0.001	***	0.155	0.002	**	-0.21	<0.001	***	0.118	0.023	*	0	0.936	
Alcohol intake	0	0.496		0	0.348		0.02	0.584		0	0.776		0	0.908		0.05	0.258	

Table 6.4 Unadjusted relationships between clinical characteristics and minimum or maximum systolic blood pressure on premorbid, home and ambulatory blood pressure readings. Dichotomous variables are mean (SD) with p-values from t-tests for absence vs presence of each characteristic. Correlations between continuous variables are given as r and p-values. * p<0.05, ** p<0.01, ***p<0.001

However, variability in SBP and DBP increased more with age in the mid-morning and evening than immediately after waking. Furthermore, the slight increase in variability in young women was only apparent immediately after waking, and was not seen in the mid-morning and evening (figure 6.2).

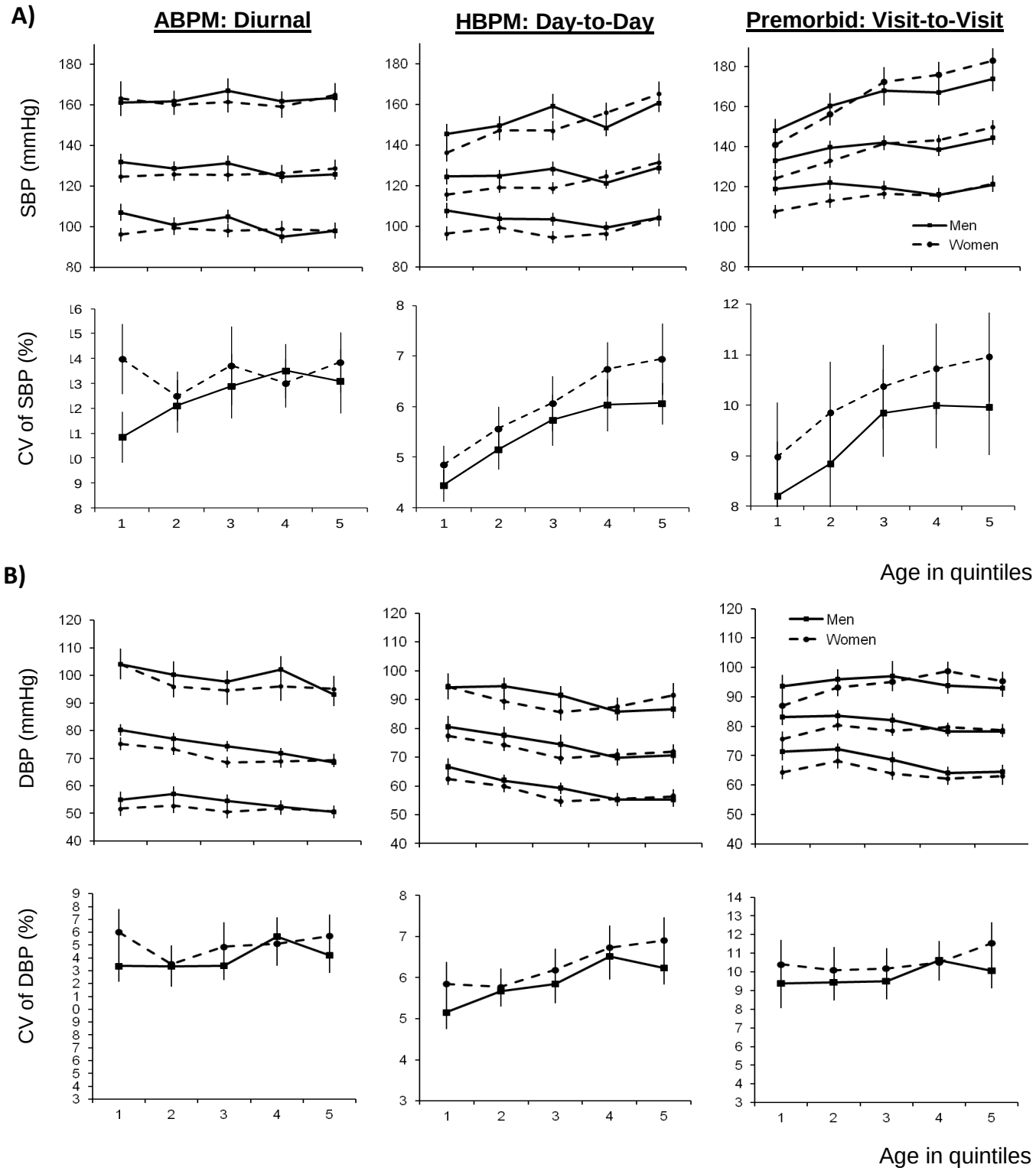

Figure 6.1. Relationship between systolic or diastolic blood pressure measures with age and gender. Age is divided into quintiles for each gender. Error bars represent 95% confidence intervals. Panel A shows SBP measures and panel B shows DBP measures.

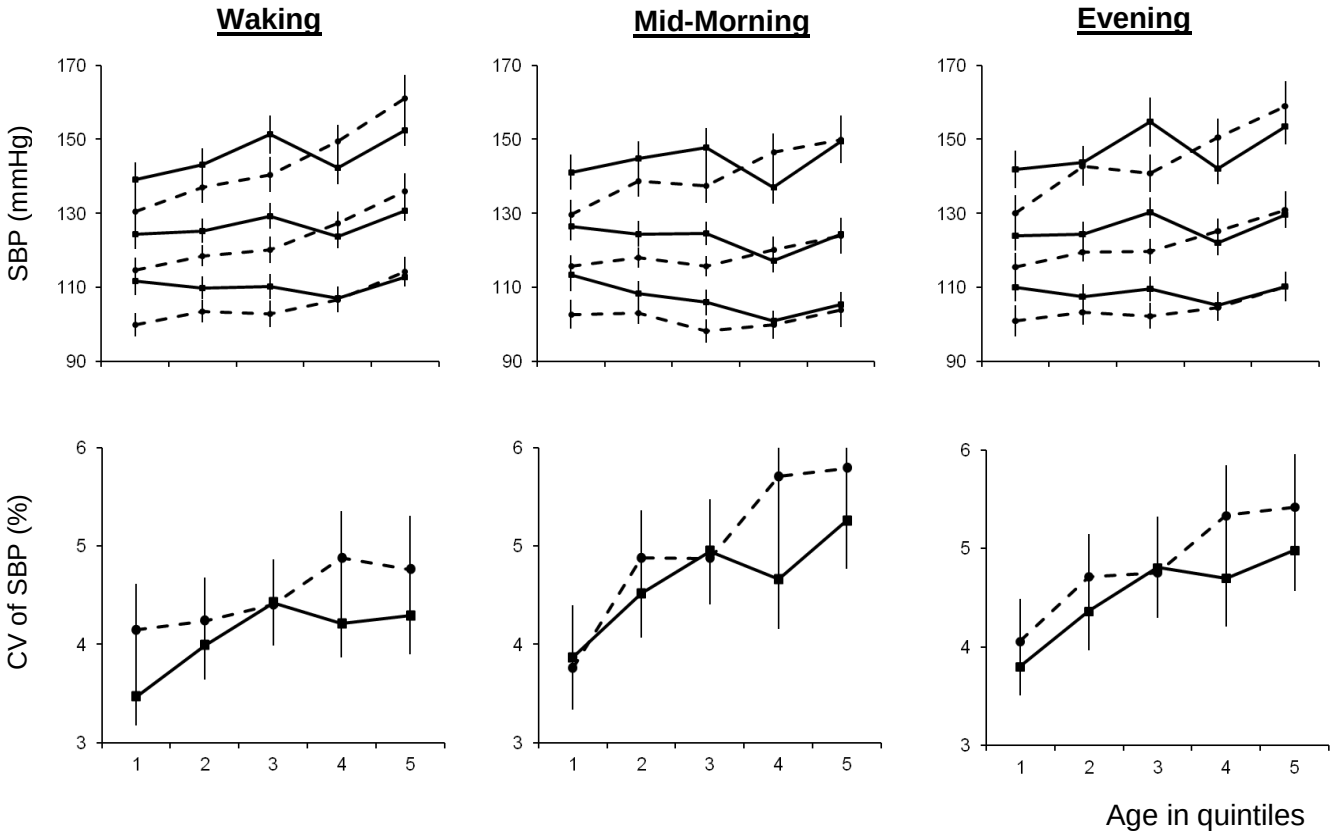

Figure 6.2. Relationship between systolic blood pressure characteristics on HBPM with age and gender at each time of day. Age is divided into quintiles for each gender. Error bars represent 95% confidence intervals. Panel A shows SBP measures and panel B shows DBP measures.

6.4.5 Associations of premorbid variability and maximum BP with ABPM and HBPM

There was no association between variability in SBP or DBP on awake ABPM with premorbid variability in BP and no significant relationships between variability in either SBP or DBP on HBPM with premorbid variability in BP when using only 1 day of home blood pressure readings. However, there was a significant relationship between variability in SBP or DBP on HBPM with variability in premorbid readings with 7 days of HBPM, and an even stronger relationship when using all eligible readings on HBPM (table 6.5). There was only a weak relationship between maximum SBP on ABPM and premorbid maximum SBP (table 6.5), with no relationship for maximum DBP. However, maximum SBP and DBP on 1 day of HBPM was significantly related to maximum SBP on premorbid readings, and the strength of the relationship increased with increasing duration of monitoring (table 6.5).

	ABPM		1 Day of HBPM		7 days of HBPM		All days of HBPM	
	r or OR	p	r or OR	p	r or OR	p	r or OR	p
Variability in SBP								
Premorbid SBP (%CV)	**0.06**	0.24	**0.05**	0.31	**0.13**	0.007	**0.14**	0.003
Creatinine (mmol/L)	**0.06**	0.20	**0.12**	0.01	**0.11**	0.01	**0.13**	0.003
Aortic PWV (m/s)	**-0.04**	0.57	**0.09**	0.32	**0.14**	0.10	**0.13**	0.13
Stroke vs TIA	**0.97** (0.92-1.03)	0.30	**0.97** (0.93-1.01)	0.13	**0.91** (0.83-1.00)	0.06	**0.92** (0.83-1.02)	0.10
Advanced Leukoaraiosis	**0.96** (0.91-1.01)	0.14	**1.07** (1.02-1.11)	0.003	**1.19** (1.08-1.30)	0.001	**1.23** (1.10-1.36)	<0.001
Fazekas Score	**1.04** (0.99-1.10)	0.12	**1.10** (1.05-1.14)	<0.001	**1.20** (1.10-1.31)	<0.001	**1.32** (1.20-1.46)	<0.001
Maximum SBP								
Premorbid SBP (mmHg)	**0.12**	0.02	**0.37**	<0.001	**0.43**	<0.001	**0.43**	<0.001
Creatinine (mmol/L)	**0.14**	0.004	**0.23**	<0.001	**0.25**	<0.001	**0.25**	<0.001
Aortic PWV (m/s)	**-0.02**	0.78	**0.19**	0.03	**0.17**	0.049	**0.23**	0.006
Stroke vs TIA	**1.00** (0.91-1.09)	0.93	**1.11** (1.00-1.24)	0.05	**1.18** (1.06-1.32)	0.002	**1.12** (1.02-1.23)	0.019
Advanced Leukoaraiosis	**0.99** (0.90-1.10)	0.92	**1.22** (1.08-1.37)	0.001	**1.22** (1.09-1.36)	<0.001	**1.24** (1.12-1.37)	<0.001
Fazekas Score	**1.02** (0.94-1.12)	0.58	**1.28** (1.15-1.43)	<0.001	**1.28** (1.16-1.42)	<0.001	**1.27** (1.16-1.40)	<0.001

Table 6.5. Relationships between variability in SBP or maximum SBP and markers of hypertensive arteriopathy and premorbid hypertension, according to duration of monitoring. Variability in SBP is defined as the coefficient of variation. Results are given as p-values plus r values from linear regression, odds ratios (OR) from binary logistic regression or ORs from ordinal regression.

6.4.6 Associations of variability and maximum SBP with hypertensive arteriopathy

There was no significant association between variability in SBP on ABPM with any marker of hypertensive arteriopathy (table 3), only a weak association between maximum SBP on ABPM with creatinine, and no association between maximum SBP on ABPM and either aortic stiffness, a diagnosis of stroke or leukoaraiosis. In contrast, with all HBPM readings, variability in SBP was significantly associated with creatinine and severity of leukoaraiosis, whilst maximum SBP was associated with all markers of hypertensive arteriopathy, including aortic stiffness, creatinine, stroke and severity of leukoaraiosis. Furthermore, the strength of the association between either variability or maximum SBP on HBPM with markers of hypertensive arteriopathy was stronger with more than 1 day of monitoring compared to only a single day of monitoring, with further increases in the strength of association between variability in SBP on HBPM with leukoaraiosis with all readings compared to 7 days of monitoring. Results were similar for variability of DBP.

6.4.7 Predictive value of variability and maximum BP for cardiovascular events

Maximum SBP and variability in SBP on ABPM or a single day of HBPM did not predict the risk of recurrent cardiovascular events (table 6.6). However, longer periods of HBPM increased the predictive value of both maximum SBP and variability in SBP on HBPM with maximum SBP significantly predicting the risk of all cause death and the risk of a composite of cardiovascular events before and after adjustment for age, gender and cardiovascular risk factors. Variability in SBP also predicted the risk of all-cause death or all cardiovascular events, but after adjustment, only the association with all cause death remained. With increasing duration of monitoring, there was a systematic increase in the strength of the relationship between CV-SBP and all events, and between maximum SBP and the risk of stroke. For non-stroke events, although the effect of increased duration of monitoring on the strength of association between maximum SBP and outcomes was less clear, the risk of all outcomes was higher when estimated with all days of monitoring compared to 7 days of monitoring.

Model	Ev	ABPM HR	ABPM 95% CI	ABPM p-val	1 day HBPM HR	1 day HBPM 95% CI	1 day HBPM p-val	7 days HBPM HR	7 days HBPM 95% CI	7 days HBPM p-val	All days HBPM HR	All days HBPM 95% CI	All days HBPM p-val
Maximum SBP													
Unadjusted Model													
Stroke, MI, PVD, CV death	29	**1.11**	(0.95 - 1.31)	0.19	**1.22**	(0.96 - 1.56)	0.1	**1.21**	(1.03 - 1.43)	0.022*	**1.27**	(1.10 - 1.48)	0.002**
All cause death	30	**1.04**	(0.87 - 1.23)	0.68	**1.39**	(1.12 - 1.72)	0.003*	**1.28**	(1.09 - 1.50)	0.002*	**1.34**	(1.16 - 1.55)	<0.001*
Cardiovascular death	13	**1.04**	(0.80 - 1.35)	0.77	**1.26**	(0.88 - 1.80)	0.21	**1.23**	(0.96 - 1.57)	0.1	**1.32**	(1.06 - 1.64)	0.014*
Stroke	20	**1.01**	(1.00 - 1.03)	0.13	**1.08**	(0.79 - 1.47)	0.62	**1.17**	(0.95 - 1.44)	0.13	**1.20**	(0.99 - 1.45)	0.06
Adjusted Model													
Stroke, MI, PVD, CV death		**1.12**	(0.95 - 1.32)	0.19	**1.12**	(0.86 - 1.46)	0.41	**1.13**	(0.95 - 1.34)	0.18	**1.21**	(1.03 - 1.43)	0.021*
All cause death	30	**1.04**	(0.87 - 1.25)	0.64	**1.22**	(0.97 - 1.53)	0.09	**1.13**	(0.95 - 1.35)	0.16	**1.22**	(1.04 - 1.43)	0.016*
Cardiovascular death	13	**1.06**	(0.82 - 1.38)	0.63	**1.08**	(0.73 - 1.60)	0.71	**1.08**	(0.83 - 1.41)	0.55	**1.20**	(0.94 - 1.53)	0.14
Stroke	20	**1.01**	(0.99 - 1.03)	0.17	**0.98**	(0.70 - 1.39)	0.92	**1.09**	(0.88 - 1.36)	0.43	**1.13**	(0.92 - 1.39)	0.25
Variability in SBP (% CV)													
Unadjusted Model													
Stroke, MI, PVD, CV death	29	**0.96**	(0.95 - 1.15)	0.36	**1.00**	(0.91 - 1.09)	0.98	**1.06**	(0.90 - 1.25)	0.48	**1.19**	(1.00 - 1.42)	0.045*
All cause death	30	**0.96**	(0.94 - 1.14)	0.44	**1.08**	(1.01 - 1.17)	0.029*	**1.21**	(1.03 - 1.41)	0.019*	**1.33**	(1.13 - 1.58)	<0.001*
Cardiovascular death	13	**0.92**	(0.95 - 1.23)	0.23	**0.99**	(0.86 - 1.14)	0.87	**1.17**	(0.92 - 1.48)	0.21	**1.28**	(0.99 - 1.64)	0.06
Stroke	20	**0.94**	(0.95 - 1.18)	0.27	**1.01**	(0.91 - 1.13)	0.8	**1.04**	(0.84 - 1.29)	0.73	**1.06**	(0.84 - 1.33)	0.62
Adjusted Model													
Stroke, MI, PVD, CV death	29	**0.95**	(0.95 - 1.16)	0.31	**0.97**	(0.88 - 1.07)	0.49	**1.11**	(0.94 - 1.31)	0.24	**1.14**	(0.94 - 1.39)	0.18
All cause death	30	**0.99**	(0.92 - 1.12)	0.8	**1.13**	(0.97 - 1.32)	0.12	**1.13**	(0.97 - 1.32)	0.12	**1.22**	(1.02 - 1.46)	0.027*
Cardiovascular death	13	**0.93**	(0.94 - 1.24)	0.3	**0.95**	(0.82 - 1.10)	0.47	**1.05**	(0.84 - 1.32)	0.65	**1.13**	(0.86 - 1.48)	0.36
Stroke	20	**0.93**	(0.95 - 1.20)	0.25	**1.00**	(0.89 - 1.12)	0.95	**1.02**	(0.82 - 1.27)	0.87	**1.01**	(0.78 - 1.30)	0.97

Table 6.6 Hazard ratios for the risk of each event per 10mmHg increase in maximum SBP or 1% increase in CV-SBP, defined by ABPM or different periods of home monitoring. Hazard ratios (HR) are generated from unadjusted Cox Proportional Hazards regression models and following adjustment for age, gender, smoking, family history of stroke, diabetes and dyslipidaemia. N=number of events; HBPM=home blood pressure monitoring; ABPM=awake ambulatory blood pressure monitoring; MI=myocardial infarction; PVD=acute peripheral vascular disease; CV Death = cardiovascular death* p<0.05

6.4.8 Relative predictive values of mean, maximum and variability in SBP

Per standard deviation of the population, maximum SBP on HBPM was more strongly associated with creatinine, leukoaraiosis, all cardiovascular events and all-cause mortality than mean SBP in univariate models (table 6.7). Furthermore, adjusting maximum SBP for mean SBP resulted in minimal attenuation of the relationship between maximum SBP and each outcome, but after adjusting mean SBP for maximum SBP, there was no relationship between mean SBP and markers of hypertensive arteriopathy or the risk of cardiovascular events. In univariate models, variability in SBP was slightly less strongly associated than mean SBP with creatinine, aortic stiffness or the risk of all cardiovascular events but was more strongly associated with leukoaraiosis and all cause mortality. However, mean SBP and variability in SBP were largely independent of each other, with minimal attenuation of these relationships after mutual adjustment (table 6.7).

Model	Creatinine		Pulse Wave Velocity		Leukoaraiosis		All CV Events		All cause mortality	
	Partial r	P	Partial r	P	OR	P	HR	p	HR	P
Unadjusted										
Mean SBP	0.22	<0.001*	0.24	0.006*	1.42	0.001*	1.47	0.009*	1.53	0.003*
Max SBP	0.25	<0.001*	0.23	0.007*	1.50	<0.001*	1.61	0.002*	1.78	<0.001*
CV SBP	0.14	0.004*	0.12	0.17	1.54	<0.001*	1.39	0.045*	1.71	0.001*
Adjusted for Mean										
Max SBP	0.12	0.011*	0.08	0.32	1.39	0.046*	1.54	0.07	1.78	0.01*
Mean SBP	0.05	0.32	0.10	0.25	1.10	0.57	1.07	0.79	1.00	0.99
CV SBP	0.13	0.004*	0.12	0.14	1.54	<0.001*	1.35	0.06	1.64	0.001*
Mean SBP	0.22	<0.001*	0.24	0.005*	1.42	<0.001*	1.47	0.012*	1.51	0.005*
Fully adjusted										
Max SBP	0.09	0.041*	-0.09	0.22	0.96	0.85	1.49	0.16	1.65	0.05
Mean SBP	0.01	0.87	0.24	0.001*	1.31	0.16	0.98	0.94	0.87	0.59
CV SBP	0.10	0.015*	-0.08	0.28	1.16	0.22	1.26	0.29	1.45	0.02*
Mean SBP	0.12	0.005*	0.26	<0.001*	1.28	0.045*	1.34	0.07*	1.30	0.09

Table 6.7. Relative strength of association between mean, maximum and variability in SBP with hypertensive arteriopathy, cardiovascular events and all-cause mortality. Partial r values are derived from linear regression, odds ratio (OR) for advanced leukoaraiosis (moderate/severe vs none/mild) from binary logistic regression and hazard ratios (HR) from Cox Regression. Models are presented unadjusted, adjusted for mean SBP and adjusted for mean SBP, age, gender, diabetes, smoking, hyperlipidaemia and family history of stroke.

6.5 Discussion

Variability and maximum SBP on HBPM were strongly associated with clinical characteristics, premorbid visit-to-visit BP readings, markers of hypertensive arteriopathy and the risk of recurrent cardiovascular events and all cause mortality, with stronger associations for maximum SBP than mean SBP and independent associations for variability and mean SBP. Variability and maximum SBP on ABPM did not demonstrate any of these associations. Although variability and maximum SBP on only 1 day of HBPM was associated with hypertensive arteriopathy, the predictive value of both variability in SBP and maximum SBP significantly increased with longer periods of monitoring.

Despite a long history of investigation,[25] the weak predictive value of variability in SBP on ABPM[1] and the lack of specific treatment options has prevented SBP variability from being widely recognised as an independent marker of cardiovascular risk until it was demonstrated that there was an increased risk of stroke and cardiovascular events associated with increased visit-to-visit BP variability and maximum SBP in clinic,[6] and that specific antihypertensive classes reduced variability in SBP and hence stroke risk.[8, 11] However, clinic blood pressure provides a less accurate estimate of mean BP than ABPM[26] whereas ABPM provides a measure of physiologically-determined diurnal variation in BP, resulting in doubts about the greater physiological, and therefore clinical, relevance of visit-to-visit BP variability. The effect on clinical outcomes has been ascribed to medication adherence[18] or demographic confounders resulting in measurement artefact, such as the association between age and the white coat effect.[27] Despite multiple subsequent demonstrations of the clinical relevance of variability in SBP on both clinic[2, 12] and home monitoring,[28, 29] independent of mean SBP and clinical characteristics, day-to-day home and visit-to-visit clinic variability in SBP are still not recognised as independent risk factors or treatment targets.[15, 16] Furthermore, although maximum SBP was an even stronger predictor of stroke risk than either mean SBP or variability in SBP in the original reports,[6] it has received little attention compared to variability in SBP,[14] perhaps due to the perception

that maximum episodic clinic hypertension reflects the white coat response rather than a physiologically-determined, recognised marker of cardiovascular risk.

In this population, the strong associations between variability and maximum SBP with clinical characteristics and markers of hypertensive arteriopathy demonstrate that such fluctuations in SBP reflect underlying physiological differences between individuals. This cannot be explained on the basis of adherence to medication given the similar associations with age and the opposite associations for gender, and is unlikely to reflect clinically irrelevant artefacts of BP measurement given the strong relationship with markers of hypertensive end-organ damage including creatinine and leukoaraiosis. Instead, fluctuations in SBP appear to reflect pathophysiological differences between individuals, either partly due to underlying hypertensive arteriopathy or possibly causing it. Furthermore, the associations with clinical characteristics were stronger for variability and maximum SBP than mean SBP. Finally, in assessing clinical risk, which is the most important measure of clinical validity, variability in SBP and mean SBP were independently associated with all outcomes, whilst maximum SBP was more strongly associated with outcomes than mean SBP, such that there was no association between mean SBP and outcomes after adjustment for max SBP, compared to minimal attenuation of the relationship between max SBP and outcomes after adjustment for mean SBP. As max SBP is also associated with CV-SBP, it suggests that max SBP provides a composite measure capturing all the relevant prognostic information given by mean SBP plus some of the prognostic information given by CV-SBP.

The weak associations for variability and maximum SBP on ABPM with clinical characteristics, premorbid BP readings and markers of hypertensive arteriopathy are consistent with the weak predictive value of variability on ABPM for the risk of cardiovascular events in this study and in previous studies.[1, 6] This may partly be explained by the duration of monitoring, with longer periods of monitoring on HBPM increasing the strength of association with clinical characteristics and hypertensive arteriopathy and

increasing the predictive value for recurrent cardiovascular events. However, maximum SBP and variability in SBP on 1 day of HBPM were still more strongly associated with clinical characteristics, hypertensive arteriopathy and the risk of all-cause mortality than ABPM. Maximum SBP on ABPM in this population may be more likely to reflect artefactual or clinically irrelevant elevations in SBP whilst variability in SBP on ABPM, which is dominated by diurnal variation, may reflect alternative physiological mechanisms with less physiological and clinical significance than day-to-day variability in SBP. This is consistent with the poor performance of mean ABPM in identifying hypertensive arteriopathy and the risk of cardiovascular events demonstrated in chapter 5, particularly due to inaccuracies in the elderly, who have the greatest variability in blood pressure.

This analysis has a number of limitations. Firstly, ABPM was only performed at one month, following initiation of therapy, whilst home monitoring was performed from the recruitment visit. Nonetheless, associations between measures of maximum SBP or variability in SBP were still stronger for 1 and 7 days of HBPM immediately prior to the ABPM. Secondly, this study only looked at patients with recent cerebrovascular events which limits its generalisability. This is also a strength of this study as it provides evidence for the optimal method of assessing BP in high risk patients with recent cerebrovascular events, but further research is needed to confirm that these findings can be extrapolated to patients without TIA or stroke. Thirdly, there were relatively few cardiovascular events during follow up in this population, which limited the sensitivity of the study to weaker associations between BP measures and cardiovascular events. However, there were significant relationships with longer periods of HBPM, and the relationships for hypertensive arteriopathy, premorbid visit-to-visit CV and premorbid max SBP with BP measures on HBPM are consistent with previous findings with visit-to-visit variability. Fourthly, as discussed in more detail in chapter 5, all measures of hypertensive arteriopathy reflect complex phenotypes with causes not related to hypertension. However, the associations

demonstrated between SBP and each of these measures does by definition reflect that component of each marker that is hypertension related.

Variability and maximum SBP are associated with each other. However, variability also captures features of blood pressure behaviour that maximum SBP does not, such as consistently larger diurnal or day-to-day fluctuations or significant dips in blood pressure. The complementary information they provide may therefore provide insights into the mechanisms underlying their relationship with stroke, with episodic elevations potentially directly causing stroke by exceeding the limits of cerebral autoregulation, whilst chronic fluctuations or dips may result in episodic hypoperfusion or else arterial changes ultimately resulting in an increased risk of stroke.

For clinical practice, this study demonstrates the usefulness of HBPM in assessing variability and maximum SBP. Specifically, these measures appear to be more accurate than awake SBP on ABPM, with greater clinical and physiological significance, but are also complementary to ABPM, which is currently the gold-standard method for assessing mean SBP in guidelines and is likely to be valid in younger patients (chapter 5). Furthermore, ABPM allows for the assessment of nocturnal blood pressure which has independent prognostic significance.[30-32] However, HBPM allows for more prolonged monitoring which improves its prognostic value and allows for initiation of treatment with rapid and accurate monitoring of response, including treatments designed to reduce BP variability. Further research is required to determine the effects of drug treatment on HBPM, and to identify which patients are most likely to benefit from a specific intervention. This is dealt with in chapter 8.

In conclusion, variability in SBP and maximum SBP on HBPM were physiologically and clinically valid markers of hypertensive arteriopathy and cardiovascular risk, but their measurement was significantly improved by more prolonged monitoring. ABPM did not give a valid estimate of either measure.

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CHAPTER SEVEN

Validation of the Montreal Cognitive Assessment (MoCA) versus Mini-Mental State Examination (MMSE) against hypertension and hypertensive arteriopathy in patients with TIA or minor stroke

7.1 Summary

To measure associations between cognitive impairment and SBP variability, a sensitive measure of vascular cognitive impairment is required. In previous studies, more patients are impaired on the Montreal Cognitive Assessment compared to the Mini-Mental State Examination (Significant vs Mild vs No impairment: MMSE<23, 23-26, ≥27; MoCA <20, 20-24, ≥25)), yet all major trials of antihypertensive medications have used the MMSE. Therefore, to validate the cognitive impairment detected by the MoCA, I measured the relationships between hypertension and hypertensive arteriopathy with global and subdomain cognitive dysfunction on the MoCA versus MMSE.

In 463 patients with TIA or minor stroke undergoing home BP monitoring, 45% had cognitive impairment on the MoCA vs 28% on the MMSE (p<0.001). Mean SBP was progressively greater for significant vs mild vs no cognitive impairment on the MoCA but not the MMSE for premorbid readings (MoCA 143 mmHg vs 140 vs 135, p<0.001; MMSE 139 vs 142 vs 137 p=0.68) and HBPM (MoCA 130 vs 125 vs 122, p<0.001; MMSE 127 vs 125 vs 123 p=0.19), whilst low MoCA vs MMSE scores were also more strongly associated with hypertensive arteriopathy (OR: creatinine 3.99, 2.06-7.73 vs 2.16, 1.08-4.33; stroke vs TIA 1.53, 1.06-2.19 vs 1.23, 0.81-1.85; aortic stiffness 1.09, 0.97-1.22 vs 0.97, 0.85-1.11; advanced leukoaraiosis 2.09, 1.42-3.06 vs 1.34, 0.87-2.07). Mean SBP was more strongly associated with impairment in all cognitive sub-domains on the MoCA vs MMSE, with the greatest difference in visuo-spatial dysfunction (ORs per 10mmHg: visuo-spatial 1.29 vs 1.05; attention 1.18 vs 1.07; language 1.22 vs 0.91; naming 1.07 vs 0.86). 16% of uniquely explained variation in the total MoCA score was determined by visuo-spatial / executive tests compared to 8% with the MMSE score.

The MoCA identified more patients with hypertension-associated cognitive impairment than the MMSE, due largely to effects on sub-domains associated with vascular cognitive impairment. Therefore future observational studies and RCTs assessing the effect of consistency of control of BP should use the MoCA.

7.2 Introduction

Vascular cognitive impairment probably results from both chronic ischaemic injury associated with small vessel disease (leukoaraiosis)[1] and from acute cerebrovascular events, particularly recurrent events and events occurring in individuals with reduced cerebrovascular reserve.[2] Hypertension is the strongest risk factor for both acute cerebrovascular events[3-5] and for the development of leukoaraiosis,[6] explaining the strong epidemiological association between hypertension and cognitive impairment.[7] However, randomised controlled trials of antihypertensive medications in both primary prevention[8-10] and secondary prevention of cerebrovascular disease[11, 12] have failed to demonstrate consistent reductions in cognitive decline despite reductions in blood pressure. This may be due to an association between progression of vascular cognitive impairment and low BP or BP variability as opposed to mean BP, but alternatively it may result from the use of the MMSE to assess cognitive status, which may be insensitive to the pattern of cognitive decline associated with hypertension and cerebrovascular disease.[13] Furthermore, given limitations of the MMSE, a sensitive test for vascular cognitive impairment is a prerequisite to investigate the relationship between variability in SBP and cognitive impairment.

Recent studies have demonstrated a greater sensitivity for apparent cognitive impairment with the Montreal Cognitive Assessment (MoCA) versus the Mini-Mental State Examination (MMSE),[14-16] particularly in patients with recent cerebrovascular events,[17] at least partly due to the visuo-executive components of the MoCA.[13] There are many alternative cognitive tests available, but the MOCA is an efficient test, easy to perform in clinic, and has been validated in cerebrovascular disease against formal neuropsychological testing.[13,17] Although the MOCA excludes some important tests of vascular-type cognitive dysfunction such as processing speed, it captures a broad range of cognitive domains in a highly efficient manner, vital for use in a large, complex epidemiological study with many forms of assessment. However, previous studies have validated impairment on the MoCA and MMSE against more extended cognitive tests using shared methodology, rather than

objective clinical outcomes. Therefore, it is unclear if the additional cognitive impairment identified by the MoCA is genuine cognitive impairment related to underlying disease, whether the MoCA is simply a harder test or whether it reflects correlated noise in similar domains of different tests, without clinical significance.

If the additional cognitive impairment identified by the MoCA is real and related to underlying vascular disease, then a low MoCA score should be more strongly associated with hypertension and hypertensive arteriopathy than a low MMSE score. Therefore I hypothesised that the MoCA would be more sensitive to genuine vascular cognitive impairment associated with a history of hypertension, identifying a population at a particularly increased risk of future cognitive decline due to hypertension.[2] In addition, this association would suggest that blood-pressure lowering may reduce cognitive decline if assessed with a tool sensitive to hypertension-associated cognitive impairment. Finally, this would suggest that the MoCA would be a valid tool for the assessment of the relationship between SBP variability and cognitive impairment in future studies.

7.3 Methods

7.3.1 Procedures

This analysis was carried out in the same population as that studied in Chapter 5, with consecutive patients recruited between April 2008 and January 2012 from the Oxford Vascular Study's (OXVASC)[18] TIA and minor stroke clinic, usually within twenty-four hours of referral.[19] Patients who were alive and seen at follow-up after the index event were administered the MMSE at the beginning and the MoCA at the end of a 45-min appointment, with the intervening time taken with health-related questions and a selective physical examination. Both the MoCA and MMSE were routinely performed at the 6 month visit and this score was used where available. Subjects who were unable to complete cognitive testing owing to dysphasia, inability to use the dominant arm, illness or poor English were excluded as described previously.[13, 20] A cutoff score of ≥27 on the MMSE[21] and ≥25 on the MoCA[22] was chosen to indicate normal cognitive function, with scores of <23 on the MMSE

and <20 on the MoCA taken to indicate significant cognitive impairment likely to impair function (an additional point being added to the total MoCA score for patients with ≤12 years of education), according to recommendations from memory clinics[22] and cerebrovascular cohorts.[23] Premorbid cognitive function was not formally assessed as the same group of patients were tested with both the MoCA and MMSE. Therefore, this is unlikely to confound any differences between the tests. Futhermore, pre-event cognitive dysfunction is also a valid substrate to compare these tests, and is equally important as post-event dysfunction..

As described in chapters 5-6, clinic BP was measured at ascertainment and the one month follow-up visit in the non-dominant arm. Up to 20 readings were used for determination of premorbid blood pressure, whilst at the 1 month follow-up visit, awake ambulatory measurements (ABPM) were performed with an A&D TM-2430 monitor in the non-dominant arm, fitted by a trained study nurse, at 30 minutes intervals during the day and 60 minute intervals at night. Home blood pressure monitoring (HBPM) and treatment of hypertension were the same as described in chapter 5. The same subgroup of 150 patients underwent measurement of aortic stiffness by applanation tonometry to determine carotid-femoral pulse wave velocity (cfPWV Sphygmocor, AtCor Medical, Sydney, Australia), and leukoaraiosis was also assessed as in chapters 5 and 6, taking 'advanced leukoaraiosis' (moderate/severe vs none/mild) and Fazekas score as the primary measures of severity.

7.3.2 Analysis

Mean and maximum SBP and DBP on home monitoring were used as the primary blood pressure indices to validate the cognitive scores. These were derived from the last 2 readings at each timepoint, including all clusters of readings from 7 days after the initial assessment. Mean and maximum SBP and DBP on ABPM were derived for awake ABPM readings following automated and manual exclusion of artefactual measurements according to predefined criteria.[24] Mean premorbid SBP and DBP were derived from the last 20 years recorded in the primary care record, from readings in the five years prior to the notification event and from readings 5-10 years prior to this event.

Given the negatively skewed distribution of total and subscores on the MMSE and MoCA, all scores were categorised as 'None', 'Mild' or 'Significant' cognitive impairment according to the criteria defined above. Relationships with discrete variables were determined by chi-squared tests whilst relationships with continuous demographic and blood pressure measures were determined by ANOVA across severity categories, with post-hoc comparisons of 'Significant cognitive impairment' vs 'None' (Tukey). Secondly, prediction of level of cognitive impairment by markers of hypertensive arteriopathy, leukoaraiosis and demographic characteristics was determined by ordinal regression. Sensitivity analyses were performed using only scores recorded at 6 months. All analyses were done for univariate associations and after adjustment for age and gender.

7.4 Findings

7.4.1 Population characteristics

Of the 520 patients consenting to BP monitoring, 492 (95%) had eligible MMSEs, with eligible MoCAs in 463 of these patients (94%). Of the 463 patients included in the primary analyses, 452 (98%) performed HBPM, 427 (92%) had at least 3 premorbid blood pressures recorded and 422 (91%) had an ABPM at 1 month. There were a median of 31 (22-71) days of HBPM with 2.9 BPs recorded at each timepoint and a median of 15 (6-31) premorbid BPs per patient.

More patients had at least mild cognitive impairment on the MoCA versus the MMSE (45% vs 28%, $p<0.001$) or had significant cognitive impairment (14.3% vs 6.7%, $p<0.001$) despite lower diagnostic thresholds with the MoCA and similar associations with demographic characteristics (table 7.1). Patients with significant cognitive impairment according to either definition were still able to perform home BP monitoring, although cognitively impaired patients recorded slightly fewer readings than non-cognitively impaired patients (number of home BPs: significantly impaired vs not: MoCA 102 vs 119, $p=0.12$; MMSE 92 vs 119, $p=0.08$).

	Cognitive Impairment							
	Significant		**Mild**		**None**		p-val	p-trend
MoCA								
Male Gender	**31**	(47%)	**77**	(52%)	**132**	(52%)	0.62	0.70
Hypertension	**50**	(76%)	**89**	(63%)	**121**	(48%)	<0.001*	<0.001*
Diabetes	**22**	(33%)	**19**	(13%)	**28**	(11%)	<0.001*	<0.001*
Dyslipidaemia	**30**	(46%)	**61**	(43%)	**94**	(40%)	0.17	0.18
Smoker	**7**	(11%)	**20**	(14%)	**37**	(15%)	0.72	0.49
Family History	**15**	(23%)	**38**	(27%)	**76**	(30%)	0.48	0.23
Previous CVD	**10**	(15%)	**33**	(23%)	**66**	(26%)	0.16	0.08
AF	**14**	(21%)	**24**	(17%)	**31**	(12%)	0.14	0.05
Age	**76.9**	(75 - 79)	**71.8**	(70 - 74)	**66.1**	(65 - 68)	<0.001*	<0.001*
BMI	**27.4**	(26 - 29)	**27.1**	(26 - 28)	**26.7**	(26 - 27)	0.6	0.62
Creatinine	**102**	(93 - 112)	**92.4**	(88 - 97)	**86.4**	(84 - 89)	<0.001*	<0.001*
Cholesterol	**5**	(4.6 - 5.4)	**5**	(4.8 - 5.2)	**5.5**	(5.2 - 5.7)	0.044*	0.18
Admission SBP	**158**	(151 - 164)	**153**	(149 - 157)	**151**	(148 - 154)	0.17	0.15
Admission DBP	**81**	(78 - 85)	**83**	(81 - 85)	**86**	(85 - 88)	0.01*	0.031*

Table 7.1 Clinical characteristics of patients according to severity of cognitive impairment, as defined by the MoCA. MoCA was divided into <20, 20-24, ≥25. P-values are derived from ANOVA tests for continuous variables and chi-squared tests for discrete variables, with a post-hoc test for trend or comparison of none vs significant.

7.4.2 Associations of home SBP with MoCA versus MMSE scores

Mean and maximum home SBP were higher in patients with significant cognitive impairment compared to mild or no cognitive impairment when defined by the MoCA test, with a significant trend across the three groups (table 7.2), both before and after adjustment for age and gender. Although the same pattern was seen with the MMSE, the differences between groups were smaller and did not reach significance. This was consistent for all readings combined (table 7.2), at all times of day (after waking, in the mid-morning and in the evening, table 7.4), and when only using scores performed at the 6 month follow-up visit (MoCA: significantly impaired 129mmHg vs not impaired 122mmHg, unadj p<0.001, adj

p<0.001; MMSE: 126mmHg vs 124mmHg, unadj p=0.33, adj p=0.11). There were no consistent differences between groups for mean or maximum DBP when patients were classified according to either test (table 7.3). Awake mean and maximum SBP on ABPM at one month after ascertainment were also higher in patients with significant cognitive impairment when defined according to the MoCA test, but there was no difference between groups defined by the MMSE (table 7.2).

7.4.3 Associations of premorbid SBP with MoCA versus MMSE scores

Premorbid mean and maximum SBP also differed significantly between the three levels of cognitive impairment with both tests (table 7.2). On the MoCA, SBP increased systematically across all three levels of cognitive impairment, but on the MMSE patients with mild cognitive impairment had the highest premorbid mean SBP, with no significant difference between significantly cognitively impaired patients and non impaired patients (table 7.2). The stronger association of the MoCA with elevated premorbid SBP was present for both recent premorbid blood pressures in the last 5 years and for blood pressures 5-10 years prior to ascertainment.

	Degree of cognitive impairment						Unadjusted		Adjusted	
	Significant		Mild		None		ANOVA p-val	None vs Sig	ANOVA p-val	None vs Sig
HBPM										
Mean										
MoCA	**129.9**	(125.9 - 133.9)	**124.6**	(122.7 - 126.6)	**121.7**	(120.2 - 123.2)	<0.001***	<0.001***	<0.001***	<0.001***
MMSE	**127.3**	(122.8 - 131.7)	**125**	(122.4 - 127.7)	**123.0**	(121.6 - 124.4)	0.12	0.19	0.38	0.27
Maximum										
MoCA	**159.3**	(153.3 - 165.3)	**153.6**	(150.6 - 156.5)	**148.2**	(145.9 - 150.6)	<0.001*	<0.001*	0.044*	0.017*
MMSE	**156.5**	(148.7 - 164.3)	**153.6**	(149.7 - 157.6)	**150.3**	(148.2 - 152.5)	0.12	0.22	0.74	0.61
ABPM										
Mean										
MoCA	**131.4**	(127.2 - 135.7)	**126.9**	(124.7 - 129.1)	**126.5**	(125.1 - 127.9)	0.028*	0.022*	0.009**	0.002**
MMSE	**128.5**	(123.1 - 133.9)	**127**	(124.4 - 129.7)	**127.3**	(125.9 - 128.6)	0.87	0.88	0.80	0.50
Maximum										
MoCA	**168.4**	(161.9 - 174.8)	**162.6**	(159.3 - 165.9)	**160.8**	(158.2 - 163.4)	0.045*	0.035*	0.15	0.17
MMSE	**165.5**	(155.5 - 175.5)	**162.6**	(158.3 - 166.9)	**161.9**	(159.7 - 164.2)	0.68	0.66	0.68	0.39
Premorbid										
Mean										
MoCA	**143.4**	(140.3 - 146.5)	**140.2**	(138.2 - 142.2)	**135.3**	(133.4 - 137.1)	<0.001***	<0.001****	0.018*	0.01**
MMSE	**138.9**	(134.6 - 143.2)	**141.8**	(139.5 – 144.1)	**136.7**	(135.2 - 138.3)	0.007**	0.68	0.05	0.58
Maximum										
MoCA	**170.9**	(164.9 - 176.9)	**164.5**	(161.1 - 167.9)	**155.9**	(153.0 – 158.96)	<0.001***	<0.001***	<0.001***	<0.001***
MMSE	**162.9**	(155.4 – 170.4)	**168.0**	(163.5 – 172.6)	**158.5**	(155.9 – 161.0)	0.002**	0.56	0.02*	0.61

Table 7.2 Differences in mean and maximum SBP on home, ambulatory and premorbid readings, in patients with different degrees of cognitive impairment defined by MMSE versus MoCA. Differences across levels of impairment are compared by ANOVA, with post-hoc comparisons between no impairment and significant impairment, with and without adjustment for age and gender. *p<0.05, **p<0.01, ***p<0.001.

	Degree of cognitive impairment						Unadjusted		Adjusted	
	Significant		Mild		None		ANOVA p-val	None vs Sig	ANOVA p-val	None vs Sig
HBPM										
Mean										
MoCA	**72.7**	(70.06 - 75.53)	**73.8**	(72.23 - 75.49)	**73.8**	(72.82 - 74.89)	0.69	0.69	0.10	0.09
MMSE	**70.2**	(67.12 - 73.4)	**73.9**	(72.04 - 75.78)	**73.9**	(72.98 - 74.97)	0.09	0.08	0.36	0.46
Maximum										
MoCA	**90.4**	(86.48 - 94.5)	**91.3**	(88.96 - 93.83)	**89.6**	(88.23 - 91.04)	0.44	0.89	0.023*	0.046*
MMSE	**87.3**	(81.77 - 92.9)	**90.8**	(88.08 - 93.6)	**90.4**	(89.04 - 91.81)	0.41	0.42	0.59	0.7
ABPM										
Mean										
MoCA	**72.0**	(69.51 - 74.55)	**71.9**	(70.45 - 73.46)	**73.3**	(72.36 - 74.32)	0.24	0.53	0.40	0.20
MMSE	**70.4**	(67.37 - 73.44)	**71.8**	(70.14 - 73.53)	**73.2**	(72.29 - 74.15)	0.12	0.20	0.92	0.71
Maximum										
MoCA	**99.2**	(94.09 - 104.4)	**100.1**	(97.08 - 103.1)	**97.2**	(95.25 - 99.28)	0.27	0.70	0.022*	0.047*
MMSE	**98.5**	(91.25 - 105.8)	**97.7**	(94.31 - 101.1)	**98.5**	(96.69 - 100.4)	0.92	1.00	0.8	0.50
Premorbid										
Mean										
MoCA	**78.1**	(75.9 - 80.4)	**79.2**	(77.8 - 80.5)	**78.6**	(77.6 - 79.6)	0.66	0.92	0.38	0.51
MMSE	**75.2**	(72.3 – 78.1)	**80.8**	(79.4 – 82.1)	**78.4**	(77.5 – 79.4)	0.002*	0.08	0.001**	0.11
Maximum										
MoCA	**94.7**	(91.1 – 98.3)	**92.7**	(90.7 - 94.6)	**90.6**	(89.2 – 92.9)	0.035*	0.032*	0.03*	0.01*
MMSE	**89.0**	(85.0 – 93.0)	**95.5**	(93.2 – 97.8)	**91.0**	(89.7 – 92.3)	0.002*	0.62	0.002*	0.32

Table 7.3 Differences in mean and maximum DBP on home, ambulatory and premorbid readings, in patients with different degrees of cognitive impairment defined by MMSE versus MoCA. Differences across levels of impairment are compared by ANOVA, with post-hoc comparisons between no impairment and significant impairment, with and without adjustment for age and gender. *p<0.05, **p<0.01, ***p<0.001.

	Degree of cognitive impairment						Unadjusted		Adjusted	
	Significant		Mild		None		ANOVA p-val	None vs Sig	ANOVA p-val	None vs Sig
Early Morning										
Mean										
MoCA	**131.3**	(127.1 - 135.5)	**126**	(123.9 - 128.1)	**122.1**	(120.5 - 123.7)	<0.001*	<0.001*	0.002**	<0.001***
MMSE	**129**	(124.6 - 133.5)	**126.6**	(123.8 - 129.4)	**123.7**	(122.2 - 125.1)	0.034*	0.09	0.30	0.26
Maximum										
MoCA	**152**	(146.3 - 157.8)	**147.4**	(144.4 - 150.4)	**140.9**	(138.7 - 143.2)	<0.001*	<0.001*	0.023*	0.013*
MMSE	**149.8**	(143.2 - 156.4)	**147.6**	(143.5 - 151.7)	**143.1**	(141.1 - 145.2)	0.037*	0.15	0.45	0.51
Mid-morning										
Mean										
MoCA	**126.6**	(122.2 - 131.1)	**121.1**	(119.2 - 123.1)	**118.9**	(117.5 - 120.3)	<0.001*	<0.001*	<0.001***	<0.001***
MMSE	**122.9**	(117.3 - 128.6)	**121.6**	(118.9 - 124.3)	**120.2**	(118.9 - 121.6)	0.44	0.55	0.28	0.23
Maximum										
MoCA	**147**	(141.2 - 152.9)	**144.3**	(141.1 - 147.4)	**139.4**	(137.3 - 141.5)	0.003*	0.01*	0.049*	0.034*
MMSE	**144.1**	(136.3 - 151.9)	**143.6**	(140.1 - 147.2)	**141.3**	(139.2 - 143.4)	0.47	0.74	0.79	0.84
Evening										
Mean										
MoCA	**131**	(126.4 - 135.7)	**124.3**	(122.1 - 126.4)	**121.6**	(120 - 123.2)	<0.001*	<0.001*	<0.001***	<0.001***
MMSE	**127.1**	(121.6 - 132.6)	**124.3**	(121.3 - 127.3)	**123.3**	(121.7 - 124.8)	0.32	0.32	0.70	0.41
Maximum										
MoCA	**153.9**	(147.5 - 160.3)	**147.2**	(144.1 - 150.2)	**142.4**	(139.9 - 144.8)	<0.001*	<0.001*	0.025	0.007
MMSE	**148.8**	(139.7 - 157.9)	**147.4**	(143.2 - 151.6)	**144.6**	(142.4 - 146.8)	0.34	0.53	0.88	0.89

Table 7.4. Differences in mean and maximum SBP on home readings at different times of day between different degrees of cognitive impairment defined by MMSE versus MoCA. Differences across levels of impairment are compared by ANOVA, with post-hoc comparisons between no impairment and significant impairment, with and without adjustment for age and gender. *p<0.05, **p<0.01, ***p<0.001.

7.4.4 Associations of hypertensive arteriopathy with MoCA versus MMSE scores

Markers of hypertensive arteriopathy were more strongly associated with cognitive impairment on the MoCA versus the MMSE (table 7.5): patients with stroke as opposed to TIA were more likely to be cognitively impaired on the MoCA than on the MMSE; there was a stronger relationship between creatinine level or aortic stiffness (aortic pulse wave velocity) and cognitive impairment on the MoCA; and there was a stronger relationship between any leukoaraiosis or advanced leukoaraiosis with increasing degrees of cognitive impairment on the MoCA compared to the MMSE.

Table 7.5 Risk of lower cognitive scores on the MoCA or MMSE with increased markers of hypertensive arteriopathy. Odds ratios (OR) are derived from ordinal regression for the risk of being in a lower category of each score: no impairment, mild impairment or significant impairment. ORs are given per 1 m/s for Aortic PWV and per 10 μmol/L for creatinine.

	MoCA			MMSE		
	OR	**CI**	**P-val**	**OR**	**CI**	**P-val**
Univariate Model						
Aortic PWV	1.09	(0.97-1.22)	0.14	0.97	(0.85-1.11)	0.70
Creatinine	3.99	(2.06 – 7.73)	<0.001*	2.16	(1.08 – 4.33)	0.029*
Stroke vs TIA	1.53	(1.06 – 2.19)	0.022*	1.23	(0.81 – 1.85)	0.33
Leukoaraiosis						
Any	2.02	(1.39 – 2.94)	<0.001*	1.60	(1.05 – 2.46)	0.03*
Moderate / Severe	2.09	(1.42 – 3.06)	<0.001*	1.34	(0.87 – 2.07)	0.18
Adjusted Model						
Aortic PWV	1.07	(0.98 – 1.04)	0.56	0.90	(0.76 – 1.06)	0.21
Creatinine	2.81	(1.35 – 5.85)	<0.001*	1.81	(0.83 – 3.94)	0.14
Stroke vs TIA	1.52	(1.05 – 2.21)	0.03*	1.20	(0.79 – 1.81)	0.40
Leukoaraiosis						
Any	1.25	(0.82 – 1.90)	0.30	1.06	(0.66 – 1.72)	0.81
Moderate / Severe	1.33	(0.88 – 2.02)	0.18	0.91	(0.57 – 1.46)	0.70

7.4.5 Relationship between cognitive subdomains and mean or maximum BP

The visuo-spatial / executive sub-domain of the MoCA test was the domain most strongly associated with mean SBP on HBPM and premorbid readings, with and without adjustment for age and gender, with a 29% increased chance of having a lower score for each 10mmHg increase in SBP. Mean SBP was also a significant predictor of a lower score on attentional and language tasks before and after adjustment for age and gender (table 7.6 and 7.7). There were univariate associations between mean SBP and scores for naming and recall (webtable 7.6), but these were not present after adjustment for age and gender. Drawing inter-locking pentagons, the only visuo-spatial / executive test on the MMSE, was also strongly associated with mean SBP on HBPM (table 7.6), with and without adjustment, but there were only weak univariate associations with recall and orientation scores and no associations with language or naming scores (tables 7.6 and 7.7).

Each subdomain of the MoCA test was more strongly associated with mean SBP than the equivalent subdomain on the MMSE, except for orientation. This partly reflected a ceiling effect with the MMSE, with more patients achieving full marks in each domain except for attention: visuo-spatial (MMSE 84% vs MoCA 37.6%, $p<0.001$); language (91.4% vs 37.1%, $p<0.001$); naming (98.5% vs 82.3%, $p<0.001$); recall (52.9% vs 13%, $p<0.001$); orientation (74.7% vs 79.7%, $p<0.001$); attention (54.2% vs 51.6%, $p=0.34$). In addition to stronger relationships within each cognitive domain, the visuo-spatial domain determined a greater proportion of the inter-individual variance in total score with the MoCA compared to the MMSE (15.6% vs 8.1% of total variance uniquely explained by sub-domains), with recall and attention scores being the next most important contributors (MoCA: recall 35.6%; attention 15%, MMSE: recall 34.7%; attention 57%). Despite contributing a third of the total MMSE score, orientation only contributed 12% of uniquely explained variance in the total score.

	MoCA			MMSE		
	OR	CI	P-val	OR	CI	P-val
HBPM						
Visuo-Spatial	1.29	(1.14 - 1.47)	<0.001***	1.36	(1.14 - 1.63)	<0.001***
Attention	1.27	(1.11 - 1.46)	<0.001***	1.1	(0.96 - 1.26)	0.17
Language	1.22	(1.07 - 1.39)	0.003**	1.21	(0.96 - 1.52)	0.1
Naming	1.29	(1.08 - 1.53)	0.005**	0.84	(0.44 - 1.58)	0.58
Recall	1.23	(1.08 - 1.39)	0.002**	1.15	(1.01 - 1.32)	0.042*
Orientation	1.19	(1.01 - 1.41)	0.036*	1.19	(1.02 - 1.39)	0.026*
Abstraction	1.12	(0.98 - 1.28)	0.1	-		
ABPM						
Visuo-Spatial	1.04	(0.9 - 1.2)	0.59	1.02	(0.83 - 1.26)	0.85
Attention	1.17	(1.01 - 1.35)	0.033*	1.12	(0.97 - 1.3)	0.12
Language	1.18	(1.02 - 1.36)	0.022*	1.06	(0.8 - 1.39)	0.7
Naming	1.2	(0.99 - 1.46)	0.06	0.93	(0.48 - 1.82)	0.83
Recall	1.06	(0.92 - 1.21)	0.41	0.95	(0.82 - 1.1)	0.49
Orientation	1.16	(0.96 - 1.39)	0.11	1.1	(0.92 - 1.3)	0.29
Abstraction	1	(0.87 - 1.16)	0.96	-		
Premorbid						
Visuo-Spatial	1.42	(1.25 - 1.62)	<0.001***	1.20	(1.00 - 1.45)	0.05
Attention	1.22	(1.06 - 1.39)	0.004**	1.11	(0.97 - 1.27)	0.12
Language	1.27	(1.11 - 1.44)	<0.001***	0.98	(0.77 - 1.25)	0.88
Naming	1.28	(1.06 - 1.54)	0.009**	0.71	(0.39 - 1.29)	0.26
Recall	1.19	(1.06 - 1.35)	0.005**	1.25	(1.09 - 1.43)	0.001**
Orientation	1.03	(0.87 - 1.22)	0.71	1.08	(0.93 - 1.27)	0.31
Abstraction	1.23	(1.07 - 1.41)	0.003**	-		

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Table 7.6. Unadjusted risk of having a lower score on each subdivision of the MoCA and MMSE per 10mmHg increase in mean SBP. Effect sizes are derived from univariate ordinal regression across all possible values for each subdivision of the tests, without adjustment for age or gender. HBPM = home BP monitoring; ABPM = ambulatory BP monitoring

	MoCA			MMSE		
	OR	CI	P-val	OR	CI	P-val
HBPM						
Visuo-Spatial	1.24	(1.08 - 1.42)	0.002**	1.29	(1.07 - 1.56)	0.009**
Attention	1.26	(1.10 - 1.45)	<0.001***	1.09	(0.95 - 1.26)	0.20
Language	1.18	(1.03 - 1.35)	0.015*	1.17	(0.92 - 1.49)	0.20
Naming	1.18	(0.97 - 1.42)	0.1	0.91	(0.49 - 1.71)	0.78
Recall	1.13	(1.00 - 1.29)	0.06	1.06	(0.92 - 1.22)	0.41
Orientation	1.14	(0.96 - 1.36)	0.14	1.13	(0.96 - 1.33)	0.13
Abstraction	1.09	(0.95 - 1.26)	0.21	-		
ABPM						
Visuo-Spatial	1.08	(0.94 - 1.25)	0.29	1.04	(0.84 - 1.29)	0.71
Attention	1.2	(1.03 - 1.39)	0.016*	1.15	(0.99 - 1.33)	0.06
Language	1.18	(1.03 - 1.36)	0.02*	1.06	(0.81 - 1.4)	0.66
Naming	1.25	(1.02 - 1.52)	0.033*	0.89	(0.45 - 1.79)	0.75
Recall	1.06	(0.92 - 1.21)	0.43	0.95	(0.82 - 1.11)	0.52
Orientation	1.17	(0.97 - 1.41)	0.09	1.11	(0.94 - 1.33)	0.23
Abstraction	1.03	(0.88 - 1.19)	0.75	-		
Premorbid						
Visuo-Spatial	1.29	(1.12 - 1.48)	<0.001***	1.05	(0.85 - 1.31)	0.64
Attention	1.18	(1.02 - 1.36)	0.025*	1.07	(0.92 - 1.24)	0.38
Language	1.22	(1.06 - 1.41)	0.005**	0.91	(0.69 - 1.2)	0.5
Naming	1.07	(0.86 - 1.33)	0.56	0.86	(0.44 - 1.67)	0.66
Recall	1.06	(0.93 - 1.21)	0.4	1.07	(0.93 - 1.25)	0.34
Orientation	0.92	(0.76 - 1.12)	0.4	0.96	(0.81 - 1.15)	0.69
Abstraction	1.16	(0.99 - 1.35)	0.044*	-		

Table 7.7. Risk of having a lower score on each subdivision of the MoCA and MMSE per 10mmHg increase in mean SBP, adjusted for age and gender. Effect sizes are derived from ordinal regression across three levels of severity for each subdivision of the tests, adjusted for age and gender. HBPM = home BP monitoring; ABPM = ambulatory BP monitoring; premorbid = up to the last 20 readings recorded in primary care.

7.5 Discussion

Cognitive impairment after TIA or non-disabling stroke was strongly associated with hypertensive arteriopathy and an elevated mean or maximum SBP on post-event home BP monitoring, ABPM and on premorbid blood pressure readings, including readings more than 5 years prior to the initial cerebrovascular event. The MoCA test was significantly more sensitive than the MMSE for hypertension-associated cognitive impairment due to stronger associations within all cognitive sub-domains and a greater contribution of visuo-spatial / executive tests to the total MoCA score.

Dementia affects 5-7% of people ≥60 years old worldwide,[25] costing EU-15 countries approximately $189 billion per year,[26] and is set to double every 20 years to affect approximately 115 million people by 2050.[25] However, there is currently no effective treatment for the prevention of either the onset or progression of cognitive impairment. Of multiple risk factors that are associated with dementia, hypertension[7] and cerebrovascular disease[2] are particularly strongly associated and are the most readily modifiable risk factors for the prevention of future cognitive decline. Unfortunately randomised controlled trials of blood-pressure lowering medications have produced mixed results. In the Syst-Eur trial,[8] randomisation to a nitrendipine based regimen reduced the future risk of cognitive decline compared to placebo, but this has not been consistently replicated in studies with other classes of antihypertensive medications in either primary prevention[9, 10, 27] or secondary prevention of cerebrovascular disease,[11, 12] and meta-analyses have produced inconsistent results.[9, 28] However, these trials have predominantly used the MMSE in assessing cognitive function even though the MMSE is insensitive to abnormalities in visuo-executive functions which are preferentially affected in vascular cognitive impairment,[13] and cause a significant burden of functional impairment and death.[29]

In previous observational studies, the MoCA test defined more patients as being cognitively impaired than the MMSE in populations with cerebrovascular disease,[20] Alzheimer's,[14, 15] and Parkinson's disease,[16] and had a greater sensitivity for cognitive

impairment defined by a gold-standard neuropsychological battery in cerebrovascular disease.[23] However, these studies only showed differences in the number of patients achieving a specific score or differences in associations with extended psychological batteries using similar measurement methods. In contrast, this study demonstrated a strong physiological association between premorbid hypertension or hypertensive arteriopathy, the most important risk factor for cerebrovascular disease, and the cognitive impairment identified by the MoCA test compared to the MMSE, thus suggesting a clinically relevant organic basis. Indeed the similar mean SBP 5-10 versus 0-5 years prior to the event, suggests that hypertension might precede and potentially cause the additional cognitive impairment identified by the MoCA.

The improved sensitivity for hypertension-associated cognitive impairment with the MoCA test was present for a wide range of cognitive domains due to a ceiling effect for most of the tests on the MMSE. However, the strongest association was with visuo-spatial /executive function which contributed more to variation in the overall MoCA score than the MMSE score, resulting in the greater overall sensitivity for vascular-type cognitive impairment, such as is associated with hypertension[6] and cerebrovascular disease.[29] Hypertension has been strongly associated with both chronic small vessel disease[6] and a risk of future cognitive decline in longitudinal studies.[7] Therefore, this study shows that the failure of trials to demonstrate improvements in cognitive dysfunction with blood pressure reduction may partly result from the low sensitivity of the MMSE for hypertension-associated, vascular-type cognitive impairment, due to under-representation of visuo-spatial / executive functions on the MMSE. It also suggests that use of the MoCA should be more effective at detecting clinically important reductions in cognitive decline following blood pressure reduction.

The MoCA test may also identify those patients with the greatest potential for cognitive benefit from blood pressure lowering. After a stroke, cognitive dysfunction can result either from the effects of the cerebrovascular event itself,[2] from associated chronic

small vessel disease,[29] from recurrent events[2] or from a combination of these, with severe cognitive decline occurring in patients with acute events on the background of decreased cognitive reserve. Therefore, cognitive impairment on the MoCA may identify patients at a particularly increased risk of future cognitive decline due to both progression of chronic cognitive impairment and the risk of recurrent cerebrovascular events. In this group, hypertension is a significant, treatable risk factor with the potential to prevent cognitive decline at an earlier stage than cognitive impairment identified on the MMSE. Trials in this population may be more sensitive to benefits of blood pressure lowering treatment, which has previously been difficult to demonstrate in larger primary prevention populations.

Finally, the greater validity and sensitivity of the MoCA in comparison to the MMSE for vascular type cognitive impairment demonstrated in this study also suggests that it will be a better test for assessing any association between cognitive impairment and variability in blood pressure. Specifically, the strong association with subdomains related to vascular dementia may help to discriminate whether BP variability is likely to be a causative factor in the progression of vascular cognitive impairment as opposed to a marker of global cognitive dysfunction, with increased BP variability due to greater inaccuracies in measurement. These associations are currently being investigated in the ongoing blood pressure monitoring study with the benefit of more prolonged follow-up.

This analysis has limitations. Firstly, the population studied included relatively healthy patients with cerebrovascular disease as they needed to be able to perform home blood pressure monitoring. This excluded patients with severe dementia or major stroke with significant residual cognitive impairment. However, this is the ideal population in whom strategies to prevent cognitive decline are likely to bring the greatest benefits. Secondly, as mentioned, there was insufficient follow-up to determine whether the MoCA test had a greater sensitivity for progression of hypertension-associated cognitive impairment. Thirdly, premorbid blood pressure readings were not available in some patients, but these were largely young patients without any cognitive impairment. Fourthly, MoCA tests were only

performed from 6 months after the clinical event. However, this demonstrates the chronic nature of the association once the cognitive effects of the acute event have passed.[30] Fifthly, we used only one marker of cerebral small vessel disease(hyperintensities on T2 weighted imaging), and did not assess associations between dysfunction on the MoCA and other markers of cerebrovascular injuries known to be associated with both hypertension and dementia, such as dilated perivascular spaces and cerebral microbleeds.[31] Although it will be important to determine the relevance of dilated perivascular spaces and cerebral microbleeds to vascular cognitive impairment in the OXVASC population and to determine the importance of hypertension given associations between BP variability and microbleeds,[32] we used the best established marker of cerebral small vessel disease to validate the cognitive tests as the precise relationships between the more novel markers and cognitive impairment are not as well defined.

In conclusion, the MoCA identifies more hypertension-associated cognitive impairment than the MMSE in patients with a history of TIA and non-disabling stroke, implying a pathophysiologically relevant basis for differences between the scores. This results from a greater sensitivity with the MoCA to hypertension-associated cognitive impairment across multiple cognitive domains, particularly due to its greater emphasis on visuo-spatial / executive function. The MoCA test may identify a cohort of patients at a particularly increased risk of future cognitive decline in whom targeted blood pressure lowering treatment may be of specific benefit, and is likely to be the optimal test for determining associations between cognitive impairment and blood pressure variability. The poor sensitivity of the MMSE to hypertension-associated cognitive impairment may explain the apparent lack of efficacy of antihypertensive medications in preventing cognitive decline in randomised controlled trials.

7.6 References

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CHAPTER EIGHT

Effects of antihypertensive drug classes and their combination on within-individual day-to-day variability in home blood pressure

8.1 Summary

In all available RCTs in Chapter 4, intra-individual visit-to-visit variability in systolic blood pressure (SBP) was reduced by calcium channel blockers (CCBs) or diuretics compared to beta-blockers or renin-angiotensin system inhibitors (RASi). I determined if class effects were manifest on home day-to-day SBP variability between each time of day or on diurnal variability.

I analysed the effect of addition or increases in dose of classes of antihypertensive drugs on BP variability on home monitoring (HBPM) in the OXVASC population. Patients were treated with drugs associated with low SBP variability (CCBs or diuretics), with high SBP variability (predominantly RASi) or with a combination of a RASi and a diuretic, at the physician's discretion. Differences in change in variability (CV) from 3-10 days before to 8-15 days after starting or increasing drug dose were compared by general linear models.

Among 288 eligible interventions in 500 patients, SBP variability was reduced by a low variability vs combination vs high variability treatment regimen (-4.0 vs 6.9 vs 7.8%, p=0.015), due to a greater reduction in max SBP (-4.6 vs -1.0 vs -1.0%, p=0.001), with no differences in effect on mean or minimum SBP. This resulted from differences in early morning CV-SBP (3.6 vs 17.0 vs 38.3 p=0.002), which was dependent on differences in max SBP (-4.8 vs -2.0 vs -0.7, p=0.001), with no differences between mid-morning readings (p=0.29), evening readings (p=0.65) or within-day (p=0.92).

Consistent with effects on clinic SBP, CCBs and diuretics reduced home day-to-day SBP variability compared to RASi. Addition of a diuretic to a RASi limited the excess increase in SBP variability. Differences in SBP variability and maximum SBP resulted from drug-class differences after waking rather than on mid-morning or evening SBP.

8.2 Introduction

Visit-to-visit variability in SBP predicts the occurrence of new and recurrent stroke, all-cause mortality and cardiovascular mortality, as demonstrated in chapter 2. It is reduced by randomisation to treatment regimens based on calcium channel blockers (CCB) or diuretics compared to beta-blockers or renin-angiotensin system inhibitors (RASi) (chapter 3), explaining effects on stroke risk and other cardiovascular events.[1-3] Drug effects on SBP variability were seen in a wide-range of patients and persist when used in combination, although this has only been shown with group inter-individual rather than intra-individual SBP variability.[4] Despite these studies, the mechanisms underlying these drug effects are unclear. Furthermore, the studies discussed in chapter 3 only assessed effects of antihypertensive medications on variability in clinic or ambulatory blood pressure whereas mean SBP, maximum SBP and variability in SBP on self-measured home blood pressure are more strongly associated with hypertension, hypertensive arteriopathy and future cardiovascular events (chapters 5-6).

The diurnal variation in risk of stroke is similar to the diurnal variation in blood pressure, with the highest risk of stroke in the early morning during the post-waking morning surge in blood pressure.[5] Differences in drug effects on SBP variability at different times of day may therefore provide alternative explanations for the greater efficacy of CCBs and diuretics at preventing stroke: either by consistently reducing diurnal variation in blood pressure or by limiting episodic peaks in blood pressure at different times of day. For example, as the morning surge in SBP is highly variable within individuals from day to day,[6] limiting excessive surges would reduce day-to-day variability.

Therefore, given that the overall effects of these drug classes have been reliably documented in RCTs, I explored the effect of different classes of antihypertensive drugs, and the effect of the combination of a RASI with a diuretic, on SBP variability on HBPM, including effects on diurnal variability and day-to-day variability at each time of day.

8.3 Methods

8.3.1 Study Population

As in chapters 5-7, consecutive patients were recruited between April 2008 and January 2012 from the Oxford Vascular Study's (OXVASC)[7] TIA and minor stroke clinic, usually within twenty-four hours of referral.[8] From the ascertainment visit, or the earliest opportunity after discharge, all patients performed sets of three home BP readings (HBPM), three times daily (on waking, mid-morning at ~10-11am and before sleep) with a Bluetooth-enabled, regularly-calibrated, telemetric BP monitor.

Patients continued home monitoring until at least the one month follow-up appointment, if tolerated, but could continue to achieve adequate BP control. Mean BP was treated to a target of <130/80 on home monitoring, except in the minority of patients with a haemodynamically significant stenosis (bilateral carotid stenosis >70% or severe end-artery stenosis) when targets were determined on an individual basis. Patients were usually treated in clinic, or after at least 1 week of home BP monitoring, most commonly following the clinic policy of a combination of perindopril arginine 5mg and indapamide 1.25mg, with subsequent addition of amlodipine 5mg before dose escalation.This regimen could be altered by the treating physician, most commonly due to their current medications, or occasionally due to the degree of hypertension or BP variability. Therefore, there is a risk of bias due to interactions with current medications or selection bias with CCBs being more likely to be given to people with variable BP, resulting in greater regression to the mean. However, this study did not set out to prove the effects of these drugs on BP variability, but to test whether their known effects can be replicated with HBPM and to understand these effects in greater detail.

8.3.2 Analysis

Analyses were performed with baseline home readings acquired from 3-10 days prior to starting or increasing the dose of a drug compared to follow-up readings acquired from 8-15 days after the intervention, to minimise the immediate effect of drug increases.

For each time period, the mean, minimum and maximum SBP and DBP were derived from the average of the last two readings of each cluster of three readings at a specific time of day. Diurnal variability in SBP was measured as the coefficient of variation of the cluster averages for each day (standard deviation of three timepoints / mean). Day-to-day variability in SBP and DBP was measured as the residual CV about a moving average over 5 days (to remove the influence of mean BP and any trend in BP) for the mean of all clusters and the mean of clusters at each time of day. All follow-up measures were then expressed as a percentage change compared to the baseline period. Eligible medication changes were identified as any initiation or dose increase with at least 7 days of BP monitoring data prior to the drug change, and a minimum of 10 days after. Increases in treatment (starting or increasing dose) were classified into drugs associated with low variability in SBP in RCTs (CCBs or diuretics); drugs associated with high variability in SBP (RASi or beta-blockers), or a combination of a drug from each group. Secondly, treatment increases were classified into CCBs, diuretics, RASi or combinations of RASi and diuretic.

8.3.3 Statistical analysis

Unadjusted differences in BP indices between intervention groups were assessed by t-tests or ANOVA. Univariate correlations with continuous demographic indices were measured by linear regression and differences between groups in frequency of discrete variables were compared by chi-squared tests. Multivariate general linear models (SPSS sum of squares type IV) were derived for the change in each SBP or DBP index from baseline with independent variables including drug class allocation, age, gender, atrial fibrillation (premorbid or diagnosed within 6 weeks of the event), creatinine, current smoking and a history of hypertension, diabetes, hyperlipidaemia, or family history of stroke. A second model included these variables plus baseline mean SBP and baseline CV.

All analyses were performed with Matlab R2012a, Microsoft Excel 2010 and IBM SPSS 20.

8.4 Results

8.4.1 Study Population

500 patients had adequate home readings, with a median of 15 premorbid BP measurements (IQR 6.4-30.5) and 83.6 BP clusters on home monitoring (IQR 56-174) over 30.8 days (IQR 21.1-64.5). Of 288 eligible drug changes, there were 131 with CCBs (69 drug initiation, 62 dose increases), 55 with RASi (35 drug initiation, 20 dose increase), 47 with diuretics (33 drug initiation, 14 dose increases), 5 with beta-blockers (4 drug initiation, 1 drug increase) and 50 with a combination of a RASi and a diuretic (12 drug initiation, 38 dose increase). Of these eligible interventions 100 were with amlodipine, 52 with perindopril (39 in combination with indapamide), 25 with ramipril and 32 with indapamide alone.

		CCB	RASi	Diuretic	RASi +Diuretic	p-value
Male	N	76	28	26	29	0.83
	Y	55	27	21	21	
Hypertension	N	47	24	20	22	0.64
	Y	84	31	27	28	
Family History	N	100	37	38	36	0.41
of stroke	Y	31	18	9	14	
Hyperlipidaemia	N	74	34	30	30	0.86
	Y	56	21	17	20	
Diabetes	N	108	46	44	41	0.30
	Y	23	9	3	9	
Heart Failure	N	102	50	44	48	0.59
	Y	11	5	2	2	
AF	N	113	53	39	44	0.16
	Y	18	2	8	6	
Smoker	N	112	49	37	43	0.52
	Y	19	6	10	7	
Stroke vs TIA	S	76	32	24	26	0.75
	T	51	21	22	22	
Myocardial	N	128	54	43	47	0.19
Infarction	Y	3	1	4	3	
Age		69.8	69.7	68.6	69.1	0.96
BMI		27.4	27.8	28.3	27.2	0.70
Creatinine		92.2	93.3	83.3	94.2	0.12
Cholesterol		5.1	5.4	5.3	5.1	0.59
TSH		2.3	2.2	2.1	2.2	0.96

Table 8.1. Characteristics of individuals starting a drug or increasing the dose for each drug class. CCB= calcium channel blocker alone; RASi=renin-angiotensin system inhibitor, with or without a diuretic; Diuretic=diuretic alone. Frequencies are compared by chi-squared tests, means by ANOVA.

8.4.2 Baseline Characteristics

Baseline demographic characteristics were well-matched between intervention groups (table 8.1), and there were no significant differences between groups in baseline SBP or DBP variability in overall, diurnal or day-to-day BP variability at any time of day (tables 8.2 and 8.3). However, baseline mean and maximum SBP were marginally higher in the patients treated with low variability drugs, largely due to higher readings in the evening, with non-significant differences after waking and minimal difference in the middle of the morning. There were no significant difference in baseline mean, minimum or maximum DBP, except for a slightly greater baseline maximum DBP in the evening with low variability drugs (table 8.3).

	3-10 days before intervention					**% Change > 8 days after intervention**				
	High	Combination	Low			High	Combination	Low		
	62	50	178	p-val		62	49	178	p-val	
All Measures										
Mean	129.5	127.7	132.4	0.038	*	-1.9	-2.4	-3	0.39	
Minimum	110.2	109.4	112.3	0.26		-1.6	-3.6	-1.3	0.26	
Maximum	149.4	147.2	154.2	0.017	*	-1	-1	-4.6	0.001	**
rCV	7.9	8	7.9	0.98		7.8	6.9	-4	0.015	*
Early Morning										
Mean	131.9	129.9	134.3	0.13		-1.6	-3	-3.7	0.09	
Minimum	120.4	117.5	122.1	0.09		-1.9	-1.7	-2.5	0.76	
Maximum	143.7	142.1	147.2	0.13		-0.7	-2	-4.8	0.001	**
rCV	5.3	5.9	5.6	0.62		38.3	17	3.6	0.002	**
Mid-morning										
Mean	126.7	124.4	128.4	0.24		-4.2	-2.6	-2.3	0.29	
Minimum	114.7	113.5	116.7	0.39		-2.9	-4.1	-0.8	0.11	
Maximum	140.3	138.9	141.5	0.64		-5.6	-3.4	-3.5	0.42	
rCV	6.7	7	6.1	0.27		4.8	37.7	17.2	0.29	
Evening										
Mean	129.1	127.3	133.5	0.006	**	-1.7	-1.8	-2.5	0.68	
Minimum	115.2	114.7	120.1	0.006	**	0.5	-1.5	-1.1	0.4	
Maximum	143.1	140.7	148.2	0.013	*	-1.5	-1.4	-3.6	0.16	
rCV	6.8	6.6	6.4	0.61		-3.3	7.5	7.5	0.65	
Diurnal SD	9.8	9.1	10.4	0.23		-0.6	0.6	-1.9	0.92	
Diurnal CV	7.5	7.4	7.8	0.64		2	3.8	1	0.92	

Table 8.2. Differences in baseline systolic BP and SBP variability and percentage change in each measure 8-15 days after starting or increasing the dose of each class of antihypertensive drug. Treatment groups are defined as low variability drugs (CCB or diuretic), high variability drugs (RASi or beta-blockers) or a combination of a RASi and a diuretic. SD=standard deviation; CV=coefficient of variation; rCV=residual CV about a 5 day moving average. Mean values are compared by ANOVA. *p<0.05; ** p<0.01; *** p<0.001.

8.4.3 Unadjusted drug class effects on overall BP variability

Consistent with the findings of previous RCTs, there was a significant reduction in overall variability in home SBP in patients treated with a low variability drug (CCBs or diuretics) compared to patients receiving drugs associated with a high variability in SBP, with an intermediate effect of a combination of a low variability drug and a high variability drug, despite no significant difference in variability between groups at baseline (table 8.2). There was no difference between CCBs and diuretics in their effects on variability in SBP or DBP and no difference in change in global variability in DBP (table 8.3).

	3-10 days before intervention					**% Change > 8 days after intervention**				
	High	Combination	Low			High	Combination	Low		
	62	50	178	p-val		62	49	178	p-val	
All Measures										
Mean	76.2	75.5	77.2	0.46		-1.8	-2.1	-3	0.27	
Minimum	63.8	64	65.2	0.49		-0.6	-2.2	-2	0.57	
Maximum	89.1	88.1	89.8	0.65		-2.6	-2.6	-4.3	0.21	
rCV	8.5	8.2	8	0.41		5	5.4	0.1	0.41	
Early Morning										
Mean	78.3	77.4	79	0.61		-1.9	-2.6	-3.4	0.24	
Minimum	70.9	69.4	71.4	0.45		-1.5	-0.3	-2.3	0.39	
Maximum	85.8	85.1	86.7	0.69		-1.7	-3.3	-4.4	0.06	
rCV	5.8	6.1	5.9	0.88		18.6	7.4	3.3	0.28	
Mid-morning										
Mean	75.1	73.5	75	0.67		-3.4	-1.9	-2.6	0.72	
Minimum	67.7	67	68.4	0.72		-1.5	-2.8	-1.9	0.85	
Maximum	83.6	81.9	82.2	0.71		-5.6	-3	-3.3	0.32	
rCV	6.9	6.8	6.1	0.25		11.5	37.1	15.9	0.29	
Evening										
Mean	75.4	74.5	77	0.19		-1.1	-0.7	-2.3	0.24	
Minimum	67.1	67.5	69	0.3		0.9	-1.6	-0.8	0.34	
Maximum	83.2	81.6	85.8	0.036	*	-0.6	1.9	-3.5	0.001	**
rCV	6.9	6.2	6.6	0.41		5.1	22.5	5.1	0.17	
Diurnal SD	5.9	5.8	5.8	0.92		8.9	-2.5	2.2	0.31	
Diurnal CV	7.7	7.7	7.6	0.97		10.9	0.7	5	0.39	

Table 8.3. Differences in baseline diastolic BP and DBP variability and percentage change in each measure 8 days after starting or increasing the dose of each class of antihypertensive drug. Treatment groups are defined as low variability drugs (CCB or diuretic), high variability drugs (RASi or beta-blockers) or a combination of a RASi and a diuretic. SD=standard deviation; CV=coefficient of variation; rCV=residual CV about a 5 day moving average. Mean values are compared by ANOVA. *p<0.05; ** p<0.01; *** p<0.001.

Drug-class effects on SBP variability were predominantly determined by effects on maximum SBP, with a greater reduction in maximum SBP in patients treated with drugs associated with low variability in SBP, reflecting reduced episodic elevations in SBP, despite no significant difference in mean or minimum SBP (table 8.2), including after adjustment for clinical characteristics (figure 8.1). The effect of treatment with a combination of a low and high variability drug was intermediate between the two monotherapy classes. There was no significant difference between groups in change in mean, minimum or maximum DBP.

8.4.4 Adjusted drug class effects on global SBP variability

Differences in SBP variability persisted after adjustment for age, gender and cardiovascular risk factors, with and without additional adjustment for baseline mean and variability in SBP, for both low variability vs high variability vs a combination of drugs, and for CCBs vs diuretics vs RASi vs combinations (table 8.4). Furthermore, the effect persisted for CCBs vs anything else and for CCBs vs diuretics vs any regimen containing a RASi (table 8.5). Differences between drug classes in variability in SBP were greatest immediately after the intervention, due largely to an increase in BP variability with RASi, but the differences persisted beyond day 8 (figure 8.1).

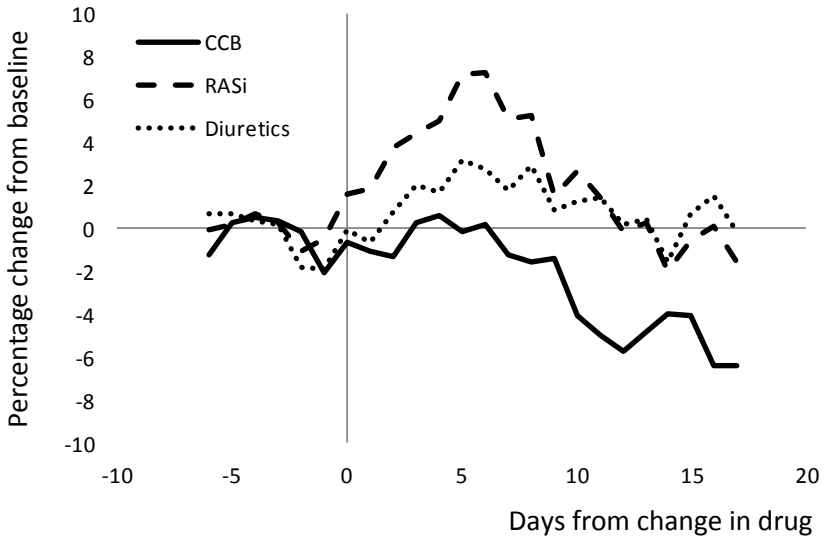

Figure 8.1. Percentage change in variability in systolic blood pressure after starting or increasing the dose of each class of drug. Variability is measured as the coefficient of variation from three days previous to three days after each timepoint.

	Low vs high vs combination			CCBs vs RASi vs combination vs Diuretic		
	η^2	Predictor	p	η^2	Predictor	P
All Timepoints						
Basic Model	0.032	Class effect	0.011	0.037	Class effect	0.018
		Low vs			CCB vs	
		High	0.015		RASi	0.019
		Combination	0.021		Combination	0.038
					Diuretic	0.53
+ *baseline BP*	0.039	Class effect	0.005	0.05	Class effect	0.004
baseline CV		Low vs			CCB vs	
		High	0.008		RASi	0.024
		Combination	0.01		Combination	0.034
					Diuretic	0.15
Early Morning						
Basic Model	0.048	Class effect	0.001	0.053	Class effect	0.002
		Low vs			CCB vs	
		High	<0.001		RASi	<0.001
		Combination	0.13		Combination	0.13
					Diuretic	0.94
+ *baseline BP*	0.066	Class effect	<0.001	0.07	Class effect	<0.001
baseline CV		Low vs			CCB vs	
		High	<0.001		RASi	<0.001
		Combination	0.016		Combination	0.026
					Diuretic	0.62
Mid-Morning						
Basic Model	0.013	Class effect	0.25	0.013	Class effect	0.43
+ *baseline BP*	0.016	Class effect	0.18	0.02	Class effect	0.31
baseline CV						
Evening						
Basic Model	0.006	Class effect	0.47	0.011	Class effect	0.41
+ *baseline BP*	0.003	Class effect	0.66	0.01	Class effect	0.55
baseline CV						
Diurnal CV						
Basic Model	0.001	Class effect	0.92	0.003	Class effect	0.90
+ *baseline BP*	0.001	Class effect	0.90	0.003	Class effect	0.86
baseline CV						

Table 8.4 Effect of drug class allocation on change in variability in SBP, adjusted for major cardiovascular risk factors and demographic characteristics. Models are presented for allocation to drugs associated with low variability in SBP (CCBs, diuretics), high variability in CCBs (ACE inhibitors, angiotensin receptor blockers, beta-blockers) or a combination of both, and for allocation to CCBs, RASi (ACEi or ARBs), diuretics or a combination of RASi and diuretic. Models are adjusted for age, gender, diabetes, history of hypertension, current smoking, family history of stroke, dyslipidaemia, atrial fibrillation and creatinine, with and without adjustment for baseline mean SBP and baseline SBP CV. The partial η^2 from general linear models describes the proportion of total variance in change in the residual CV at follow-up compared to baseline explained by drug class allocation.

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	CCBs vs all other Drugs			CCBs vs any RASi regimen vs Diuretic		
	η^2	Lower rCV	p	η^2	Lower rCV	p
All Timepoints						
Basic Model	0.012	CCB vs all	0.07	0.037	Drug effect	0.006
					CCB vs RASi ± D	0.006
					CCB vs Diuretic	0.53
+ *baseline BP baseline CV*	0.01	CCB vs all	0.14	0.05	Drug effect	0.001
					CCB vs RASi ± D	0.007
					CCB vs Diuretic	0.15
Early Morning						
Basic Model	0.025	CCB vs all	0.009	0.042	Drug effect	0.004
					CCB vs RASi ± D	0.001
					CCB vs Diuretic	0.93
+ *baseline BP baseline CV*	0.029	CCB vs all	0.005	0.06	Drug effect	<0.001
					CCB vs RASi ± D	<0.001
					CCB vs Diuretic	0.63
Mid-Morning						
Basic Model	0.001	CCB vs all	0.60	0.001	Drug effect	0.88
+ *baseline BP baseline CV*	0.001	CCB vs all	0.62	0.004	Drug effect	0.65
Evening						
Basic Model	0.008	CCB vs all	0.15	0.009	Drug effect	0.32
+ *baseline BP baseline CV*	0.003	CCB vs all	0.36	0.004	Drug effect	0.59
Diurnal CV						
Basic Model	0.002	CCB vs all	0.49	0.002	Drug effect	0.76
+ *baseline BP baseline CV*	0.002	CCB vs all	0.46	0.003	Drug effect	0.71

Table 8.5. Effect of drug class allocation on change in variability in SBP, adjusted for major cardiovascular risk factors and demographic characteristics. Models are presented for allocation to CCBs vs anything else and for allocation to CCBs, diuretics or any regimen containing a RASi. Models are adjusted for age, gender, diabetes, history of hypertension, current smoking, family history of stroke, dyslipidaemia, atrial fibrillation and creatinine, with and without adjustment for baseline mean SBP and baseline SBP CV. The partial η^2 from general linear models describes the proportion of total variance in change in the residual CV at follow-up compared to baseline explained by drug class allocation. P-values are given for the overall effect of drug class allocation, and post-hoc contrasts for low variability drugs vs other groups, or for CCBs for other groups

8.4.5 Differences in drug class effects by time of day

The significant differences between drug groups in reduction in global variability in SBP were primarily dependent upon significant differences in day-to-day variability in SBP in the early morning, with a significant increase in patients treated with RASi, no significant change in patients treated with CCBs or diuretics and an intermediate effect of treatment with a combination of the two classes (table 8.2). There was no significant difference between groups in change in day-to-day variability in SBP in the middle of the morning or in the evening, and no difference between groups in change in diurnal variability. Again, the differences between drug groups in day-to-day SBP variability immediately after waking persisted after adjustment for age, gender and cardiovascular risk factors, and also persisted after additional adjustment for baseline mean SBP and baseline variability in SBP.

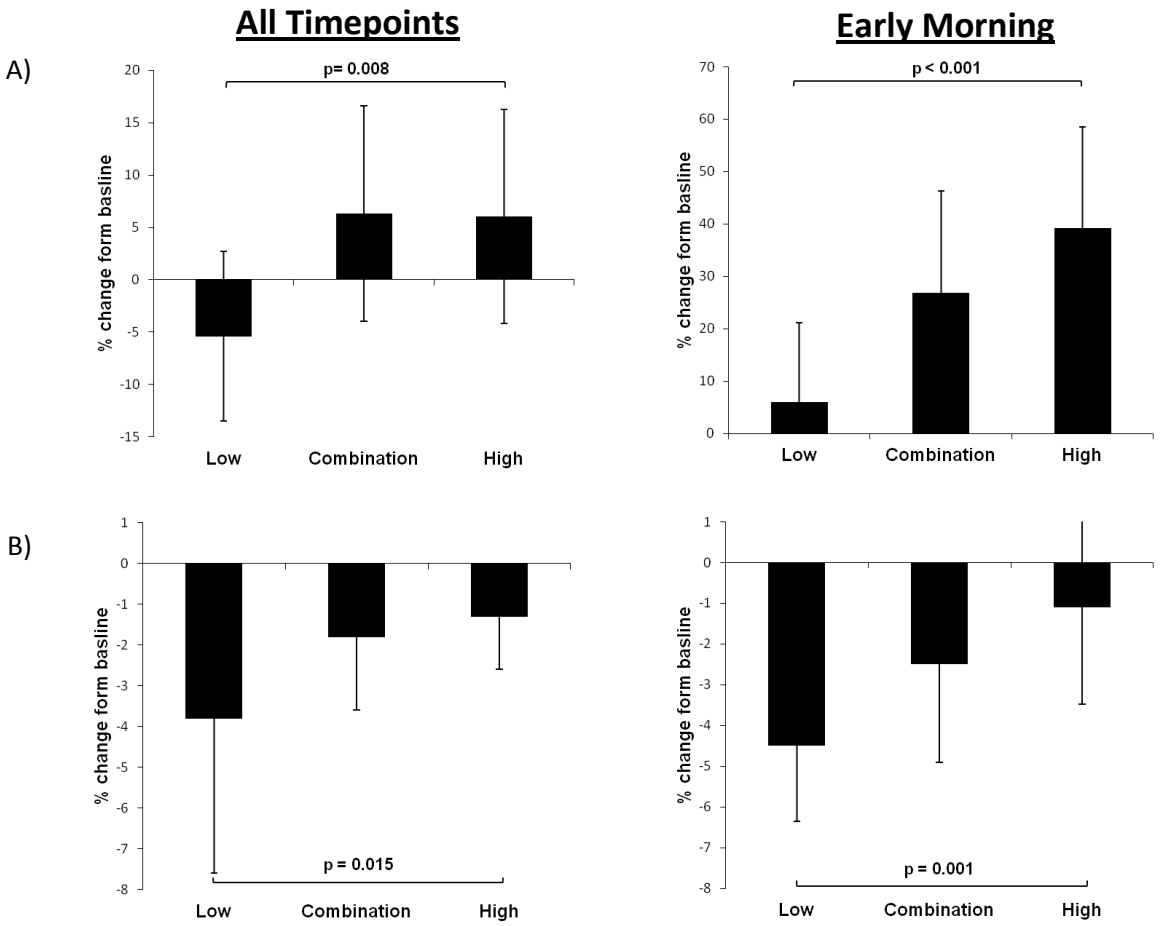

Figure 8.2. Differences between change in variability or maximum SBP after initiation of drugs associated with lower SBP variability, higher SBP variability or a combination. Results are mean percentage change in maximum SBP or residual coefficient of variation (RCV) in SBP for days 8-15 after starting or increasing each treatment compared to 3-10 days before the intervention, after adjustment. Error bars represent confidence intervals. A) Changes in SBP variability; B) Changes in maximum SBP.

Similar to the effect on global variability in SBP, the differences between groups in day-to-day SBP variability after waking was associated with a significant reduction in maximum SBP after waking in the CCB and diuretic groups, with much less reduction in the group treated with RASi alone (table 8.2) and an intermediate effect of treatment with a combination therapy. There was no difference in change in mean or minimum SBP between groups, despite a higher mean SBP at baseline in the group treated with low variability drugs. In the middle of the morning and the evening, there was no difference in change in mean, minimum or maximum SBP between groups, despite greater baseline measures in patients treated with low variability drugs in all groups. Again there was no difference in any measure between groups in mean, minimum, maximum or day-to-day variability in DBP at any time of day except for slightly greater reductions in maximum DBP in patients treated with CCBs or diuretics compared to RASi in the middle of the morning and the evening.

8.5 Discussion

After TIA or non-disabling stroke, CCBs and diuretics reduced self-measured, day-to-day SBP variability relative to an increase in variability with RAS inhibitors, consistent with the effects of these drugs on visit-to-visit clinic variability in the primary prevention of stroke in large randomised controlled trials (chapters 2-3). Drug-class effects persisted when used in combinations, with a combination of low and high variability drugs resulting in an intermediate effect on variability in SBP, despite similar effects on mean SBP. These effects were seen with day-to-day variability early in the morning, but not at other times of day or for diurnal variability within a day. They resulted from a significantly greater reduction in maximum SBP after waking, with no differences between drugs in reduction of mean SBP at any time of day.

CCBs and diuretics reduced visit-to-visit variability in SBP compared to beta-blockers in the large ASCOT-BPLA and MRC trials,[2] and also reduced variability in SBP in comparison with both beta-blockers and RASi in the meta-analysis of all published studies

(chapter 3). In these trials, the effects on SBP variability explained the difference in stroke risk between treatment arms that was not explained by differences in mean SBP alone. However, these trials were primary prevention studies. Therefore, this is the first study to demonstrate differences in drug class effects on change in intra-individual variability in SBP in the secondary prevention of cerebrovascular disease. The consistent effect on variability in SBP in this secondary prevention study therefore supports the hypothesis that the benefits of CCBs and diuretics in the primary of prevention of stroke may also be present for the secondary prevention of stroke.

This is also the first study to demonstrate these drug class effects on self-measured home blood pressure. This indicates a common mechanism underlying variability in SBP on visit-to-visit readings and home blood pressure readings, consisted with the similarity between the predictive value of SBP variability in clinic and at home (chapter 2). This supports the validity of home BP monitoring as an appropriate method for the assessment of blood pressure and demonstrates that home monitoring can be used to measure changes in BP variability in response to drug treatment, unlike ambulatory monitoring.

This study also furthers our understanding of the mechanism of the effect of drug classes on SBP variability as it is the first study to demonstrate effects on day-to-day variability in SBP at different times of day. The benefit of CCBs or diuretics compared to RASi immediately after waking were not seen at later times of day or for diurnal variability in SBP. Furthermore, there was a strong effect of CCBs and diuretics on maximum SBP after waking, but no difference in mean or minimum SBP after waking, or maximum SBP at other times of day. This is consistent with the stronger relationship between clinical characteristics and SBP variability in the morning compared to later times of day (chapter 6). This implies that the most important effect of CCBs or diuretics on SBP variability results from limiting episodic peaks in SBP immediately after waking, which is consistent with evidence showing a greater prognostic significance of morning day-to-day variability in SBP compared to the evening.[9] This probably demonstrates an important effect on the morning

surge in blood pressure, which is predictive of future cardiovascular events,[10] and the timing of which matches the increased risk of stroke in the morning compared to later in the day.[5] Specifically, as there was no difference in mean diurnal variability, the effect probably results from limiting episodic, day-to-day variations in the post-waking surge. This cannot be explained by drug half-life as although amlodipine has a longer half-life, the half life of indapamide and the active metabolite of perindopril, perindoprilat, are very similar at ~17 hours. Furthermore, any differences in half-life would cause a consistent difference in diurnal CV rather than limit episodic differences from day-to-day which are more likely to be due to underlying physiological processes.

Finally, this study demonstrated that the combination of a RASi and indapamide resulted in an intermediate effect on day-to-day SBP variability compared to RASi or diuretics alone. This is consistent with a previous meta-analysis of RCTs[4] which used inter-individual SBP variability as an indirect measure of intra-individual SBP variability. Therefore, we can be confident that in patients with increased SBP variability on a RASi, the addition of a diuretic will limit variability in SBP, although potentially not as much as stopping the RASi. Furthermore, as the effect of CCBs was present despite a high rate of prior use of RASi, this is very likely to be true for the use of CCBs as well.

There are limitations to this study. Firstly, patients received antihypertensive drugs at the non-randomised discretion of the treating physician. However, the unbiased effect of each drug class on intra-individual variability in SBP has already been demonstrated in large randomised trials. Therefore, the primary aim of this study was to investigate the effects of antihypertensive treatment on SBP variability at different times of day rather than prove the existence of an effect on SBP variability. Furthermore, despite the lack of randomisation, the groups were very well balanced for clinical characteristics and there were no significant differences between treatment groups in baseline variability in SBP over any timeframe and no difference in change in mean SBP at follow-up. The second limitation of the study is that it was performed in patients with acute TIA or minor stroke. However,

this group of patients are at the highest risk of recurrent stroke, and currently there is only limited evidence of the effect of antihypertensives on SBP variability in secondary prevention, unlike studies in primary prevention.[3] Therefore this is the optimal group in whom to identify therapeutic targets and methods of monitoring of BP variability in order to reduce the risk of recurrent stroke. Nonetheless, the findings of this study at different times of day ideally need replication in primary prevention populations. Thirdly, diurnal variability was only measured at three timepoints in each day rather than using ambulatory blood pressure monitoring. However, repeated ABPM is impractical for the assessment of a response to treatment and by monitoring daily there were up to 7 estimates of diurnal variability at baseline and follow-up for each individual, producing at least as reliable an estimate as a single day of ambulatory readings.[11] Finally, all readings were taken in a relaxed sitting position at home, which may not accurately reflect real-life blood pressure behaviour. However, this is true of most blood pressure studies, including all studies demonstrating a prognostic benefit from antihypertensive treatment, and limits the occurrence of measurement artefact that is commonly seen with ambulatory readings.[12, 13]

In summary, CCBs and diuretics reduced self-measured, home blood pressure variability in the secondary prevention of cerebrovascular events compared to RASi, due largely to a reduction in day-to-day variability and maximum SBP after waking. These effects persisted when used in combinations. This supports the use of these drugs in the secondary prevention of patients with cerebrovascular disease, particularly in patients with increased BP variability or excessive morning surges in SBP, and supports the use of home BP monitoring as a method of monitoring the response to SBP variability directed treatment.

8.6 References

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CHAPTER NINE

Increased cerebral arterial pulsatility

in patients with leukoaraiosis:

arterial stiffness enhances transmission of aortic pulsatility

9.1 Summary

Small vessel stroke associated with leukoaraiosis may be particularly associated with blood pressure variability, but this relationship may depend upon associated changes in cerebral perfusion. One current hypothesis states that arterial stiffening reduces dampening of the arterial waveform and hence increases pulsatility of cerebral blood flow, damaging small vessels. To test this hypothesis as a precursor to measuring associations with BP variability, I determined associations between leukoaraiosis and aortic and middle cerebral artery stiffness and pulsatility. Patients were recruited from the Oxford Vascular Study within 6 weeks of a TIA or minor stroke. Leukoaraiosis was categorised on MRI by two independent observers with the Fazekas and ARWMC scales. MCA stiffness (transit time: MCA-TT) and pulsatility (Gosling's index: MCA-PI) were measured with transcranial ultrasound, and aortic pulse wave velocity (ao-PWV) and aortic systolic, diastolic and pulse pressure (SBP, DBP, PP) by applanation tonometry (Sphygmocor).

In 100 patients, MCA-PI was significantly greater in patients with leukoaraiosis (0.91 vs 0.73, $p<0.0001$). Severity of leukoaraiosis was associated with MCA-PI and aortic PWV (Fazekas: $\chi^2=0.39$, MCA-PI $p=0.01$, ao-PWV $p=0.06$; ARWMC: $\chi^2=0.38$, MCA-PI $p=0.015$; ao-PWV $p=0.026$) for periventricular and deep white matter lesions, independent of aortic SBP, DBP and PP and MCA-TT. In a multivariate model ($r^2=0.68$, $p<0.0001$), MCA-PI was independently associated with aortic-PWV ($p=0.016$) and aortic-PP ($p<0.0001$) and inversely associated with aortic-DBP ($p<0.0001$) and MCA-TT ($p=0.001$).

MCA pulsatility was the strongest physiological correlate of leukoaraiosis, independent of age, and was dependent upon aortic-DBP and PP and aortic and MCA stiffness, supporting the hypothesis that large artery stiffening results in increased arterial pulsatility, with transmission to the cerebral small vessels resulting in leukoaraiosis.

9.2 Introduction

Small vessel stroke associated with leukoaraiosis is the most likely stroke subtype to be dependent on blood pressure variability. If blood pressure variability is associated with stroke due to associated changes in cerebral perfusion, as indicated by the correlation between antihypertensive effects on headache and effects on blood pressure variability described in chapter 4, then the relationship between leukoaraiosis and cerebral perfusion may be key. However, the pathogenesis of small vessel disease and any relationship with haemodynamic changes in the cerebral circulation is poorly understood. Therefore, in order to understand whether the relationship between blood pressure variability and stroke risk may be confounded by changes in the cerebral circulation we must first understand whether small vessel disease is related to cerebral and systemic haemodynamic factors. Therefore I investigated how chronic small vessel disease (leukoaraiosis) is dependent upon cerebral haemodynamic measures, and how these relate to the changes in the systemic circulation.

In addition to improving our understanding of whether stroke and changes in the cerebral circulation are associated with changes in blood pressure variability, a better understanding of the pathogenesis of leukoaraiosis has significant potential health benefits in itself. Prevention of premature leukoaraiosis by treating the underlying causes in middle age may reduce the risk of stroke[1] and dementia,[2] and other consequences of cerebral small vessel disease.[3, 4] However, the relative importance of haemodynamic factors as opposed to a primary microangiopathy[5] in the development of leukoaraiosis is unclear and associations with age, hypertension and diabetes are consistent with both processes.[6] Previous studies have suggested a relationship between increased middle cerebral artery (MCA) pulsatility measured by transcranial Doppler ultrasound (TCD) and leukoaraiosis or lacunar infarction in patients with hypertension[7] and diabetes,[8] although not necessarily independent of age. However, increased cerebral pulsatility has often been interpreted as a consequence of small vessel disease due to changes in downstream resistance,[9] rather than as a causal factor related to increased central arterial stiffness and reduced damping

of the cerebral arterial waveform.[10] Yet the cerebral circulation appears to be specifically adapted to dampen the arterial waveform[11] and increased aortic stiffness has been associated with leukoaraiosis,[12] lacunar stroke,[13] and cerebral pulsatility.[10] However, these relationships all strongly covary with age and are susceptible to residual confounding. Previous studies have not measured leukoaraiosis, aortic pulse wave velocity (PWV) and middle cerebral pulsatility optimally in the same patient group and no study has also measured aortic pulsatility and middle cerebral artery stiffness, key components of the hypothesised mechanism in which increased aortic pulsatility is transmitted via stiff large vessels to the cerebral microvasculature.

Therefore I performed the first study assessing the dependence of leukoaraiosis on arterial stiffness and pulsatility in both the aorta and middle cerebral artery in patients with recent TIA or minor stroke, to assess the degree to which leukoaraiosis depends independently on each of these measures, after adjustment for significant clinical features, particularly age. Understanding these relationships is a necessary prerequisite for further studies looking at the relationship between systemic and cerebral physiological changes associated with blood pressure variability (chapter 10).

9.3 Methods

9.3.1 Study population

Consecutive consenting and eligible participants within 6 weeks of a TIA or minor stroke (NIHSS<5) were recruited to a physiological substudy of the Oxford Vascular Study (OXVASC)[14] between January and December 2011 from the acute TIA and stroke clinic associated with the study. Participants were excluded if they were under 18 years, unable to have an MRI scan, cognitively impaired (MMSE<23), pregnant or had had a recent myocardial infarction (<1 month), unstable angina, heart failure (NYHA 3-4 or ejection fraction <40%) or untreated severe bilateral carotid stenosis (>70%) or occlusion. The study was approved by the Oxfordshire Research Ethics Committee.

9.3.2 Procedures

MRI scans were performed during the acute clinical assessment on a 3T MRI system (Siemens Magnetom Verio) according to a standardised protocol using vendor-designed sequences. The protocol comprised T2-weighted TSE and FLAIR sequences, diffusion and susceptibility-weighted images, a T1-weighted spin-echo 2D sequence post contrast application as well as a time-of-flight MRA of the intracranial vessels and a contrast enhanced MRA of the large neck arteries.

All axial T2 scans were scored according to a modified version of the Fazekas[15] scale by an experienced observer (M Simoni) blinded to clinical and physiological data, as this score is the simplest, most commonly used and well-validated semi-quantitative score for leukoaraiosis. Scans were also graded by the ARWMC[16] score to demonstrate the consistency of the results. Finally, leukoaraiosis was also independently scored by a consultant neuroradiologist (W Kuker), who was not blinded to the patient's clinical details, on a simple 4 point scale: 'None', 'Mild,' 'Moderate' or 'Severe' relative to the patient's age (Oxford scale). For comparison, the Fazekas and ARWMC scores were also categorised into four approximately equally sized groups (Fazekas: none 0, mild 1, moderate 2, severe ≥3; ARWMC: none 0, mild 1-3, moderate 4-9, severe ≥10).

Physiological tests were performed at rest in a quiet, dimly-lit, temperature-controlled room (21-23^{0}C). Applanation tonometry (Sphygmocor, AtCor Medical, Sydney, Australia) was used to measure carotid-femoral pulse wave velocity (aortic-PWV), aortic augmentation index and central aortic systolic, diastolic and pulse pressure (ao-SBP, ao-DBP, ao-PP),[17] calibrated to the average of 3 brachial blood pressures measured supine after at least 10 minutes rest. TCD (Doppler Box, Compumedics DWL, Singen, Germany) was performed with a handheld 2MHz probe at the temporal bone window on the same side as carotid applanation. The waveform envelope was acquired at 100Hz simultaneously with ECG and blood pressure at 200Hz (Finometer, Finapres Medical Systems, The Netherlands), via a Powerlab 8/30 with LabChart Pro software (ADInstruments, USA). The

MCA was insonated at 50mm, or if this was not adequate, at the depth giving the optimal waveform. Data were exported to Matlab R2010a for calculation of mean MCA transit time (MCA-TT) measured from the QRS complex to the foot of at least 7 beats as identified by intersecting tangents.[18] All waveforms were visually inspected and beats corrupted by artefact were excluded. MCA-PWV was calculated as the distance between the sternal notch and the temporal bone window divided by MCA-TT.[19] MCA pulsatility was calculated as Gosling's pulsatility index (MCA-PI= (systolic CBFV-diastolic CBFV) / mean CBFV). All physiological tests were performed by one investigator (Alastair Webb).

9.3.3 Statistical analysis

Kappa statistics were derived to assess inter-rater agreement for assessment of leukoaraiosis with the Oxford score, and agreement of severity of leukoaraiosis between the Fazekas and ARWMC scales. Differences between patient groups in continuous variables were assessed by t-tests or ANOVA, with tests for linear trend for severity of leukoaraiosis, whilst differences in frequencies were compared by chi-squared tests. Univariate relationships between continuous variables were assessed by linear regression. Multivariate predictors of continuous physiological outcome variables were determined by general linear models but due to the non-normal, positively skewed distribution of the semi-quantitative scores for leukoaraiosis, relationships between leukoaraiosis severity and either clinical or physiological measures were assessed with ordinal regression. Relationships were assessed with and without adjustment for age and gender and also adjusted for additional cardiovascular risk factors including: history of hypertension, stroke, hypercholesterolaemia, current smoking, family history of stroke, diabetes, height, and brachial systolic and diastolic BP.

9.4 Results

9.4.1Study population

Of 110 patients recruited, 10 (9%) had inadequate temporal bone windows for TCD. 30 patients had no leukoaraiosis on the Fazekas scale (38 had no periventricular leukoaraiosis and 42 had no deep white matter lesions), compared to 39 on the ARWMC and Oxford scales. The inter-rater agreement for leukoaraiosis in 100 consecutive cases imaged by MRI and rated by the Oxford scale was good (k=0.78, 95% CI 0.65-0.90 for presence of leukoaraiosis and weighted k=0.66, 0.56-0.76 for severity of leukoaraiosis). Agreement in assessment of the severity of leukoaraiosis between the ARWMC and Fazekas scales was also good (weighted k=0.60, 0.48-0.72).

	Fazekas Scale Score				
	0 (n=30)	1 (n=21)	2 (n=24)	≥3 (n=25)	p-value
Age	53 (15)	66.5 (12)	68.5 (11)	74.9 (7.9)	<0.0001
Male	22 (73)	13 (62)	14 (58)	17 (68)	0.58
Event type:					
Stroke	11 (37)	9 (43)	9 (38)	9 (36)	0.76
TIA	19 (63)	12 (57)	15 (63)	16 (64)	
Hypertensive	9 (30)	7 (33)	12 (50)	17 (68)	0.03
Diabetes	2 (6.7)	3 (14)	2 (8.3)	6 (24)	0.10
Family History*	5 (17)	5 (24)	5 (21)	10 (40)	0.08
Hyperlipidaemia	9 (30)	8 (38)	7 (29)	12 (48)	0.27
Atrial Fibrillation	0 (0)	1 (4.8)	3 (13)	3 (12)	0.05
Current smoker	7 (23)	2 (9.5)	4 (17)	5 (20)	0.82
Blood Pressure:					
Systolic	124.1 (16.4)	132.9 (14.9)	131.6 (18.8)	129.6 (19.9)	0.28
Diastolic	78.7 (11.8)	77.6 (11.1)	74.4 (12.7)	70.7 (12.3)	0.01
Creatinine	79.8 (15.4)	75.3 (16)	77.5 (17.9)	89.6 (25.7)	0.08
BMI	28.1 (5.9)	27.5 (5.3)	27.5 (5.5)	26.9 (3.8)	0.44

Table 9.1 Demographic characteristics of patients according to severity of leukoaraiosis. Severity of leukoaraiosis is measured according to the total score on the Fazekas scale. Continuous variables are presented as mean (SD) with p-values for trend across levels of leukoaraiosis. Frequencies are presented as number (%), with p-values for trend. *Family History refers to a reported history of stroke in either parent.

9.4.2 Clinical associations with leukoaraiosis or physiological measures

In univariate comparisons, age, frequency of hypertension and a lower diastolic blood pressure were associated with increasing severity of leukoaraiosis (table 9.1). MCA-PI increased with age, female sex, diabetes, creatinine and a lower DBP whereas aortic pulse pressure was associated with elevated SBP, age and female gender (table 9.2). Aortic PWV was similarly associated with age, SBP, hypertension and creatinine but MCA-TT was only associated with age. There was no relationship between event type (stroke vs TIA), aetiology or territory and either leukoaraiosis or physiological measures.

	Pulsatility				**Arterial Stiffness**			
	MCA Pulsatility Index		Aortic PP (mmHg)		MCA Transit time (ms)		Aortic PWV (m/s)	
Discrete	No	Yes	No	Yes	No	Yes	No	Yes
Male	0.91 (0.2)	0.83 (0.2) *	48 (16)	41 (11) *	153 (18)	158 (19)	9.6 (3)	9.9 (3)
Hypertension	0.82 (0.2)	0.91 (0.2) *	40 (12)	48 (13) **	158 (17)	154 (21)	9 (2)	10.8 (3) ***
Diabetes	0.84 (0.2)	0.97 (0.2) *	44 (13)	42 (14)	156 (18)	156 (23)	9.6 (3)	11.5 (3) *
Family History	0.84 (0.2)	0.9 (0.2)	43 (12)	45 (15)	156 (19)	156 (19)	9.7 (3)	10.1 (3)
Hyperlipidaemia	0.84 (0.2)	0.89 (0.2)	43 (13)	45 (13)	157 (18)	154 (21)	9.7 (3)	10.1 (2)
Atrial Fibrillation	0.85 (0.2)	0.95 (0.2)	43 (13)	48 (16)	156 (18)	162 (28)	9.9 (3)	9.6 (4)
Current Smoker	0.87 (0.2)	0.8 (0.2)	44 (13)	41 (13)	157 (19)	154 (21)	10 (3)	8.9 (2)
Stroke vs TIA	0.86 (0.2)	0.85 (0.2)	44 (12)	43 (14)	154 (19)	160 (20)	10 (3)	10 (3)
Continuous	r^2	p-value	r^2	p-value	r^2	p-value	r^2	p-value
Age	0.387	<0.001	0.224	<0.001	0.102	0.001	0.359	<0.001
Systolic BP	0.006	0.40	0.444	<0.001	0.01	0.15	0.165	<0.001
Diastolic BP	0.292	<0.001	0	0.99	0.051	0.02	0	0.79
Creatinine	0.053	0.02	0	0.97	0	0.97	0.073	0.007
Cholesterol	0	0.34	0	0.54	0	0.59	0.01	0.07
BMI	0.01	0.16	0	0.33	0	0.84	0.029	0.08

Table 9.2 Relationships between physiological measures and demographic characteristics. Group differences are presented as mean (SD) and compared by t-tests. For comparisons of continuous variables, r^2 and p-values are derived from univariate linear regression. *p<0.05 **p<0.01 ***p<0.001.

9.4.3 Associations between leukoaraiosis and physiological measures

Patients with leukoaraiosis had significantly greater MCA-pulsatility (0.91 vs 0.73, p<0.0001), aortic PWV (10.5 vs 8.1 m/s, p<0.0001), aortic pulse pressure (47.3 vs 35.8 mmHg, p<0.0001) and MCA stiffness, whether measured as mean transit time (153 vs 164 ms, p<0.0001) or MCA-PWV (1.38 vs 1.31 m/s, p=0.016), on all scales. Furthermore, these relationships showed a dose-response relationship with increasing severity of leukoaraiosis. MCA-PI and aortic-PWV were independent predictors of total score on the Fazekas and ARWMC scales (Ordinal regression: Fazekas χ^2=0.39, MCA-PI p=0.01, ao-PWV p=0.06; ARWMC χ^2=0.38, MCA-PI p=0.015; ao-PWV p=0.026) in models including MCA-PI, MCA-TT, ao-PWV, ao-PP, ao-SBP and ao-DBP. In models adjusting for age, gender and major cardiovascular risk factors, only MCA-PI and age remained as independent predictors (table 9.3). The same associations with total Fazekas score were also found for periventricular (χ^2=0.31, MCA-PI p=0.029, ao-PWV p=0.044) and deep white matter scores (χ^2=0.34, MCA-PI p=0.03, ao-PWV p=0.08) except that aortic-PWV was not independently associated with deep lesions. Models including aortic pulsatility index instead of aortic PP and MCA-PWV instead of MCA-TT were not significantly different, and the same results were found with adjusted logistic regression for leukoaraiosis versus no leukoaraiosis.

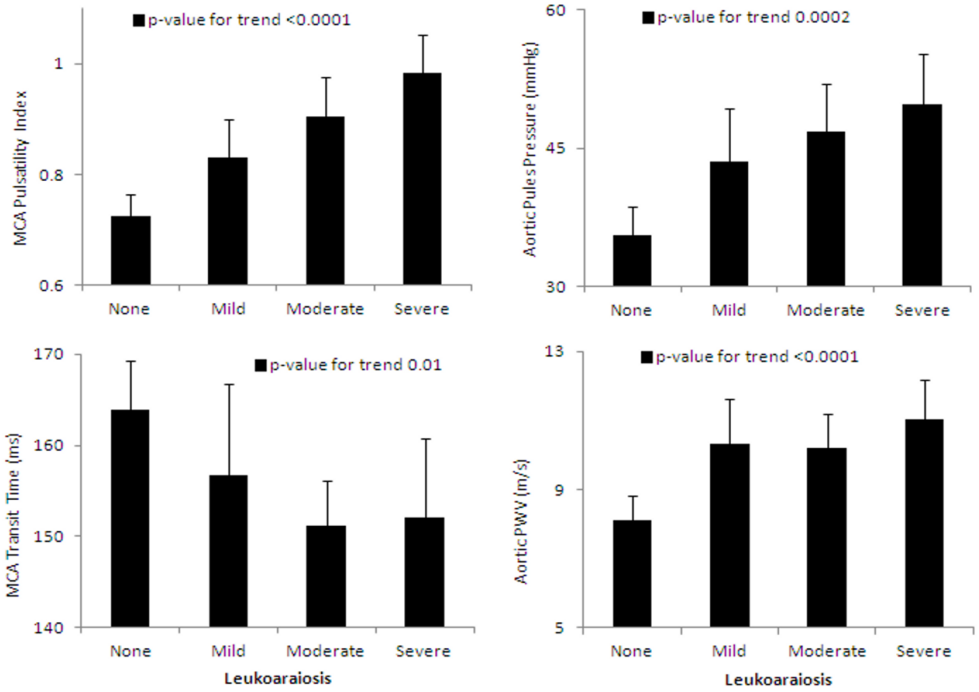

Figure 9.1 Relationship between severity of leukoaraiosis and stiffness or pulsatility in the aorta and middle cerebral artery. Severity of leukoaraiosis is classified according to the total score on the Fazekas scale (None=0, mild =1, moderate=2, severe ≥3). Groups are mean (95%CI), with p-values by a linear test for trend across groups.

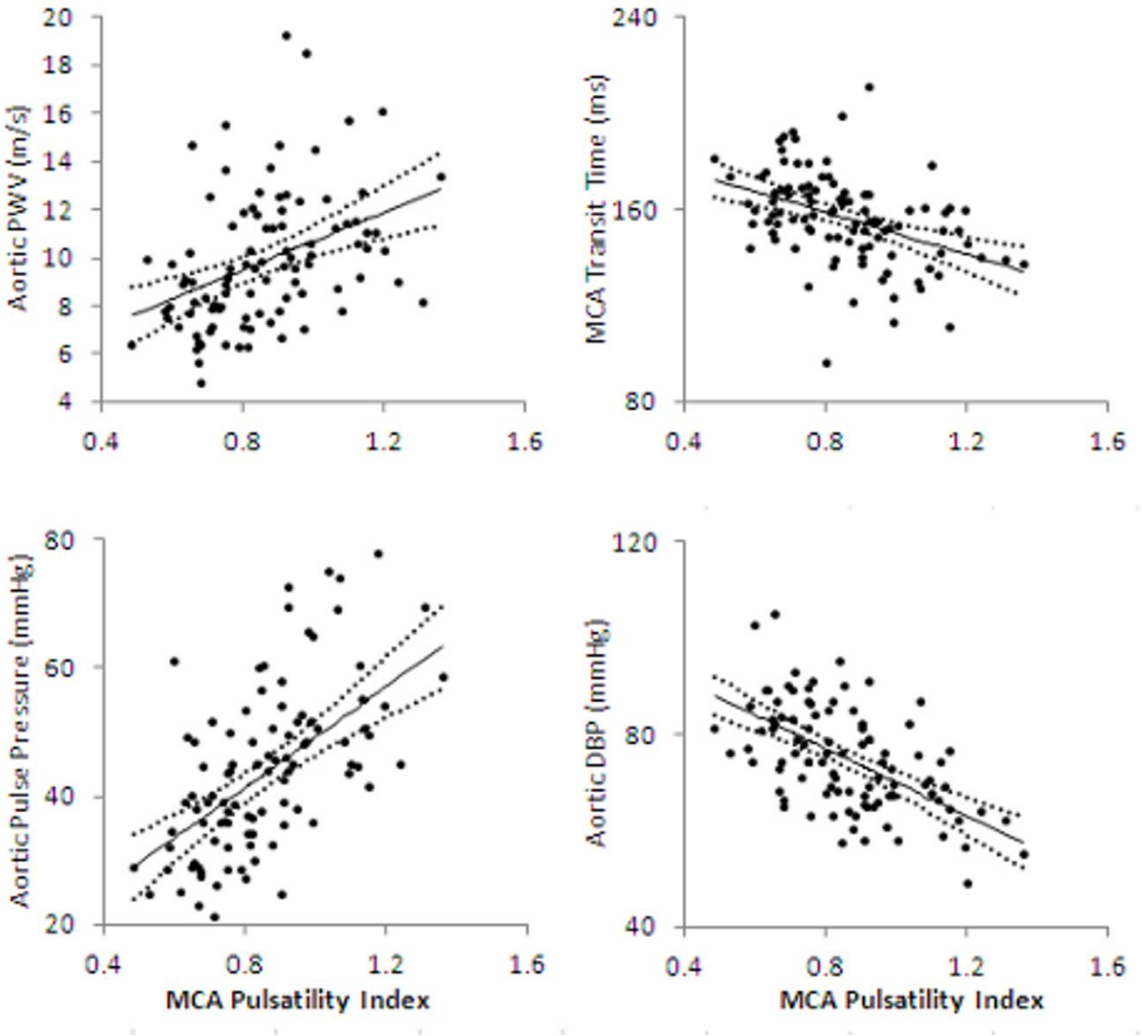

Figure 9.2 Associations between middle cerebral artery pulsatility index (MCA-PI) and aortic pulse wave velocity, MCA transit time, aortic pulse pressure and aortic diastolic blood pressure. All relationships depicted are derived from univariate linear regression with 95% confidences intervals, but these relationships are independent in stepwise multivariate general linear models (see table 9.3).

9.4.4 Physiological determinants of cerebral pulsatility

MCA-PI was dependent upon both pulsatility and arterial stiffness in both the aorta and the MCA with strong associations with ao-PP, ao-PWV and MCA-TT and, whilst there was no association with SBP, there was a strong negative association with DBP (figure 9.2). In addition, there was a relationship between aortic and middle cerebral artery stiffness but only when the analysis was limited to patients with less variable ao-PWV (SD for repeated measures <2): ao-PWV vs MCA-TT r^2=0.075, p=0.013; ao-PWV vs MCA-PWV r^2=0.063, p=0.023. In multivariate comparisons, MCA-PI was independently associated with

aortic-DBP, aortic-PP, aortic-PWV and MCA-TT (r^2=0.680, ao-PP p<0.0001, ao-DBP p<0.0001, MCA-TT p=0.001, ao-PWV p=0.016), all of which were independent of age and cardiovascular risk factors except for aortic-PWV (see table 9.3).

	Global model			Independent Associations		
Outcome	**Model design**	**r^2 / χ^2**	**p-value**	**Variable**	**β**	**p-value**
Fazekas Scale (adj physiology)	Ordinal Regression*	39.44	<0.001	MCA-PI Aortic PWV	4.79 0.15	0.01 0.06
Fazekas Scale (adj age+gender)	Ordinal Regression†	48.07	<0.001	MCA-PI Age	4.75 0.074	0.011 0.003
Fazekas Scale (adj all variables)	Ordinal Regression‡	48.98	<0.001	MCA-PI Age	4.33 0.089	0.037 0.002
MCA – PI (adj physiology)	GLM *	0.680	<0.001	Aortic PP Aortic DBP Aortic PWV MCA-TT	0.006 -0.009 0.011 -0.002	<0.0001 <0.0001 0.016 0.001
MCA – PI (adj age+gender)	GLM †	0.686	<0.001	Aortic PP Aortic DBP Aortic PWV MCA-TT	0.005 -0.008 0.009 -0.002	<0.001 <0.001 0.079 0.004
MCA – PI (adj all variables)	GLM ‡	0.744	<0.001	Aortic PP Aortic DBP MCA-TT Diabetes	0.006 -0.006 -0.002 0.101	0.004 0.007 0.006 0.005

Table 9.3 Associations of severity of leukoaraiosis and middle cerebral artery pulsatility in multivariate models including demographic and physiological variables. Severity of leukoaraiosis is measured according to the total score on the Fazekas scale. Ordinal regressions are presented for severity of leukoaraiosis due to the non-Normal distribution of leukoaraiosis severity, whilst physiological determinants of MCA-PI are assessed by general linear models (GLM), with and without adjustment for clinical features. *Physiological variables include aortic SBP and DBP and pulse pressure, aortic stiffness (PWV), MCA stiffness (transit time) and MCA pulsatility (MCA-PI). †Additionally adjusted for age and gender; ‡ additionally adjusted for history of hypertension, stroke, hypercholesterolaemia, current smoking, family history of stroke, diabetes, height, and brachial systolic and diastolic BP.

9.5 Discussion

This study demonstrates a significant relationship between MCA pulsatility and the presence and severity of leukoaraiosis in a cohort of patients with recent TIA and minor stroke, with similar results for both periventricular and deep white matter disease. This relationship was independent of age and other physiological measures, and was significantly stronger than the association between leukoaraiosis and aortic stiffness or aortic pulsatility. The very strong association (r^2>0.6) of MCA-PI with aortic pulsatility, diastolic BP, aortic stiffness and MCA stiffness, further suggests that MCA-PI is mainly dependent upon these measures, rather than on distal small vessel resistance.

Leukoaraiosis is strongly associated with cognitive impairment,[1, 2] an increased risk of stroke,[1] increased morbidity as a result of stroke[20, 21] and increased mortality.[1] However, it is unclear whether leukoaraiosis has a predominantly ischaemic aetiology due to either chronic ischaemia[22, 23] or incomplete episodic infarction, or whether it represents a primary microangiopathy that directly causes both leukoaraiosis and the associated physiological changes.[5, 24] Whilst both hypotheses could explain the clinical associations, the former hypothesis is supported by studies showing a relationship between the anatomical distribution of leukoaraiosis and lower cerebral blood flow[22] or cerebrovascular reactivity,[25] whilst the latter hypothesis is supported by independent genetic associations with leukoaraiosis,[26] superficially similar white matter disease in CADASIL[27] and COL4A1 mutations[28] and the demonstration of increased blood-brain barrier permeability in patients with leukoaraiosis, both in lesions and in normal appearing white matter.[5, 24] However, ultimately it is likely that these two mechanisms are not mutually exclusive.

Mine is the first study to assess the association of leukoaraiosis with stiffness and pulsatility in both the aorta and cerebral arteries in one cohort. I demonstrated a significantly stronger association of leukoaraiosis with MCA-PI than with any other physiological measure, despite similar associations with age, suggesting a more direct pathophysiological relationship. In addition, this means that it is unlikely that differences in

leukoaraiosis and cerebral pulsatility are solely due to independent effects of age on the brain. The very strong correlation of MCA-PI with aortic pulsatility and large artery stiffness also suggests a causative pathophysiological relationship. Together these findings imply that increased arterial stiffening causes increased transmission of enhanced aortic pulsatility to the cerebral circulation, causing leukoaraiosis either due to alterations in perfusion during diastole, due to increased endothelial shear stress or due to impaired cerebral autoregulation of fluctuations in blood pressure. Previous studies demonstrating a relationship between leukoaraiosis and either cerebral pulsatility[7] or aortic stiffness[12] have only assessed one component of this mechanism and could not determine whether increased cerebral pulsatility results from leukoaraiosis or whether arterial stiffening and leukoaraiosis are only independent markers of age. However, the methods used in this study detect associations rather than determine causation, and it is feasible that the inferred direction of causation from aortic stiffness to cerebral pulsatility to leukoaraiosis is incorrect. It is possible that there is reverse causation with leukoaraiosis reflecting a systemic arteriopathy causing increased pulsatility and secondary stiffening of the aorta, although this pathway would function in the opposite direction to the strengths of association. The direction of causation could be more formally assessed with methods for causal inference, including structural equation monitoring (where the direction of effect is formalized in a testable set of assumptions), or propensity score matching (which seeks to match groups of patients differing by the independent variable of interest by potential covariates), but these methods are beyond the scope of this study.

This study has some limitations. First, it was a cross-sectional, observational study and therefore it is possible that the physiological associations with leukoaraiosis are confounded by a systemic primary microangiopathy, but this is unlikely given the strength of the relationship between the physiological variables and MCA-PI. Nonetheless, larger longitudinal studies will be required to confirm these findings. Second, the patients were heterogeneous in both age and stroke aetiology. This resulted in an increased range of

leukoaraiosis, increasing the sensitivity of the study, but there were insufficient patients to identify whether these associations differed by specific subgroups, particularly whether the same associations applied to patients with lacunar and non-lacunar stroke. Finally, I did not address whether there were coexistent changes in blood brain barrier permeability in this patient group.

The strong association between leukoaraiosis and middle cerebral artery pulsatility suggests that stroke risk is likely to be associated with cerebral haemodynamic factors, whether cerebral pulsatility or potentially cerebral autoregulation or reactivity. This could partly explain the relationship between blood pressure variability and stroke risk if there is a similarly strong relationship between blood pressure variability and either cerebral haemodynamics, or else the systemic physiological measures that cerebral pulsatility is dependent upon including aortic stiffness or pulsatility (chapter 10).

Assessing the potential contribution of haemodynamic factors to the aetiology of leukoaraiosis is important for guiding the development of interventions, especially as no direct interventions exist to treat a primary microangiopathy. Current antihypertensive medications may reduce cerebral arterial pulsatility, and this could potentially be part of the explanation for differences between antihypertensive medications in the resultant risk of stroke[29] and cognitive impairment,[30] possibly by effects on blood-pressure variability or associated mechanisms. In addition, therapies directed at reducing aortic stiffness in middle-age could delay the development of leukoaraiosis. Further research needs to assess the longitudinal relationship between cerebral pulsatility and the development of leukoaraiosis, and ideally test whether interventions which reduce cerebral pulsatility or aortic stiffness also prevented development of leukoaraiosis (chapter 11).

In summary, leukoaraiosis is closely associated with cerebral arterial pulsatility, which is strongly dependent upon aortic pulsatility and large artery stiffness. This is consistent with the hypothesis that arterial stiffening results in increased aortic pulsatility and its transmission to the cerebral circulation and may play a pathophysiological role in the

development of leukoaraiosis and its clinical sequelae. Ultimately, treatment aimed at reducing arterial stiffness in middle age might be most effective in preventing stroke, dementia and other consequences of cerebral small vessel disease.

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CHAPTER TEN

Associations between beat-to-beat, day-to-day and visit-to-visit variability in systolic blood pressure with cerebral pulsatility and reactivity

10.1 Summary

Systolic blood pressure (SBP) variability is associated with an increased risk of cardiovascular events (chapters 2+6) whilst cerebral pulsatility is associated with leukoaraiosis and stroke (chapter 9). Moreover, drug-class dependent changes in SBP variability were associated with incident headache, potentially reflecting changes in cerebrovascular reactivity (chapter 4). Therefore I aimed to determine the relationships between SBP variability and both cerebral pulsatility and reactivity.

Consecutive patients with TIA and non-disabling stroke were recruited from the OXVASC clinic. The coefficient of variation (CV=standard deviation / mean) of SBP on 5 minutes beat-to-beat monitoring, awake ABPM and home blood pressure monitoring (HBPM 3 measurements, 3 times daily) was related to middle cerebral artery pulsatility (MCA-PI), aortic pulsatility (PP=pulse pressure) and aortic stiffness (PWV). Cerebrovascular reactivity was determined by breath-holding (BHI) and hyperventilation.

In 177 of 200 eligible patients who had adequate TCD and beat-to-beat SBP readings, SBP variability was associated with MCA-PI (beat-to-beat CV $r=0.317$ $p<0.0001$; HBPM CV $r=0.334$ $p<0.001$), aortic PP (beat-to-beat 0.287 $p<0.001$; HBPM 0.277 $p<0.001$), response to BHI (beat-to-beat $r=-0.211$ $p=0.018$; home $r=-0.176$ $p=0.06$) and response to hyperventilation (bt-to-bt 0.228 $p=0.04$; home 0.295 $p=0.018$), whilst response to hyperventilation was associated with cerebral pulsatility ($r=0.271$ $p=0.025$). Cerebral pulsatility was related to daytime ($r=0.269$ $p=0.001$) and evening ($r=0.274$ $p=0.0001$) SBP variability whilst response to hyperventilation was related to early morning SBP variability ($r=0.340$ $p=0.004$).

SBP variability was associated with both cerebral pulsatility and reactivity, potentially explaining, at least in part, the association with stroke risk. However, mechanisms underlying the association between SBP variability with cerebral pulsatility and reactivity may differ.

10.2 Introduction

Visit-to-visit variability in systolic blood pressure (SBP) and episodic hypertension in clinic are associated with an increased risk of stroke and all cardiovascular events, independent of mean BP (chapter 2). Furthermore, visit-to-visit SBP variability is reduced by calcium channel blockers but increased with beta-blockers, potentially explaining differences in stroke risk that are not explained by differences in mean SBP (chapters 3 and 8). The strong relationship between maximum blood pressure and stroke risk suggests that acute elevations in blood pressure may underlie the relationship between SBP variability and stroke risk,[1] but an alternative possibility is that increased variability in blood pressure either causes or is associated with an underlying chronic arteriopathy that results in an increased risk of stroke by alternative mechanisms.[2]

As demonstrated in chapter 9, cerebral pulsatility is associated with leukoaraiosis. Furthermore, cerebral pulsatility was dependent upon aortic pulsatility and arterial stiffness, supporting the hypothesis that leukoaraiosis partly results from increased arterial stiffness causing greater transmission of the pulsatile arterial waveform to the cerebral circulation, and so potentially explaining some of the relationship between aortic stiffness and stroke risk.[3] Impairment of cerebral reactivity is also associated with an increased risk of stroke in occlusive large artery disease,[4] but few studies have assessed its contribution to recurrent stroke risk in the absence of large artery disease. Therefore, in an extended cohort from the same population based study, I determined whether variability in blood pressure from beat-to-beat, day-to-day and visit-to-visit was associated with either increased cerebral pulsatility or measures of cerebral reactivity.

10.3 Methods

10.3.1 Study population

This analysis was carried out in all eligible patients included in the physiological substudy of the Oxford Vascular Study (OXVASC)[5] who underwent transcranial doppler ultrasound (TCD) performed between January 2011 and December 2012. Patients were recruited from the acute TIA and stroke clinic associated with the study, as described in chapter 9, but including additional patients in whom there was no MRI-based assessment of leukoaraiosis. Participants were excluded if they were under 18 years, cognitively impaired (MMSE<23), pregnant, had a recent myocardial infarction (<1 month), unstable angina, heart failure (NYHA 3-4 or ejection fraction <40%), untreated severe bilateral carotid stenosis (>70%) or occlusion, a condition likely to result in autonomic dysfunction or which to confounded the test measures. Patients with atrial fibrillation (AF) were excluded from this analysis as AF randomly increases SBP variability. The study was approved by the Oxfordshire Research Ethics Committee.

10.3.2 Laboratory Procedures

Laboratory tests were performed at rest in a quiet, dimly-lit, temperature-controlled room (21-23^{0}C). Applanation tonometry (Sphygmocor, AtCor Medical, Sydney, Australia) was used to measure carotid-femoral pulse wave velocity (aoPWV) and central aortic systolic, diastolic and pulse pressure (aoSBP, aoDBP, aoPP),[6] calibrated to the average of 3 brachial blood pressures measured supine after at least 10 minutes rest. Transcranial Doppler ultrasound (TCD, Doppler Box, Compumedics DWL, Singen, Germany) was performed with a handheld 2MHz probe at the temporal bone window, on the same side as carotid applanation tonometry, to determine middle cerebral artery velocities and pulsatility. For carbon dioxide (CO2) reactivity testing, bilateral TCD monitoring was performed with 2MHz probes attached to a DiaMon headset. The waveform envelope was acquired at 100Hz simultaneously with ECG, blood pressure (Finometer, Finapres Medical Systems, The Netherlands) and end tidal CO2 (EtCO2, Capnocheck Plus, Smiths Medical) at 200Hz,

acquired via a Powerlab 8/30 (ADInstruments, USA). The bifurcation into MCA and ACA was identified and the MCA was insonated superficial to this, ideally at a depth between 50-60mm. Data were exported to Matlab R2010a for calculation of mean MCA transit time (MCA-TT) measured from the QRS complex to the foot of at least 7 beats as identified by intersecting tangents.[7] All waveforms were visually inspected and beats corrupted by artefact were excluded. MCA-PWV was calculated as the distance between the sternal notch and the temporal bone window divided by MCA-TT.[8] MCA pulsatility was calculated as Gosling's pulsatility index (MCA-PI= (systolic CBFV-diastolic CBFV) / mean CBFV), and Pourcelot's resistive index (MCA-RI = (systolic CBFV-diastolic CBFV) / peak CBFV).

To determine cerebrovascular reactivity to carbon dioxide, participants were asked to hold their breath for 30 seconds, with the quality of the breath-hold determined by capnography. The breath-holding index (BHI) was calculated as: 100*((MCA velocity at end of breath hold – MCA velocity at baseline) / MCA velocity at baseline) / duration of breath hold. Patients with a rise in CO2 <5% on repeated trials were excluded. After 2 minutes rest, patients were asked to hyperventilate for 30s at normal tidal volumes, replicating a demonstration by the investigator. Tests of cerebrovascular reactivity were only introduced after the initial study described in chapter 9, with breath-holding index introduced first, followed by hyperventilation, once the protocol for dual-channel TCD monitoring was established, and so there are relatively limited patients undergoing these tests.

10.3.3 Blood Pressure Measurement

Beat-to-beat variability in supine SBP was assessed for 5 minutes after 20 minutes of supine rest (Finometer, Finapres Medical Systems) with readings calibrated to 2 supine brachial blood pressure readings. Slow drifts in the recordings were removed by cubic regression to improve stationarity. The lifetime medical record held by the primary care physician was manually reviewed and all recorded premorbid BPs ascertained. From the ascertainment visit, or the earliest opportunity after discharge, all patients performed sets of three home BP readings (HBPM), three times daily (on waking, mid-morning and before

sleep) with a Bluetooth-enabled, regularly-calibrated, telemetric BP monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT. Patients were instructed to relax in a chair for 5 minutes before performing readings in the non-dominant arm, or the arm with the higher reading if the mean SBP differed by >20mmHg between arms, and were assessed at doing so at ascertainment. Anonymised measures were transmitted by Bluetooth radio to a mobile phone, for secure transmission to a server hosting a password-protected website for review and download of readings (t+ Medical, Abingdon, UK). At the 1 month follow-up visit, awake ambulatory measurements (ABPM) were performed with an A&D TM-2430 monitor in the non-dominant arm, fitted by a trained study nurse, at 30 minutes intervals during the day and 60 minute intervals at night.

Patients continued home monitoring until the one month follow-up appointment, if tolerated, but could continue monitoring to achieve adequate BP control. Mean BP was treated to a target of <130/80 on home monitoring or mean ABPM, except in the presence of haemodynamically significant stenosis (bilateral carotid stenosis >70% or end-artery stenosis >70%) when targets were determined on an individual basis. Choice of antihypertensive agent was tailored to the individual patient but standard first-line treatment was a combination of perindopril arginine 5mg and indapamide 1.25mg, followed by amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion.

10.3.4 Analysis

Analyses of home SBP variability used all home readings acquired from 7 days after the recruitment visit (to reduce acute treatment or event effects) until readings were not performed on at least 3 days of the week, the monitor was returned or 90 days had elapsed, taking the average of the last two readings of each BP cluster. SBP and DBP on ABPM were derived for awake readings following automated and manual exclusion of artefactual measurements according to predefined criteria.[9] Premorbid SBP and DBP were derived from all readings recorded in the lifetime primary care record and from readings in

the five years prior to the notification event. SBP variability was defined as the coefficient of variation (CV=100 * standard deviation / mean) for awake and premorbid readings, and as residual CV about a moving average over 9 days for all home BP readings or for early morning, mid-morning and evening separately.

Physiological predictors of variability in home, beat-to-beat or awake SBP variability were determined by general linear models (GLM), unadjusted and adjusted for age and gender. Physiological predictors of cerebral pulsatility were also assessed by GLMs with and without variability in SBP to determine independence. Secondly, significant physiological predictors were categorised into tertiles of the population and differences across tertiles assessed by ANOVA.

All analyses were performed in Matlab R2010b, Microsoft Excel 2010 and IBM SPSS 20.0.

10.4 Findings

10.4.1 Study population

Of 200 eligible patients, 11 (5.5%) were excluded due to atrial fibrillation and 12 had inadequate bone windows (6%). The remaining 177 patients had adequate assessment of aortic blood pressure, brachial blood pressure and beat-to-beat blood pressure variability, 155 (88%) underwent HBPM, 165 (93%) had awake ambulatory blood pressure monitoring and 165 (93%) had premorbid blood pressure readings available.

Characteristic	Men (119)	Women (58)	All (177)
Age	64.1 (13.4)	67.1 (12.3)	65.1 (13.1)
Risk Factors			
Hypertension	59 (50)	31 (53)	90 (50)
Hyperlipidaemia	35 (29)	17 (29)	52 (29)
Diabetes	19 (16)	6 (10)	25 (14)
Family history of stroke	34 (29)	18 (31)	52 (29)
History of Atrial Fibrillation	14 (12)	7(12)	21 (12)
Heart Failure	1 (0.8)	1 (1.7)	2 (1.1)
Migraine	32 (27)	25 (42)	57 (32)
Smoker	23 (19)	10 (17)	33 (18)
Height (cm)	175.5 (8.0)	163.2 (7.9)	171.5 (9.8)
Weight (Kg)	84.4 (16.4)	72.5 (15.1)	80.5 (16.9)
BMI	27.4 (4.8)	27.3 (6.0)	27.3 (5.2)
Blood Pressure			
Brachial supine SBP	129.2 (18.9)	128.7 (18.9)	129 (18.8)
Brachial supine DBP	77 (12.2)	75.0 (10.3)	76.4 (11.6)
Aortic supine SBP	118.3 (18.3)	118.2 (19.1)	118.3 (18.6)
Aortic Supine DBP	76.2 (12)	75.2 (11.4)	75.2 (11.4)
Home SBP	126.7 (13.7)	120 (11.1)	124.4 (13.2)
Home DBP	77.5 (8.7)	72.4 (7.7)	75.7 (8.7)
Awake ABPM SBP	128.2 (13.7)	125.4 (9.4)	127.2 (12.4)
Awake ABPM DBP	76.1 (8.5)	72.4 (7.7)	75.7 (8.7)
Blood Tests			
Creatinine	88.3 (22.3)	71.6 (16.3)	82.8 (21.9)
Total Cholesterol	5.2 (3.0)	5.6 (1.3)	5.3 (2.6)
Event Aetiology			
Large Artery Disease	19 (16)	3 (5)	22 (12)
Cardioembolic	11 (9)	6 (10)	17 (10)
Lacunar	23 (19)	12 (20)	35 (20)
Other	2 (2)	0 (0)	2 (1)
Undetermined / multiple	65 (54)	37 (63)	102 (57)
Event Territory			
Carotid	54 (45)	26 (44)	80 (45)
Vertebrobasilar	55 (46)	25 (42)	80 (45)
Unknown / both	10 (9)	8 (14)	18 (0)

Table 10.1 Population characteristics. Frequencies are given as number (%) with p-values from chi-squared tests, whilst continuous variables are expressed as mean (SD) with p-values for gender difference from t-tests.

10.4.2 Associations between variability in SBP and physiological measures

Variability in systolic blood pressure on home and beat-to-beat blood pressure monitoring was associated with MCA-PI, with and without adjustment for age and gender (table 10.2), with a significant trend across tertiles of MCA-PI for both home and beat-to-beat SBP variability (figure 10.1). There was no association with awake SBP variability on ABPM either as CV or as ARV (table 10.6). There was a similarly strong relationship with aortic pulse pressure, but a weaker relationship with brachial pulse pressure that was not present for home SBP variability after adjustment for age and gender. SBP variability was associated with aortic pulsatility despite minimal associations with baseline SBP or DBP or absolute cerebral blood flow velocity. Beat-to-beat SBP variability was also associated with aortic (aoPWV) or middle cerebral artery stiffness (MCA-TT), but after adjustment for age and gender this was only significant for MCA-TT. There was no direct relationship between measures of arterial stiffness and either home or ambulatory blood pressure variability (table 10.2).

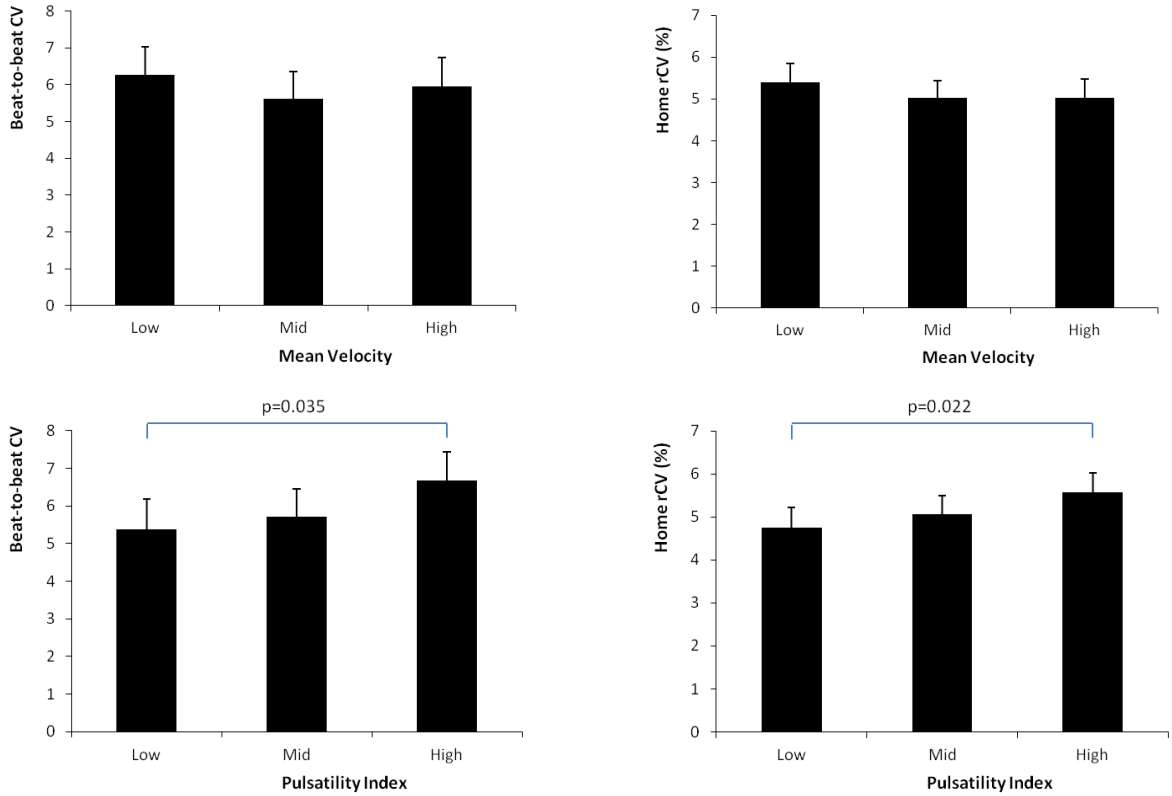

Figure 10.1. Differences in home and beat-to-beat blood pressure variability by tertile of middle cerebral artery mean velocity and pulsatility index. Columns represented marginal means from General Linear Models, adjusted for age and gender, with 95% confidence interval error bars. p-values represent post-hoc comparisons between extreme groups

Measure	N	Beat-to-Beat CV			Home rCV			Awake CV		
		r	Unadj p	Adj p	r	Unadj p	Adj p	r	Unadj p	Adj p
Age	**177**	**0.279**	<0.001*	n/a	**0.271**	<0.001*	n/a	**0.120**	0.13	n/a
Creatinine	**177**	**0.202**	0.007*	0.05	**0.160**	0.047*	0.01*	**0.051**	0.85	0.19
BMI	**177**	**-0.040**	0.60	0.63	**-0.045**	0.58	0.91	**0.015**	0.85	0.78
Systemic Measures										
Aortic PWV	**174**	**0.266**	<0.001*	0.09	**0.089**	0.27	0.63	**0.011**	0.89	0.61
Aortic SBP	**177**	**0.155**	0.04*	0.07	**0.123**	0.13	0.04*	**-0.054**	0.49	0.40
Aortic DBP	**177**	**-0.096**	0.21	0.74	**-0.142**	0.08	0.48	**-0.127**	0.10	0.37
Aortic PP	**177**	**0.287**	<0.001*	0.004*	**0.277**	<0.001*	0.014*	**-0.029**	0.71	0.75
Brachial SBP	**177**	**0.205**	0.008*	0.013*	**0.098**	0.24	0.26	**-0.072**	0.37	0.34
Brachial DBP	**177**	**-0.099**	0.20	0.93	**-0.120**	0.15	0.94	**-0.109**	0.17	0.47
Brachial PP	**177**	**0.333**	<0.001*	0.001*	**0.215**	0.009*	0.14	**-0.005**	0.95	0.46
TCD Measures										
Mean interval	171	**-0.233**	0.002*	0.019*	**-0.128**	0.12	0.50	**-0.028**	0.73	0.77
PWV	171	**0.189**	0.014*	0.06	**0.108**	0.20	0.70	**-0.038**	0.63	0.53
Peak Velocity	177	**-0.111**	0.14	0.70	**-0.034**	0.68	0.80	**0.048**	0.54	0.64
Trough Velocity	177	**-0.277**	<0.001*	0.07	**-0.246**	0.002*	0.06	**0.001**	0.99	0.43
Mean Velocity	177	**-0.204**	0.007*	0.27	**-0.148**	0.067	0.28	**0.028**	0.72	0.50
Pulsatility Index	177	**0.317**	<0.001*	0.003*	**0.334**	<0.001*	0.008*	**0.07**	0.37	0.72
Resistive Index	177	**0.281**	<0.001*	0.01*	**0.316**	<0.001*	0.013*	**0.097**	0.22	0.93

Table 10.2 Associations between measures of blood pressure variability and determinants of cerebral pulsatility. R and p values are derived from linear regression, with and without adjustment for age and gender. * p<0.05

10.4.3 Associations between physiological measures and premorbid BP readings

Middle cerebral artery pulsatility, aortic stiffness and aortic pulsatility were associated with elevated mean premorbid SBP, including for readings in the last 5 years, before and after adjustment for age and gender. However, premorbid SBP variability was only associated with cerebral pulsatility (table 10.3). Home and beat-to-beat SBP variability were only weakly associated with premorbid hypertension or premorbid SBP variability.

		Premorbid Mean SBP			**Premorbid CV**		
Measure	**N**	R	Unadj p	Adj p	r	Unadj p	Adj p
SBP Variability							
Beat-to-beat	163	**0.174**	**0.03***	**0.26**	**0.058**	**0.48**	**0.45**
Home	155	**0.194**	**0.02***	**0.06**	**0.219**	**0.01***	**0.02***
Awake	155	**-0.050**	**0.54**	**0.41**	**0.048**	**0.56**	**0.75**
Aortic Measures							
Aortic PWV	162	**0.399**	**<0.001***	**<0.001***	**0.082**	**0.26**	**0.26**
Aortic SBP	165	**0.356**	**<0.001***	**<0.001***	**0.088**	**0.28**	**0.27**
Aortic DBP	165	**0.100**	**0.20**	**0.006***	**0.023**	**0.77**	**0.99**
Aortic PP	165	**0.394**	**<0.001***	**<0.001***	**0.098**	**0.22**	**0.23**
TCD Measures							
TCD arrival time	159	**-0.193**	**0.015***	**0.10**	**-0.110**	**0.18**	**0.27**
Peak Velocity	165	**-0.058**	**0.46**	**0.58**	**0.214**	**0.007**	**0.012***
Trough Velocity	165	**-0.250**	**0.001**	**0.40**	**0.110**	**0.17**	**0.13**
Mean Velocity	165	**-0.160**	**0.04***	**0.94**	**0.170**	**0.033***	**0.034***
Pulsatility Index	165	**0.323**	**<0.001***	**0.008***	**0.166**	**0.039***	**0.033***
TCD Reactivity							
Breath-holding							
Peak BHI	133	**-0.184**	**0.034***	**0.12**	**0.050**	**0.58**	**0.57**
Trough BHI	133	**-0.129**	**0.14**	**0.36**	**-0.002**	**0.98**	**0.97**
Hyperventilation							
Peak fall	70	**0.175**	**0.15**	**0.07**	**0.236**	**0.052**	**0.07**
Peak fall (%)	70	**0.081**	**0.50**	**0.53**	**0.077**	**0.53**	**0.60**
Trough fall	70	**0.132**	**0.28**	**0.22**	**0.107**	**0.39**	**0.38**
Trough fall (%)	70	**0.132**	**0.28**	**0.51**	**0.001**	**0.99**	**0.97**

Table 10.3 Associations between premorbid blood pressure measures, cerebral pulsatility, cerebral reactivity and determinants of cerebral pulsatility. R and p values are derived from linear regression, with and without adjustment for age and gender. * p<0.05

10.4.4 Independence of associations with SBP variability

In models combining aoPWV, aoPP and MCA-PI, beat-to-beat and home SBP variability were most strongly predicted by MCA-PI before (beat-to-beat p=0.01; home p=0.003) and after adjustment (beat-to-beat p=0.03; home p=0.07), with no independent contribution of any other predictor of blood pressure variability. However, MCA pulsatility was strongly determined by arterial stiffness and aortic pulsatility in univariate (aoPP r^2=0.26 p<0.0001; aoPWV r^2=0.10 p<0.0001; MCA-TT r^2=0.18 p<0.0001) and combined models (r^2=0.34, aoPP p<0.0001; aoPWV p=0.18; MCA-TT p<0.0001).

10.4.5 Associations between cerebrovascular reactivity and SBP variability

The tertile with the lowest BHI or the greatest reduction in cerebral blood flow with hyperventilation had the highest beat-to-beat SBP variability after adjustment for age and gender (figure 10.2) and after adjusting for mean cerebral blood flow velocity, with the greatest home SBP variability in patients with the largest response to hyperventilation. This was consistent with the continuous association between response to hyperventilation, but was not explained by an association between cerebral reactivity and either cerebral pulsatility or mean cerebral blood flow velocity (table 10.3).

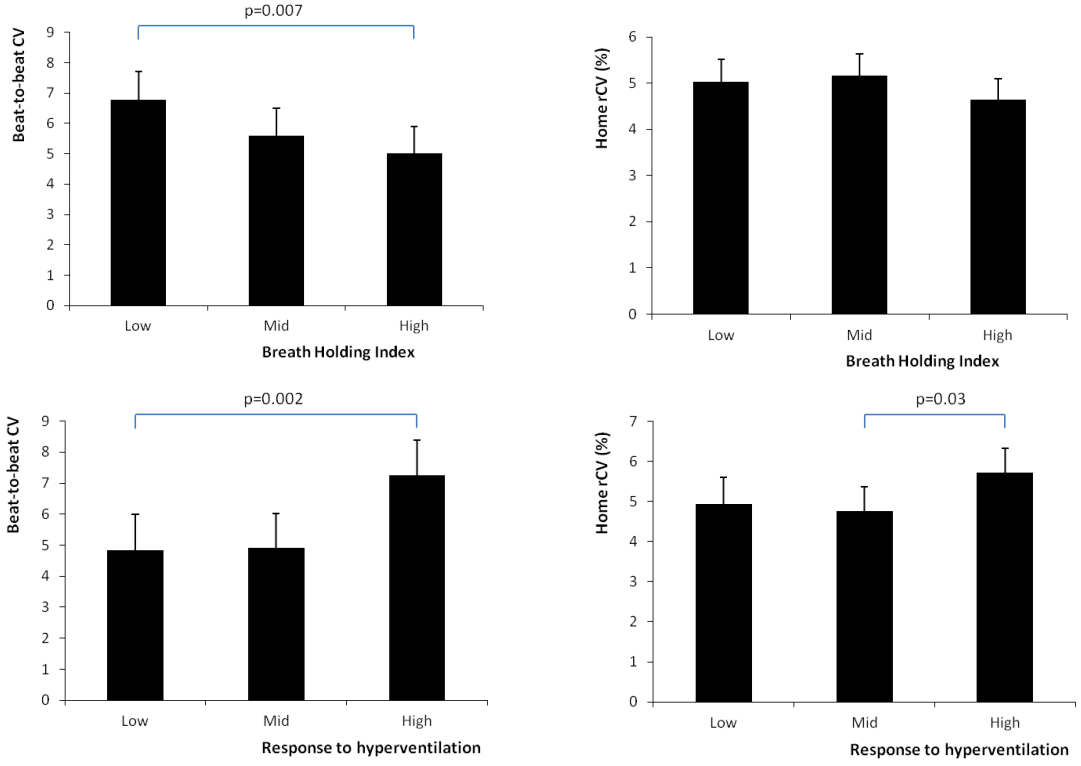

Figure 10.2. Differences in home and beat-to-beat blood pressure variability by tertile of middle cerebral artery reactivity, increases with breath holding or fall with hyperventilation.

Measure	N	Beat-to-Beat CV			Home rCV			TCD Mean Velocity			TCD Pulsatility Index		
		R	Unadj p	Adj p	r	Unadj p	Adj p	r	Unadj p	Adj p	R	Unadj p	Adj p
Breath-Holding													
Peak Velocity													
Absolute Rise	128	**-0.156**	**0.078**	**0.32**	**-0.135**	**0.15**	**0.20**	**0.301**	**0.001***	**0.02***	**-0.033**	**0.71**	0.61
% Rise	128	**-0.134**	**0.16**	**0.73**	**-0.022**	**0.81**	**0.36**	**0.054**	**0.54**	**0.29**	**-0.004**	**0.96**	0.90
BHI	126	**-0.211**	**0.018***	**0.06**	**-0.176**	**0.061**	**0.13**	**0.084**	**0.35**	**0.92**	**-0.208**	**0.02***	0.07
Trough Velocity													
Absolute Rise	128	**-0.051**	**0.57**	**0.14**	**-0.039**	**0.68**	**0.99**	**0.201**	**0.03***	**0.10**	**0.015**	**0.87**	0.25
% Rise	128	**-0.023**	**0.80**	**0.45**	**-0.021**	**0.83**	**0.99**	**0.063**	**0.48**	**0.48**	**0.089**	**0.32**	0.16
BHI	126	**-0.077**	**0.39**	**0.58**	**-0.028**	**0.77**	**0.56**	**0.012**	**0.90**	**0.65**	**-0.131**	**0.15**	0.25
Hyperventilation													
Peak Velocity													
Absolute fall	80	**0.228**	**0.042***	**0.043***	**0.295**	**0.012***	**0.018***	**0.354**	**0.001***	**0.001***	**0.271**	**0.015***	0.025*
%Fall	80	**0.232**	**0.038***	**0.05**	**0.203**	**0.09**	**0.11**	**-0.012**	**0.92**	**0.95**	**0.111**	**0.33**	0.49
Trough Velocity													
Absolute fall	80	**0.194**	**0.08**	**0.08**	**0.237**	**0.045***	**0.04***	**0.239**	**0.03***	**0.03***	**-0.018**	**0.87**	0.90
%Fall	80	**0.273**	**0.014***	**0.029***	**0.194**	**0.10**	**0.14**	**-0.150**	**0.19**	**0.42**	**-0.058**	**0.61**	0.28

Table 10.4 Associations between measures of cerebrovascular reactivity to CO_2 with SBP variability on home and beat-to-beat readings and with mean velocity and pulsatility of cerebral blood flow. R and p values are derived from general linear models, with and without adjustment for age and gender. * p<0.05

10.4.6 Associations with home SBP variability at each time of day

Relationships between aortic or cerebral arterial pulsatility with SBP variability were strongest in the mid-morning or evening but, unlike cerebral pulsatility, the relationship between response to hyperventilation and blood pressure variability was strongest for early morning readings rather than readings later in the day.

		Waking SBP rCV			Mid-Morning SBP rCV			Evening SBP rCV		
Measure	**N**	R	Unadj	Adj	r	Unadj	Adj p	r	Unadj	Adj p
Aortic Measures										
Aortic PWV	153	**0.032**	**0.70**	**0.97**	**0.090**	**0.29**	**0.74**	**0.137**	**0.096**	**0.67**
Aortic SBP	153	**0.062**	**0.45**	**0.43**	**0.017**	**0.84**	**0.88**	**0.158**	**0.053**	**0.06**
Aortic DBP	153	**-0.048**	**0.56**	**0.75**	**-0.168**	**0.046***	**0.13**	**-0.023**	**0.78**	**0.53**
Aortic PP	153	**0.121**	**0.14**	**0.30**	**0.155**	**0.07**	**0.23**	**0.234**	**0.004***	**0.045***
TCD Measures										
TCD arrival time	148	**-0.115**	**0.17**	**0.37**	**-0.126**	**0.14**	**0.30**	**-0.266**	**0.001***	**0.21**
Peak Velocity	154	**0.035**	**0.67**	**0.88**	**0.095**	**0.27**	**0.19**	**0.050**	**0.54**	**0.37**
Trough Velocity	154	**-0.072**	**0.38**	**0.54**	**-0.096**	**0.26**	**0.76**	**-0.142**	**0.083**	**0.62**
Mean Velocity	154	**-0.017**	**0.84**	**0.84**	**-0.001**	**0.99**	**0.56**	**-0.049**	**0.56**	**0.82**
Pulsatility Index	154	**0.144**	**0.08**	**0.33**	**0.269**	**0.001***	**0.015***	**0.274**	**0.001***	**0.036***
TCD Reactivity										
Breath-holding										
Peak BHI	126	**-0.060**	**0.53**	**0.52**	**-0.238**	**0.016***	**0.025***	**-0.147**	**0.13**	**0.20**
Trough BHI	126	**-0.008**	**0.93**	**0.96**	**-0.107**	**0.28**	**0.34**	**-0.019**	**0.84**	**0.96**
Hyperventilation										
Peak fall	71	**0.340**	**0.004***	**0.01***	**0.258**	**0.039***	**0.06**	**0.192**	**0.11**	**0.16**
Peak fall (%)	71	**0.203**	**0.09**	**0.12**	**0.224**	**0.08**	**0.10**	**0.115**	**0.35**	**0.40**
Trough fall	71	**0.294**	**0.013***	**0.011***	**0.124**	**0.33**	**0.33**	**0.269**	**0.03***	**0.024***
Trough fall (%)	71	**0.213**	**0.08**	**0.07**	**0.158**	**0.21**	**0.25**	**0.260**	**0.03***	**0.04***

Table 10.5 Associations between day-to-day variability in SBP at each time of day with cerebral pulsatility, cerebrovascular reactivity and determinants of cerebral pulsatility. R and p values are derived from general linear models, with and without adjustment for age and gender. * p<0.05. rCV = residual coefficient of variation; PWV = pulse wave velocity; PP = pulse pressure; TCD =transcranial Doppler ultrasound.

10.4.7 Associations with asleep versus awake BP

Mean blood pressure whilst either awake or asleep was positively correlated with aortic stiffness and both systolic and diastolic blood pressure during awake and asleep periods, with no association with dipping status, the difference between asleep and awake BP (table 10.6). Similarly, aortic, brachial and cerebral arterial pulsatility were all associated with mean SBP whilst awake or asleep, but there was no association with the difference between these timeperiods after adjusting for age. However, there was a weak association between a greater fall in cerebral blood flow velocity and the fall in BP whilst asleep compared to awake periods. However, these associations were not sufficiently strong to suggest that the association between awake BP variability and these physiological measures is confounded by an association between nocturnal BP or dipping status with BP variability.

Measure	N	Awake Mean SBP			Asleep Mean SBP			Awake – Asleep Mean SBP			Awake ARV SBP		
		R	Unadj p	Adj p	r	Unadj p	Adj p	r	Unadj p	Adj p	R	Unadj p	Adj p
Age	**165**	**-0.097**	0.21	n/a	**0.172**	0.028*	n/a	**-0.316**	0*	n/a	**0.025**	0.75	n/a
Creatinine	**165**	**0.036**	0.64	0.78	**0.146**	0.06	0.22	**-0.157**	0.045*	0.18	**0.026**	0.74	0.30
BMI	**165**	**0.029**	0.71	0.77	**-0.034**	0.67	0.76	**0.079**	0.32	0.42	**0.008**	0.92	0.92
Systemic Measures													
Aortic PWV	**165**	**0.141**	0.07	0.005*	**0.285**	<0.001*	0.004*	**-0.232**	0.003*	0.30	**0.042**	0.60	0.51
Aortic SBP	**165**	**0.378**	<0.001*	<0.001*	**0.241**	0.002*	0.003*	**0.038**	0.63	0.43	**0.082**	0.30	0.29
Aortic DBP	**165**	**0.287**	<0.001*	0.001*	**0.068**	0.39	0.12	**0.176**	0.024*	0.28	**0.004**	0.96	0.70
Aortic PP	**165**	**0.274**	<0.001*	<0.001*	**0.267**	0.001*	0.003*	**-0.088**	0.26	0.80	**0.106**	0.18	0.23
Brachial SBP	**165**	**0.415**	<0.001*	<0.001*	**0.314**	<0.001*	<0.001*	**-0.006**	0.94	0.89	**0.126**	0.12	0.12
Brachial DBP	**165**	**0.297**	<0.001*	0.001*	**0.105**	0.19	0.032*	**0.145**	0.07	0.68	**0.023**	0.77	0.60
Brachial PP	**165**	**0.292**	<0.001*	<0.001*	**0.316**	<0.001*	0.003*	**-0.121**	0.13	0.91	**0.141**	0.08	0.23
TCD Measures													
Mean interval	**165**	**-0.118**	0.14	0.041*	**-0.244**	0.002*	0.009*	**0.222**	0.005*	0.08	**-0.027**	0.73	0.91
PWV	**165**	**-0.006**	0.94	0.96	**0.134**	0.09	0.24	**-0.207**	0.009*	0.06	**-0.065**	0.42	0.47
Peak Velocity	**165**	**0.115**	0.14	0.11	**0.034**	0.67	0.27	**0.067**	0.4	0.97	**0.164**	0.036*	0.07
Trough Velocity	**165**	**0.063**	0.42	0.75	**-0.096**	0.22	0.99	**0.188**	0.016*	0.72	**0.100**	0.20	0.13
Mean Velocity	**165**	**0.092**	0.24	0.31	**-0.036**	0.65	0.57	**0.137**	0.08	0.81	**0.141**	0.07	0.08
Pulsatility													
Pulsatility Index	**177**	**0.076**	0.33	0.03*	**0.213**	0.006*	0.04*	**-0.208**	0.008*	0.44	**0.065**	0.41	0.66
Resistive Index	**177**	**0.089**	0.26	0.022*	**0.208**	0.008*	0.04*	**-0.189**	0.016*	0.48	**0.085**	0.28	0.50
Breath-holding													
BHI	**128**	**-0.055**	0.53	0.47	**-0.035**	0.69	0.95	**0.037**	0.67	0.96	**-0.007**	0.93	0.89
Absolute rise	**128**	**-0.030**	0.73	0.59	**-0.100**	0.25	0.36	**0.152**	0.08	0.26	**0.056**	0.52	0.47
Relative rise	**128**	**-0.075**	0.38	0.32	**-0.105**	0.22	0.33	**0.091**	0.29	0.52	**-0.022**	0.80	0.79
Hyperventilation													
Absolute fall	**74**	**0.205**	0.08	0.08	**-0.048**	0.69	0.81	**0.217**	0.07	0.09	**0.275**	0.018*	0.03*
Relative fall (%)	**74**	**0.239**	0.04*	0.05	**-0.081**	0.49	0.42	**0.279**	0.017*	0.012*	**0.147**	0.22	0.26

Table 10.6 Associations between awake or asleep mean BP, and the difference between them, with physiological measures. R and p values are derived from general linear models, with and without adjustment for age and gender. * p<0.05. ARV= absolute real variation.

10.5 Discussion

Variability in beat-to-beat and home SBP were strongly associated with cerebral and aortic pulsatility, independent of age and gender, despite weak or absent relationships with aortic SBP or DBP. Associations between SBP variability and arterial stiffness were partly explicable by the relationship between cerebral pulsatility and arterial stiffness. Cerebral reactivity was also associated with both beat-to-beat and home variability in SBP, but it was associated particularly with day-to-day variability after waking whilst cerebral pulsatility was associated with day-to-day variability in the mid-morning and evening.

This study demonstrates an association between two novel markers of cerebrovascular risk. Visit-to-visit variability in SBP was a strong predictor of stroke and other cerebrovascular events in multiple cohorts with cerebrovascular disease or high-risk patients with hypertension (chapters 2 and 6). This risk was modifiable with calcium channel blockers reducing blood pressure variability in comparison to beta-blockers and thereby reduced the subsequent risk of stroke (chapter 3). However, the physiological mechanisms relating SBP variability to stroke risk are unknown, and it is unclear which stroke types are associated with BP variability, although effects on AF are unlikely to explain the association.[10] Unfortunately, there are currently too few patients with each stroke subtype to reliably determine differences in BP variability in this study. Ideally, this question would best be addressed by longitudinal effects of increased BP variability and recurrent stroke risk comparing different events types or progression of leukoaraiosis, and this data should be acquired within the ongoing OXVASC study. Potential hypotheses explaining this association include: acute elevations in BP resulting directly in stroke; chronic fluctuations or episodic peaks causing a chronic arteriopathy that increases the risk of stroke; or SBP variability representing a secondary feature of an underlying arteriopathy that causes stroke by an alternative mechanism. Alternatively, it is likely that more than one of these mechanisms is involved. The second factor that has been a focus of recent research is the physiological mechanisms underlying leukoaraiosis, with postulated theories including a

haemodynamic origin due to increased cerebral pulsatility (chapter 9) versus leukoaraiosis as the cerebral manifestation of a systemic arteriopathy characterised by altered blood-brain barrier permeability.[11] In chapter 9, I demonstrated the relationship between leukoaraiosis and cerebral pulsatility and the dependence of cerebral pulsatility on aortic pulsatility and arterial stiffness, supporting the hypothesis that leukoaraiosis depends upon increasing central aortic stiffness increasing transmission of the arterial waveform to the cerebral circulation.

The association between cerebral pulsatility and SBP variability suggests that these markers of increased cerebrovascular risk are part of an overlapping cardiovascular phenotype. This has significant ramifications. Firstly, it is unlikely that cerebral pulsatility causes SBP variability but both may be features of an underlying chronic arteriopathy, at least in part. The relationship between premorbid mean and variability in SBP and both cerebral pulsatility and SBP variability suggests that both mean hypertension and SBP variability may play a role in the development of this arteriopathy. Secondly, although this study demonstrates a clinically important relationship, the large amount of unexplained variation in SBP variability implies that other mechanisms are also likely to be responsible for the relationship between stroke and increased blood pressure variability beyond those also responsible for increased cerebral pulsatility. These other mechanisms may also have independent prognostic significance.

The association between cerebrovascular reactivity and blood pressure variability may reflect an additional phenotype contributing to blood pressure variability, as cerebrovascular reactivity was only weakly associated with cerebral pulsatility and was associated with day-to-day SBP variability at different times of day to cerebral pulsatility. In particular, patients with the smallest response to breath-holding or the largest response to hyperventilation had the highest SBP variability independent of mean flow velocity, suggesting greater basal cerebrovascular dilatation with reduced capacity for further dilatation and a greater capacity for constriction. Abnormalities of cerebral reactivity may

also reflect a reduced capacity to compensate for acute fluctuations in systemic blood pressure, resulting in a synergistic relationship between SBP variability and cerebral reactivity increasing the risk of stroke.

This study has some limitations. Firstly, the cross-sectional nature of the study prevents elucidation of the temporal pattern of the associations, and therefore it is difficult to reach firm conclusions about the direction of causation, although the associations with premorbid SBP and SBP variability imply a role for prior hypertension. Secondly, measures of cerebrovascular reactivity were only introduced in this cohort after the study in chapter 9 was underway, and therefore the number of patients undergoing testing of cerebral reactivity is relatively small, despite the significant relationships demonstrated. Thirdly, there is currently inadequate follow-up to determine whether these potential measures of cardiovascular risk are actually associated with recurrent cardiovascular events and specifically whether the relationship between SBP variability and stroke risk could be explained by its relationship with cerebral pulsatility. Finally, the degree of significance for some of these tests is limited, and given the number of physiological measures assessed, there is a risk that some of the more borderline significant results may reflect chance occurrence rather than true association.

This study implies that abnormalities in the cerebral circulation are associated with increased SBP variability and are likely to play a role in the relationship between SBP variability and stroke risk. However, it is likely that multiple factors affect SBP variability and these may also be responsible for the increase in stroke risk. The critical test is to determine which factors are modifiable, and result in a reduction in risk. To achieve this, it will be necessary to firstly identify which of the mechanisms responsible for increased variability in SBP are responsible for the resulting risk of stroke, then to identify which are modifiable by treatment with established treatments that reduce SBP variability and stroke risk (such as CCBs) and finally to identify additional mechanisms which may be amenable to alternative interventions. Indeed, this study raises a question as to whether CCBs reduce

cerebral pulsatility and reactivity relative to other antihypertensive classes, in association with their effect on SBP variability. Nonetheless, prior to further studies, identification of increased cerebral pulsatility on TCD implies that assessment of SBP variability may be beneficial.

In conclusion, this study demonstrates significant, independent relationships between beat-to-beat, day-to-day or premorbid visit-to-visit SBP variability with cerebral pulsatility or reactivity to carbon dioxide. These may partly explain the association with the risk of stroke and imply that leukoaraiosis and lacunar stroke may be particularly associated with SBP variability compared to other stroke subtypes. Finally, it implies that cerebral pulsatility is an important, novel and modifiable potential risk factor for stroke which may be amenable to treatment with calcium channel blockers.

10.6 References

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CHAPTER ELEVEN

Conclusions and Implications for Future Research

11.1 Introduction

In this thesis I have addressed some of the outstanding questions that have arisen from the demonstration that visit-to-visit blood pressure variability is associated with an increased risk of stroke and that it is amenable to treatment by the use of specific antihypertensive medications. Firstly, I have used clinical trial data to define and validate the relationship between blood pressure variability and cardiovascular risk and to define the effect of blood pressure lowering medications. Secondly, I have investigated a population of patients performing home blood pressure monitoring (HBPM) after a TIA or minor stroke as part of the population-based Oxford Vascular Study. Thirdly, I have established a physiological study within this population to determine associations between BP variability and other physiological markers of cardiovascular risk. Using these studies, I have attempted to address the aims stated in chapter 1:

1. Confirm and validate the observation that medium-term blood pressure variability is related to an increased risk of cardiovascular events;
2. Further characterize the effects of different classes of antihypertensive agent on blood pressure variability and the related risk of stroke;
3. Determine the optimal method of assessing blood pressure variability;
4. Identify the clinical and physiological determinants of medium-term blood pressure variability;
5. Assess whether medium-term variability may be related to a risk of stroke or dementia through associated effects on cerebral haemodynamics;
6. Establish a cohort of patients with detailed blood pressure monitoring and physiological assessment for future determination of cardiovascular risk.

11.2 Summary of main findings

PANEL 11.1 Summary of Conclusions

- Variability in SBP is a valid, clinically significant predictor of stroke and cardiovascular events, confirmed in a large number of patients and studies.
- Antihypertensive drug classes differ significantly in their effects on consistency of control of BP within and between individuals, probably explaining differences in stroke risk.
- The design of large RCTs of antihypertensive medications with add on non-randomised medications has resulted in significant under-estimation of drug class differences in effects on BP variability and the risk of cardiovascular events.
- Home blood pressure monitoring was a more valid method than ABPM at identifying residual hypertension and recurrent cardiovascular events after TIA or minor stroke, due to the limited value of ABPM in the elderly. This is likely to be true in primary prevention, in contrast to current guidelines.
- HBPM is the optimal method for assessing BP variability, balancing clinical significance, cost and practicality.
- The MoCA is more sensitive than the MMSE in detecting hypertension-associated cognitive impairment and should be used in future trials of antihypertensive medications and observational studies to determine associations with BP variability.
- Day-to-day BP variability is strongly associated with age, female gender and creatinine, potentially explaining some of the unexplained risk of stroke in these patient groups.
- Clinically significant variability in SBP and its reduction by calcium channel blockers or diuretics is largely due to effects on day-to-day variability immediately after waking, particularly as a result of changes in maximum SBP.
- Variability in SBP is associated with other cardiovascular physiological changes that may explain part of the increased risk of stroke, particularly cerebral pulsatility and reactivity.

11.2.1 Validity of BP variability as a marker of cardiovascular risk

In 318,700 patients from 43 independent cohorts (chapter 2), SBP variability was associated with a clinically significant >20% increased risk of stroke and myocardial infarction per standard deviation across the population, with a weaker association with cardiovascular death, independent of mean SBP. The large size, broad population and inclusion of extensive data from all trials within the Blood Pressure Lowering Trialists' Collaboration reduces the likelihood of publication or reporting bias and represents the most reliable estimate of the BP variability-associated risk of cardiovascular events that has yet been performed. In the OXVASC study, a similar 30% increased risk of cardiovascular events was found for SBP variability on HBPM after TIA and minor stroke, consistent with the demonstration of its physiological validity by the strong association with hypertensive arteriopathy and premorbid BP readings (chapter 6).

This demonstration of the statistical, physiological and clinical validity of variability in SBP has resolved conflict between studies reporting inconsistent results for the association with cardiovascular risk.[1-6] It demonstrates that assessment of BP variability through previous clinic readings or HBPM is an important component of cardiovascular risk assessment and identifies patients at an increased risk of stroke in particular. In addition, it suggests that in patients with cerebrovascular disease, active assessment of BP variability after the initiation of treatment may identify a treatable population at an increased risk of recurrent events. However, for BP variability to become part of routine clinical practice, more precise definition of thresholds at which BP variability represents a significant increase in risk and the degree to which BP variability improves risk stratification beyond currently accepted models is required. Further clarification is required to determine which cardiovascular outcomes are dependent upon BP variability, which patient groups are at the greatest risk and which non-cardiovascular outcomes are associated with BP variability, such as dementia.[7, 8]

11.2.2 Effects of antihypertensive drugs on BP variability and cardiovascular events

In 244,479 patients from 32 trials for which intra-individual BP variability was available, randomisation to a CCB or diuretic versus a renin-angiotensin inhibitor (RASi) or beta-blocker was associated with improved consistency of blood pressure control within individuals and in group mean SBP between individuals (chapter 3). These effects were probably attenuated by addition of drugs from other classes in RCTs, obscuring a greater effect on BP variability during monotherapy treatment in the first year that may result in the 25% reduction in stroke risk for CCBs or diuretics versus other drugs during this period. This was consistent across patient groups and was not determined by drug half-life. I replicated these findings on HBPM after TIA or minor stroke in the OXVASC population (chapter 8), further demonstrating that the effect was drug-class specific rather than determined by half-life; that it was predominantly due to a reduction in day-to-day variability in the early morning, potentially due to limiting the morning surge in blood pressure; and that the addition of a diuretic to a RASi attenuated the resulting increase in BP variability.

This is the most comprehensive and reliable demonstration of the associated effects of antihypertensive medications on BP variability and the risk of stroke, demonstrating that the current design of RCTs with addition of non-randomised drug classes has obscured drug class differences in effects on outcomes, resulting in large meta-analyses erroneously concluding that drug class differences are clinically insignificant.[9, 10] New guidelines should take account of the benefit of CCBs and diuretics in populations at a high risk of stroke and these drugs should be used preferentially unless specific contraindications exist, although use of RASi is still likely to be beneficial when the risk of morbidity and mortality due to coronary events is high. However, further research is required: to define thresholds for specific treatment of BP variability; the optimal combination of drugs for treating mean and variability in BP; determination of which other outcomes are reduced by BP-variability directed therapy (cognition, renal impairment); and ideally confirmation of these results in a prospectively designed RCT to definitively test the hypothesis in an appropriate population.

11.2.3 Identifying the optimal method for blood pressure assessment

HBPM was a more valid method of measuring mean SBP (chapter 5) and BP variability (chapter 6) than ABPM, with stronger associations with premorbid BP readings, 5 markers of hypertensive arteriopathy and greater predictive value for recurrent cardiovascular events, such that residual hypertension on HBPM after initial treatment was associated with a 140% increased risk of cardiovascular events, independent of other major risk factors. Its validity improved with longer duration of monitoring rather than increased frequency of monitoring (chapter 5 and 6) whilst the limited validity of ABPM in the OXVASC population was greater in patients >65 years of age (chapter 5). Furthermore, HBPM can be used to determine the effects of treatment on BP variability (chapter The stronger association between recurrent cardiovascular events and HBPM compared to ABPM provides the best evidence for the greater clinical relevance of home SBP after TIA or minor stroke, but mean and variability in SBP were also validated against physiological markers of "hypertensive arteriopathy." This concept was defined as measures known to be associated with hypertension, and therefore replicating these associations with mean SBP on each method would provide an additional validation of each BP measurement method. However, all 5 markers of hypertensive arteriopathy reflect complex phenotypes with multiple causes that may be independently associated with cardiovascular risk, for example creatinine is strongly dependent on age, and increases with diabetes.[11] Leukoaraisosis in particular is commonly thought of as a marker of hypertensive disease, but the appearance on CT or MRI scans is unlikely to represent a single process, with significant heterogeneity in white matter hyperintensities (including confluent periventricular changes or demarcated deep lesions), and in associated MRI findings such as dilated perivascular spaces and cerebral microbleeds,[12] whose aetiology may differ by location.[13] Furthermore, there is significant heterogeneity in the aetiology of leukoaraiosis, with multiple factors associated with leukoaraiosis independent of hypertension, including age, diabetes, monogenic diseases (CADASIL, CARASIL, COL4A1) and cerebral amyloid angiopathy.[12] However, these alternative causes of leukoaraiosis and the other markers of "hypertensive arteriopathy" are

very unlikely to confound the associations with SBP on HBPM or ABPM in this study, as any hypertension-independent aetiological factor is by definition not associated with hypertension. These results challenge current guidelines advocating the preferential use of ABPM over HBPM to determine mean BP, due to assumed greater prognostic value and cost-effectiveness.[14] These guidelines are based almost entirely on studies in younger age groups, and have had to assume superiority of ABPM due to the lack of studies directly comparing ABPM and HBPM. As approximately 50% of all new diagnoses of hypertension are made in patients >65 years old in developed nations,[15] a large burden of preventable hypertension-related disease is likely to be missed, and the use of ABPM is very unlikely to be more cost-effective than HBPM in any age group, as this would require ABPM to be significantly more predictive as it is more expensive. Therefore, current recommendations should not result in wholesale purchase of ABPM machines in primary care, and research is urgently required to confirm these findings in elderly patients and in primary prevention studies to determine whether changes in current guidance are required. Future research investigating BP variability in addition to mean BP should also use HBPM as it also provides an assessment of BP variability; is simple to use; assesses multiple forms of day-to-day BP variability; and can be used to determine response to treatment. This research needs to define the optimal monitoring schedule, treatment thresholds for both mean and variability in SBP and to assess whether patient-recorded as opposed to telemetric home BP monitoring is equally valid.

11.2.4 Identifying an optimal method for detection of vascular cognitive impairment

The Montreal Cognitive Assessment (MoCA) detected more cognitively impaired patients than the MMSE (chapter 7), and this additional burden of cognitive impairment was associated with a current and premorbid history of hypertension and hypertensive arteriopathy. This resulted from a greater sensitivity of the MoCA in multiple cognitive domains, including a greater sensitivity to impairment in domains associated with vascular disease, and a greater representation of these domains in the overall score.

Despite the sensitivity of the MoCA, it is not designed as a comprehensive test of cognition as it was developed for undifferentiated mild cognitive impairment, with formal neuropsychological testing still being the gold standard method. In particular, the MoCA does not formally assess processing speed, and has relatively limited tests of planning and executive function, with a stronger emphasis on visuo-spatial function. However, it is a rapid test to perform, with a broader range of tests than the MMSE, which takes approximately the same length of time to carry out, and was recommended by the National Institute of Health for detection of vascular cognitive impairment. More detailed screening tests such as the Addenbrooke's Cognitive Examination are more unwieldy, and less practical for a large volume epidemiological study in which multiple assessments are made at each follow up.

The greater sensitivity of the MoCA for hypertension-associated cognitive impairment suggests that the MoCA should be used in clinical practice as well as future studies assessing cognitive impairment after TIA or minor stroke and potentially in patients presenting with cognitive impairment alone. In particular, the low sensitivity of the MMSE may explain the lack of an effect of blood pressure lowering on cognitive decline in RCTs which have predominantly used the MMSE. Furthermore, these analyses suggest that future studies identifying the relationship between BP variability and cognitive decline should determine the predictive value of BP variability on HBPM for longitudinal cognitive decline on the MoCA in prospective observational studies, and the effect of BP variability-directed therapy on the reduction in future cognitive decline in RCTs.

11.2.5 Determinants of BP variability

Age and female gender were the strongest clinical determinants of day-to-day BP variability, along with atrial fibrillation, creatinine and aortic stiffness (chapter 6). Blood pressure variability was predominantly associated with increased maximum blood pressure rather than minimum or mean blood pressure, suggesting that it reflects episodic peaks in blood pressure rather than troughs, particularly early in the morning, as reflected in the greater effect of BP variability reducing medications in the early morning rather than later in the day (chapter 8). Although maximum SBP was more strongly associated with male gender and variability in SBP with female gender, both maximum and variability in SBP increased more in women with increasing age than mean SBP, although with anomalously higher variability in the youngest women compared to the youngest men.[16]

These associations may explain some of the unexplained increased risk of stroke in these patients groups, including the excess risk of stroke relative to coronary disease in elderly women compared to men,[17] the risk of stroke associated with renal dysfunction[18] and the unexplained increased risk of stroke in young women. Furthermore, the demonstration that BP variability in the early morning is particularly associated with cardiovascular risk and hypertensive arteriopathy (chapter 6) and is more responsive to treatment with CCBs or diuretics suggests that some of the risk relationship is due to episodic elevations in the morning surge in blood pressure. Future research needs to address whether this results from an association between day-to-day variability with either non- or reverse dipper nocturnal blood pressure behaviour.[19] Furthermore, in addition to the identified relationship with arterial stiffness, further research is required to determine the physiological basis of increased blood pressure variability in these patient groups in order to define treatment options, determine how different antihypertensive medications reduce BP variability and to define novel treatment targets.

Panel 11.2 Implications for clinical practice

- Day-to-day and visit-to-visit variability in BP are independent risk factors for cardiovascular disease in clinical practice, although further work to define treatment thresholds is required.
- Assessment of BP variability can be used to identify patients at an increased risk of cardiovascular events, particularly in patients with recent TIA or stroke.
- In patients requiring treatment for hypertension, elevated BP variability favours the use of calcium channel blockers or diuretics.
- HBPM should be the method of choice for prospectively assessing BP variability and potentially for formally diagnosing hypertension in place of ABPM, with at least 1 week of monitoring required.
- The MoCA should be used in preference to the MMSE for detection of cognitive impairment in patients after stroke or TIA.

11.2.6 Covariance between SBP variability and abnormal cerebral haemodynamics

Antihypertensive drug class effects on group BP variability in RCTs were inversely associated with effects on the incidence of headache (chapter 4), suggesting that effects on peripheral arterial tone may determine effects on BP variability whilst effects on central arterial tone determine effects on stroke risk. Home BP variability was also associated with cerebral pulsatility and cerebral reactivity (chapter 10), which could potentially explain the relationship with the risk of stroke as cerebral pulsatility was strongly associated with leukoaraiosis (chapter 9). Furthermore, cerebral pulsatility was dependent upon aortic pulsatility and stiffness of the large conduit vessels, suggesting that leukoaraiosis and the associated risk of stroke may result from increased transmission of the arterial waveform to the brain via stiffer arteries.

These associations suggest that the relationship between BP variability and stroke risk may partly be explained by associated changes in cerebral haemodynamics. These may simply be correlated physiological abnormalities of an aging vascular system, but it is also possible that they are both manifestations of an underlying systemic arteriopathy or that alterations in cerebral haemodynamics result from chronic BP variability. Finally, it is feasible

that the two processes are synergistic, with abnormal cerebral haemodynamics preventing acute adaptation to episodic peaks in blood pressure, increasing the likelihood of BP related acute cerebral ischaemia. However, it is unlikely that this relationship explains all the relationship between BP variability and the risk of stroke, given the relationship between hypertensive arteriopathy and BP variability in the morning rather than evening (chapter 6). Nonetheless, there are likely to be many physiological and clinical abnormalities that are associated with both BP variability and an increased risk of stroke, and future research needs to systematically identify these relationships, determine the relative strength of these associations and to determine the effect of CCBs and diuretics on these physiological measures, BP variability and the subsequent risk of stroke, in the same population.

11.3 Research implications: Ongoing work

Despite the analyses described in this thesis, our understanding of medium-term variability in blood pressure as a risk factor for cardiovascular events and dementia remains immature. This thesis has demonstrated the validity and clinical significance of BP variability and has identified an optimal method of assessing it, at least in populations with recent TIA or minor stroke. This thesis has also cast some light on the mechanisms and clinical associations of BP variability and potential pathways by which BP variability may be associated with the risk of stroke. However, further work is still required (panel 11.3).

11.3.1 Systematic Review and Meta-analysis

The systematic review and meta-analyses described in chapters 2-4 represents the largest dataset of published BP data available, with many potential avenues of investigation. I am currently carrying out analyses focussing on the implications of these results, including more detailed characterisation of the effects of antihypertensive medications on blood pressure variability and the associated risk of cardiovascular events. In addition, I am performing a systematic review and meta-analysis of side-effects of anti-hypertensive medications other than the effects on headache, focussing on the effect of these medications on sleep deprivation and fatigue. This addresses the hypothesis that low quality

sleep results in a greater nocturnal blood pressure due to sympathetic over-activity, loss of the normal nocturnal dipping behaviour and a greater variability in the morning surge in blood pressure, potentially explaining stronger association for BP variability after waking versus later times of day (figure 11.1).

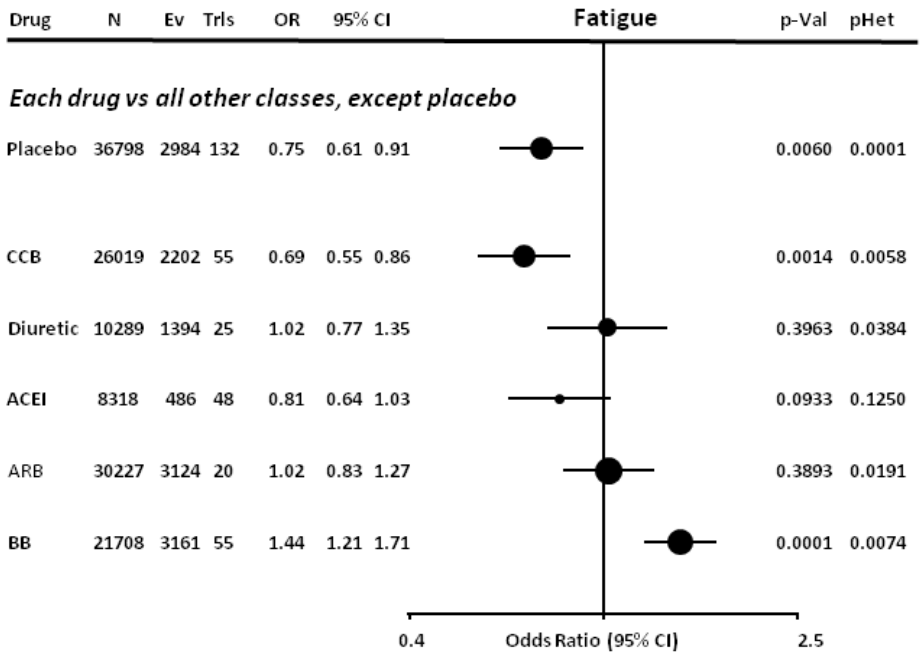

Figure 11.1 Random-effects meta-analysis of the effects of randomisation to different classes of antihypertensive medications in comparison to all other classes on the incidence of patient reported fatigue. Each comparison is between the named class with all other drug classes, excluding placebo. There is a significant reduction in fatigue in patients randomised to CCBs, with an increase in fatigue in patients randomised to beta-blockers, with the same pattern as that demonstrated for blood pressure variability.

11.3.2 Physiological determinants of BP variability

The physiological substudy described in chapters 9-10 includes a number of tests in addition to tests of short-term BP variability and cerebral blood flow. The other arm of this study includes tests designed to identify physiological processes underlying BP variability. These include tests of orthostatic blood pressure control, applanation tonometry to define aortic BP parameters and arterial stiffness as described in chapter 9, measures of resting state baroreceptor sensitivity and measures of cardiovascular reactivity to stress, including a mental arithmetic test and the cold pressor test (appendix 5). Currently, this study has recruited 280 participants and is aiming to recruit another 220 participants over the next 2

years. This population of 500 patients, the majority of whom will also undergo ABPM and HBPM, will allow a detailed characterisation of the physiological abnormalities responsible for short-term, diurnal and day-to-day blood pressure variability in patients with cerebrovascular disease. These patients will also continue to be followed up as part of the OXVASC study so that the independent predictive value of each of these measures for the risk of future cardiovascular events and cognitive decline can be determined.

11.3.3 Associations between BP variability and development of cognitive impairment

In chapter 7 I demonstrated that the MoCA was more sensitive than the MMSE for hypertension-associated vascular cognitive impairment, with stronger associations with hypertension for impairment in cognitive domains associated with vascular disease. The majority of these patients have also undergone home blood pressure monitoring, ambulatory blood pressure monitoring and have premorbid blood pressure readings available. I am therefore analysing the cross-sectional association between blood pressure variability and cognitive impairment on the MoCA in this patient group. However, given that patients with significant cognitive impairment may forget to take medications and may have excessive blood pressure responses to mild stress, it is impossible to determine in a cross-sectional study whether increases in blood pressure variability are an artefact of underlying cognitive impairment or manifestations of abnormal cardiovascular physiology, or whether BP variability causes vascular cognitive impairment. With more prolonged follow-up and repeat cognitive testing as part of OXVASC, it will possible to determine associations between BP variability and progression of cognitive impairment, independent of baseline cognitive impairment, and whether increased BP variability can predict the onset of cognitive impairment in patients not previously known to be cognitively impaired.

11.3.4 Associations between biomarkers and blood pressure variability

Patients recruited to the OXVASC study provide blood samples for research purposes, including for the measurement of biomarkers associated with an increased risk of

stroke. As part of this study, biomarkers such as copeptin[20] are being measured in patients recruited to the physiological substudy to determine if there are serum markers associated with increased blood pressure variability in patients with recent TIA or minor stroke, and whether these biomarkers are also associated with physiological determinants of blood pressure variability.

11.3.5 Drug class effects on BP variability and cerebral pulsatility in healthy subjects

To determine the effects of calcium channel blockers versus beta-blockers on the physiological mechanisms controlling BP variability and on cerebral haemodynamics, I have carried out a pilot study in 10 healthy volunteers who received amlodipine or propranolol in randomised order (appendix 6). On each drug and at baseline, they underwent the physiological tests included in the physiological substudy described above as well as a valsalva manoeuvre and tilt-testing. They then underwent a research-protocol MRI scan utilising novel sequences and novel methods of physiological monitoring to determine baseline cerebral perfusion, cerebrovascular autoregulation, response to carbon dioxide challenge and cerebrovascular dampening of the arterial waveform. Finally, they underwent a specialised 24 hour ABPM with measurement of aortic blood pressure and carotid-femoral pulse wave velocity (appendix 6). I am currently analysing these data, including developing novel methods for the analysis of high temporal resolution BOLD MRI, demonstrating greater cerebral arterial pulsations during treatment with propranolol than amlodipine (figure 11.2).

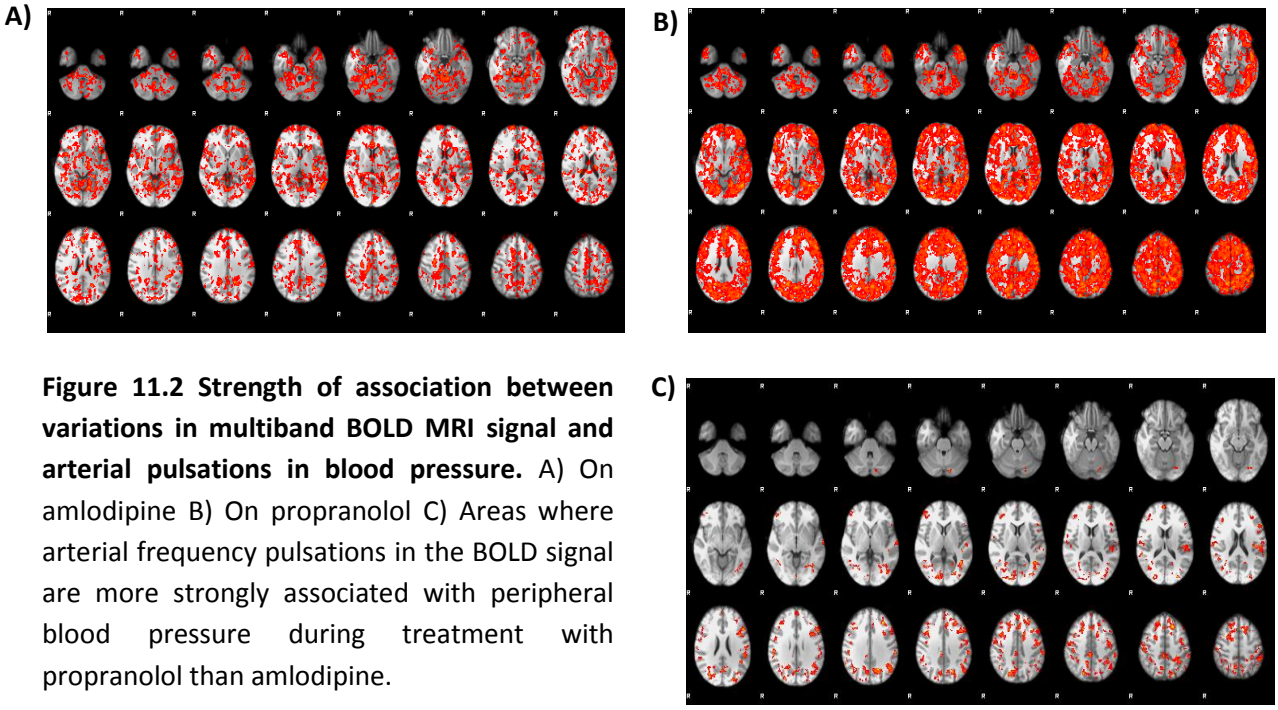

Figure 11.2 Strength of association between variations in multiband BOLD MRI signal and arterial pulsations in blood pressure. A) On amlodipine B) On propranolol C) Areas where arterial frequency pulsations in the BOLD signal are more strongly associated with peripheral blood pressure during treatment with propranolol than amlodipine.

11.3.6 Drug class effects on BP variability and cerebral pulsatility in patients

As part of their routine clinical care, patients presenting to the OXVASC TIA or minor stroke clinic continue to perform home blood pressure monitoring as described in chapter 5. These patients are most commonly treated with a perindopril-based regimen or an amlodipine-based regimen if requiring treatment for hypertension. Therefore, to measure the association between changes in aortic and cerebral pulsatility with changes in home and ambulatory blood pressure variability, I am currently applying for ethical approval for a study randomising these patients to amlodipine or perindopril for one month, with measurement of their cerebral haemodynamics by transcranial Doppler ultrasound, HBPM and a 24 hr ABPM at baseline and one month (appendix 7).

11.4 Research implications: Future avenues of investigation

Many of the outstanding research questions listed in panel 11.3 are the focus of the ongoing work described in section 11.3, but further research is still required, some of which can be addressed with available data or ongoing studies within the Stroke Prevention Research Unit, and some of which will require additional studies, resources and cooperation with other groups.

The large dataset of individual RCT patient data that has been gathered through the Blood Pressure Lowering Trialists' Collaboration and through direct communication with authors of other major RCTs is the best available resource to answer a number of questions. Specifically, it will be possible to estimate treatment thresholds for BP variability that will result in significant reductions in the subsequent risk of cardiovascular events. Furthermore, it may be possible to use individual patient data to identify those patient groups who will particularly benefit from BP variability directed therapy. Finally, it would be ideal to perform a large, multicentre RCT to determine the effects of BP variability directed therapy strategies on the risk of cardiovascular disease. The feasibility of such a study may be demonstrated by the physiological pilot study described in 11.3.6. However, a future RCT within a secondary prevention population with randomisation to amlodipine vs perindopril based

Panel 11.3 Outstanding Research Issues

Determinants of BP variability

- Further define the clinical characteristics associated with BP variability, and their prognostic significance, particularly the potential importance of excess BP variability in young women
- Define the physiologic changes leading to increased BP variability, including abnormalities in BP reactivity to stimuli and impaired BP control mechanisms.
- Identify which physiological mechanisms determine which forms of BP variability in which patient groups.
- Identify if there are genetic determinants of BP variability, independent of genetic contributions to elevated mean BP.
- Directly measure the impact of medication adherence on blood pressure variability.
- Determine the mechanisms by which calcium channel blockers and diuretics reduce BP variability (association between medium-term variability with vasodilatation, secondary sympathetic activity, heart rate etc).

Determinants of the relationship between BP variability and the risk of cardiovascular events

- Define which forms of BP variability carry the greatest prognostic significance.
- Identify associations between medium-term BP variability and other BP-related pathologies that may carry prognostic significance (orthostatic responses, nocturnal hypertension / dipping).
- Further identify and characterise associations between medium-term variability and pathological changes in cardiovascular physiology that may be related to the risk of stroke (cerebral pulsatility, cerebrovascular reactivity, blood-brain barrier breakdown, vessel rarefaction).
- Measure whether effects of antihypertensive medications on medium-term BP variability are correlated with effects on associated BP-related and physiological abnormalities.

BP variability as a practical, treatable risk factor

- Determine the validity and accuracy of HBPM for assessing mean BP and variability in BP in primary prevention populations in comparison to the accepted standard, ABPM.
- Definition of treatment thresholds for initiation of variability-directed treatment (CCBs or diuretics), independent of underlying mean blood pressure level.
- Identification of non-cerebrovascular patient groups most likely to benefit from variability directed treatment (cognitive impairment, renal disease, young vs old).
- Further definition of the optimal treatment combination for control of both mean SBP or DBP and BP variability, stratified by patient group
- Ideally, prospective demonstration of a reduction in cardiovascular events with variability-directed antihypertensive therapy in a randomised trial, initially in a secondary prevention population

regimens is the next step, followed by larger, multi-centre collaborative studies in primary prevention populations.

As this dataset utilises data from RCTs, the included populations are selected and trials often actively exclude patients with increased blood pressure variability. Therefore for a reliable estimation of the risk relationship between BP variability and cardiovascular outcomes, a collaboration of observational, population based studies of blood pressure assessment in primary prevention would be the optimal dataset, ideally including HBPM and ABPM. OXVASC represents one such study, but data from equivalent primary prevention studies is not yet available, and will depend upon future collaboration with other groups. Observational studies are also required to determine the relationship between BP variability and other outcomes including cognitive dysfunction and renal impairment. Again, associations with cognitive dysfunction are already being determined within OXVASC, and within RCTs for which this information is available, but these findings will need confirmation in independent populations, and particularly in patients presenting with mild cognitive impairment and in primary prevention.

Prospective studies of physiological characteristics in patients undergoing HBPM and ABPM will be required to further investigate the physiological determinants of BP variability; to identify other physiological changes which are correlated with BP variability but not directly related; and to measure how these relationships affect associations with cardiovascular risk. The current OXVASC physiological cohort and the interventional study described in 11.3.6 are starting to address these questions, but similar studies in primary prevention populations would be beneficial. Ideally, these studies should test a wide range of potential contributors to BP variability to determine the relative importance of different blood pressure control mechanisms in different groups. However, this may need an unfeasibly large study to assess the association between multiple physiological mechanisms, BP variability and cardiovascular outcomes, particularly in younger patients with a low absolute risk of cardiovascular events. Therefore, the results of the current OXVASC physiological

substudy will hopefully guide more focussed assessments to be performed in larger populations. Finally, determination of the genetic contribution to blood pressure variability, independent of mean SBP, could be assessed through genome wide association studies in the first instance, although these have been relatively unsuccessful at identifying clinically significant associations with mean BP.[21]

11.5 Conclusions

The findings of this thesis have confirmed the physiological and clinical significance of BP variability from day-to-day and clinic visit-to-visit in primary prevention and secondary prevention of cardiovascular events, particularly stroke. Furthermore, they have confirmed the efficacy of calcium channel blockers and diuretics in reducing BP variability and the associated risk of stroke. In addition, I have demonstrated that home BP monitoring is likely to be the optimal method of assessing both mean BP and variability in BP, particularly in elderly patients and patients with pre-existing cerebrovascular disease, and probably in all patients. Similarly, I have provided evidence for the use of the MoCA in preference to the MMSE for identification of vascular type dementia, and established that it is the optimal method to determine associations between BP variability and the risk of hypertension associated cognitive decline in OXVASC and other studies. Finally, I have identified clinical and physiological associations of BP variability that are associated with increased BP variability and may also explain its association with the risk of cardiovascular events.

These findings are reliable and demonstrate that BP variability is clinically significant. BP variability should be an important part of cardiovascular risk assessment and should affect treatment decisions in current clinical practice and in future guidance, particularly in patients at an increased risk of cerebrovascular events. However, further research is required to define thresholds at which BP variability directed treatment should be initiated, the optimal treatment strategy and to identify the mechanisms responsible for BP variability and its association with cardiovascular events. Many of these questions are being addressed by ongoing research within the Stroke Prevention Research Unit.

11.6 References

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APPENDICES

APPENDIX ONE

Glossary of Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
ANOVA	Analysis of Variance
ARB	Angiotensin receptor blocker
ARWMC	Age related white matter change scale
BB	Beta-blocker
BHI	Breath-holding index
BMI	Body mass index
BOLD	Blood oxygen level dependent (MRI)
BP	Blood pressure
BPLTC	Blood Pressure Lowering Triallists' Collaboration
CBFV	Cerebral blood flow velocity
CCB	Calcium channel blocker
CCBND	Non-dihydropyridine calcium channel blocker
CI	Confidence interval
CV	Coefficient of variation
DBP	Diastolic blood pressure
FE	Fixed effects (refers to meta-analysis)
GLM	General linear model
G-VR	Group variance ratio
HBPM	Home blood pressure monitoring
HR	Hazard ratio
IPD	Individual patient data
IQR	Inter-quartile range
I-VR	Intra-individual variance ratio
Max	Maximum
MCA	Middle cerebral artery
MI	Myocardial infarction
Min	Minimum
MoCA	Montreal Cognitive Assessment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
M-VR	Mean SBP/DBP variance ratio
NICE	National Institute of Clinical Excellence

NIHSS	National Institute for Health Stroke Scale
NYHA	New York Heart Association (scale)
OR	Odds ratio
OXVASC	Oxford Vascular Study
pHet	p-value for heterogeneity
PI	Pulsatility index (Gosling's)
PP	Pulse pressure
pVal	p-value for primary comparison / association
PVD	Peripheral vascular disease
PWV	Pulse wave velocity
RAS (i)	Renin angiotensin system inhibitor
rCV	Residual coefficient of variation (usually about a moving average)
RCT	Randomised controlled trial
RE	Random effects (refers to meta-analysis)
ROC	Receiver operator characeristic
SBP	Systolic blood pressure
SD	Standard deviation
TIA	Transient ischaemic attack
TCD	Transcranial Doppler ultrasound
TT	Transit time
VR	Variance ratio = $SD^2_{group1}/SD^2_{group2}$

APPENDIX TWO

Characteristics of trials with individual patient data available. G-SD is at visit closest to 1 year follow up, Mean and SD based on measurements from 6 months onwards. I-SD = intra-individual standard deviation in SBP; G-SD = group standard deviation in SBP.

Trials		N	Trial design	Entry criteria*	Follow-up (years)	Follow-up BP visits	Mean SBP (M-SD)	I-SD	G-SD
ACE inhibitor vs. Placebo									
BENEDICT	Trandolapril	302	DB	HBP+DM	3.6	27	138.5 (11.39)	9.07	14.36
	Placebo	302					140.7 (11.04)	9.40	14.44
DIAB-HYCAR	Ramipril	2,443	DB	DM+nephropathy	3.9	12	143.2 (11.72)	9.84	15.18
	Placebo	2,469					144.0 (12.49)	10.01	15.78
EUROPA	Perindopril	6,110	DB	CHD	4.2	10	129.7 (12.50)	10.51	16.52
	Placebo	6,118					134.6 (12.28)	10.73	16.20
PART2	Ramipril	308	DB	CHD or CVD	4.7	21	123.5 (13.34)	10.63	15.47
	Placebo	309					130.5 (13.99)	10.11	17.06
PROGRESS	Perindopril (+/- indapamide)	3,051	DB	Cerebrovascular disease	3.9	10	133.7 (13.78)	10.10	17.40
	Placebo(s)	3,054					142.7 (14.38)	10.47	18.33
SCAT	Enalapril	230	DB	CHD	4.0	15	122.4 (14.14)	11.67	18.07
	Placebo	230					131.0 (14.14)	12.12	18.87
PREVEND-IT	Fosinopril	431	DB	microalbuminuria	3.8	5	126.7 (17.07)	7.75	18.10
	Placebo	433					131.1 (16.45)	7.75	18.43
ADVANCE	Perindopril + indapamide	5569	DB	DM+RF	4.3	13	134.5 (14.65)	11.15	18.55
	Placebo	5571					140.2 (14.33)	11.73	18.72
Calcium antagonist vs. placebo									
BENEDICT	Verapamil	303	DB	HBP+DM +nephropathy	3.6	27	141.3 (10.87)	9.17	13.00
	Placebo	302					140.7 (11.04)	9.40	14.44
PREVENT	Amlodipine	417	DB	CHD	3.0	3	126.0 (12.15)	5.74	11.97
	Placebo	408					132.3 (14.18)	6.94	14.83
SYST-EUR	Nitrendipine	2,398	DB	HBP, ≥ 60 years	2.6	32	151.3 (10.94)	10.94	13.98
	Placebo	2,297					161.4 (13.52)	13.52	17.58
ACE inhibitor plus calcium antagonist vs. placebo									
BENEDICT	Trandolapril + verapamil	302	DB	HBP+DM +nephropathy	3.6	27	139.4 (12.18)	9.45	12.51

	Placebo	302					140.7 (11.04)	9.40	14.44
Diuretic vs placebo									
HYVET	Indapamide	1,933	DB	HBP, ≥80 years	1.8	13	146.9 (12.69)	9.58	15.77
	Placebo	1,912					157.5 (15.36)	9.36	18.08
MRC1	Bendrofluazide	4,297	SB	HBP, 35-64 years	5.3	7	135.5 (13.12)	9.52	15.37
	Placebo	8,654					147.7 (14.37)	10.89	17.59
MRC2	Amiloride + hydrochlorothiazide	1,081		HBP, 65-74 years	5.8	16	150.3 (12.42)	12.31	16.65
	Placebo	2,213					167.2 (12.44)	13.40	17.46
ß-blocker vs. placebo									
DUTCH	Atenolol	732	DB	Cerebrovascular disease	2.6	13	148.3 (18.23)	13.43	22.35
	Placebo	741					151.5 (18.20)	13.37	22.31
MRC1	Propanolol	4,403	SB	HBP, 35-64 years	5.3	7	138.6 (12.69)	11.02	17.39
	Placebo	8,654					147.7 (14.37)	10.89	17.59
MRC2	Atenolol	1,102	SB	HBP, 65-74 years	5.8	16	153.8 (12.01)	14.25	18.81
	Placebo	2,213					167.2 (12.44)	13.40	17.46
TRIALS COMPARING MORE INTENSIVE AND LESS INTENSIVE REGIMENS									
ABCD (H)	DBP < 75 mmHg	237	Open	HBP+DM	5.3	10	133.2 (11.76)	8.56	12.60
	DBP <90 mmHg	233					138.8 (11.79)	7.65	11.30
ABCD (N)	DBP 10 mmHg below baseline	237	Open	DM	5.3	10	128.2 (11.25)	6.85	12.00
	DBP 80-89 mmHg	243					136.3 (11.15)	7.05	12.07
HOT**	DBP ≤ 80 mmHg	6,262	Open	HBP	3.8	11	139.7 (11.65)	8.63	14.46
	DBP ≤ 85 mmHg	6,264					141.4 (11.66)	8.69	14.48
	DBP ≤ 90 mmHg	6,264					143.7 (11.31)	8.73	14.18
UKPDS-HDS	DBP < 85 mmHg	758	Open	HBP+DM	8.4	10	143.5 (14.80)	12.74	19.16
	DBP < 105 mmHg	390					154.8 (15.83)	12.37	19.84
TRIALS COMPARING REGIMENS BASED ON ANGIOTENSIN RECEPTOR BLOCKERS AND CONTROL REGIMENS									
MOSES	Eprosartan	681	DB	HBP +CVD RF	4.8	13	136.6 (11.56)	8.60	14.41
	Nitrendipine	671					135.8 (10.73)	8.53	14.64

TRIALS COMPARING REGIMENS BASED ON DIFFERENT DRUG CLASSES

ACE inhibitor vs. diuretic- or ß-blocker

ALLHAT	Lisinopril	9,054	DB	HBP + RF	4.9	28	138.7 (13.10)	13.05	18.26
	Chlorthalidone	15,255					136.1 (11.23)	11.57	15.89
ANBP2	Enalapril	3,044	Open^	HBP, 65-84 years	4.1	20	145.2 (10.15)	13.24	16.75
	Hydrochlorothiazide	3,039					144.5 (10.36)	12.77	16.35
CAPPP	Captopril	5,492	Open^	HBP	6.1	8	150.4 (12.75)	11.76	17.50
	ß-blocker or diuretic	5,493					147.9 (12.90)	11.13	17.20
STOP-2	Enalapril or lisinopril	2,205	Open^	HBP, 70-84 years	5.0	14	160.7 (12.52)	13.30	17.96
	atenolol or metoprolol or pindolol or hydrochlorothiazide + amiloride	2,213					158.5 (12.19)	12.85	17.77
UKPDS-HDS	Captopril	400	DB	HBP+DM	8.4	10	143.9 (14.24)	12.98	19.26
	Atenolol	358					143.1 (15.39)	12.49	20.49

Calcium antagonist vs. diuretic- or ß-blocker

ALLHAT	Amlodipine	9,048	DB	HBP+ RF	4.9	28	137.1 (10.54)	11.37	14.68
	Chlorthalidone	15,255					136.1 (11.23)	11.57	15.89
ASCOT	Amlodipine	9,639	Open^	HBP + CVD RF	5.5	15	131.9 (11.1)	10.99	15.84
	Atenolol	9,618					131.8 (13.0)	13.42	19.18
CONVINCE	COER-Verapamil	8,179	DB	HBP+ RF	3.0	6	136.5 (10.27)	8.66	13.17
	Hydrochlorothiazide or atenolol	8,297					136.7 (10.85)	9.03	13.79
ELSA	Lacidipine	1,177	DB	HBP	4.0	13	142.6 (11.02)	8.46	13.42
	Atenolol	1,157					141.9 (12.22)	8.91	15.34
INVEST	Verapamil SR plus trandolapril	11,267	Open	HBP + CHD	2.8	17	132.4 (12.45)	9.94	15.50
	Atenolol plus hydrochlorothiazide	11,309					132.8 (13.67)	10.30	16.65
NICS-EH	Nicardipine	215	DB	HBP, ≥ 60 years	5.0	9	149.5 (12.56)	11.04	16.36
	Trichlormethiazide	214					149.5 (13.33)	10.90	16.27
NORDIL	Diltiazem	5,410	Open^	HBP	5.0	6	154.9 (12.92)	10.57	16.45
	ß--blocker or diuretic	5,471					151.6 (13.58)	11.11	17.44
STOP-2	Felodipine or isradipine	2,196	Open^	HBP, 70-84 years	5.0	14	160.6 (11.93)	12.64	16.31

	Atenolol or metoprolol or pindolol or hydrochlorothiazide + amiloride	2,213					158.5 (12.19)	12.85	17.77
VHAS	Verapamil	707	DB/Open	HBP	2.0	10	143.5 (9.56)	7.36	12.34
	Chlorthalidone	707					141.7 (9.45)	7.20	12.08
ACE inhibitor vs. calcium antagonist									
ABCD (H)	Enalapril	235	DB	HBP+DM	5.3	10	135.8 (12.24)	8.30	13.07
	Nisoldipine	235					136.0 (11.97)	7.91	11.37
ABCD (N)	Enalapril	246	DB	DM	5.3	10	132.5 (13.14)	7.09	14.32
	Nisoldipine	234					132.2 (10.50)	6.81	11.28
ALLHAT	Lisinopril	9,054	DB	HBP +CVD RF	4.9	28	138.7 (13.10)	13.05	18.26
	Amlodipine	9,048					137.1 (10.54)	11.37	14.68
BENEDICT	Trandolapril	302	DB	HBP + DM	3.6	27	138.5 (11.39)	9.07	14.36
	Verapamil	303					141.3 (10.87)	9.17	13.00
JMIC-B	ACE inhibitor	822	Open^	HBP +CHD	3.0	9	138.8 (15.52)	11.27	19.05
	Nifedipine	828					136.5 (13.90)	11.38	17.86
STOP-2	Enalapril or lisinopril	2,205	Open^	HBP, 70-84 years	5.0	14	160.7 (12.52)	13.30	17.96
	Felodipine or isradipine	2,196					160.6 (11.93)	12.64	16.31
Diuretic vs ß-blocker									
MRC1	Bendrofluazide	4,297	SB	HBP, 35-64 years	7	5.3	135.5 (13.12)	9.52	15.37
	Propanolol	4,403					138.6 (12.69)	11.02	17.39
MRC2	Amiloride + hydrochlorothiazide	1,081	SB	HBP, 65-74 years	5.8	16	150.3 (12.42)	12.31	16.65
	Atenolol	1,102					153.8 (12.01)	13.40	18.81

Afr, African American; CHD, coronary heart disease; COER, controlled onset-extended release; CVD, cardiovascular disease; DB, double-blind; DBP, diastolic blood pressure; DM, diabetes mellitus; GITS, gastrointestinal transport system ; HBP high blood pressure; MAP, mean arterial pressure; N, number of all randomized participants (with and without diabetes); RF, other CVD risk factor; SB, single blind.

#These placebo-controlled trials either had similar blood pressure goals in each randomized group or introduced active treatment into the placebo arm for another reason for a large proportion of participants prior to the completion of follow-up.

^ PROBE (Prospective, Randomized, Open with Blinded Endpoint evaluation) design trials

**HOT trial data analysed as most intensively treated group vs. others

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APPENDIX THREE

Medication use during follow-up in trials with individual patient data.

Trials	Primary comparison in analysis	N	Trial design	Per-protocol add-on medication	Follow-up (years)	Primary use at 1-year % cases	Primary use at final visit % cases	Add-on use at 1-year % cases	Add-on use at final visit % cases	Use of only primary at 1-year	Use of only primary at final visit
ARB vs. CCB											
MOSES	Eprosartan	681	DB	Diuretic or β-blocker or α-blocker[1]	4.8	na	Na	na	65.6	na	34.4
	Nitrendipine	671		Diuretic or β-blocker or α-blocker[1]		na	Na	na	66.9	na	33.1
ACE inhibitor vs. diuretic- or ß-blocker											
ALLHAT	Lisinopril	9,054	DB	Atenolol or clonidine or reserpine	4.9	82.4	72.6	32.6	43.0	47.1	18.9
	Chlorthalidone	15,255		Atenolol or clonidine or reserpine		87.1	80.5	26.7	40.7	59.8	31.2
ANBP2	Enalapril	3,044	Open^	CCB or β-blocker or α-blocker[1]	4.1	na	58	na	na	na	<50†
	Hydrochlorothiazide	3,039		CCB or β-blocker or α-blocker[1]		na	62	na	na	na	<50†
CAPPP	Captopril	5,492	Open^	Diuretic then CCB	6.1	na	Na	na	na	na	na
	ß-blocker or diuretic	5,493		Both protocol drugs, then CCB		na	Na	na	na	na	na
STOP-2	Enalapril or lisinopril	2,205	Open^	Hydrochlorothiazide	5.0	na	61.3	na	46†	na	33.1†
	Atenolol/metoprolol/pindolol or hydrochlorothiazide + amiloride	2,213		Combined diuretic + β-blocker		na	62.3	na	46†	na	33.6†
UKPDS-HDS	Captopril	400	DB	Both groups: Furosemide, nifedipine, methyldopa or prazosin	8.4	na	78	38	66	na	26.5†
	Atenolol	358				na	65	48	65	na	22.8†
Calcium antagonist vs. diuretic- or ß-blocker											
ALLHAT	Amlodipine	9,048	DB	Atenolol or clonidine or reserpine	4.9	83.5	72.1	25.9	39.5	58.3	28.0
	Chlorthalidone	15,255		Atenolol or clonidine or reserpine		87.1	80.5	26.7	40.7	59.8	31.2
ASCOT	Amlodipine	9,639	Open^	Perindopril	5.5	88.2	79.2	39.1	54.2	na	15
	Atenolol	9,618		Bendroflumethiazide + potassium		87.4	73.9	49.1	55.7	na	9
CONVINCE	COER-Verapamil	8,179	DB	Hydrochlorothiazide	3.0	73	60.6	58	70	42.0	28.4
	Hydrochlorothiazide or atenolol	8,297		Combined diuretic + β-blocker		73	60.3	60	73	40.0	26.1
ELSA	Lacidipine	1,177	DB	Hydrochlorothiazide	4.0	na	89.4	na	31.8	na	57.6
	Atenolol	1,157		Hydrochlorothiazide		na	97.8	na	35.9	na	61.9
INVEST	Verapamil SR	11,267	Open	Trandolapril	2.8	87.8	81.5 [2]	75.9	81.5	22.7	17.4 [2]
	Atenolol	11,309		Hydrochlorothiazide		81.2	77.5 [2]	76.5		22.1	18.1 [2]
NICS-EH	Nicardipine	215	DB	No add-on drugs allowed	5.0	na	95.3	na	6.4	na	88.9

	Trichlormethiazide	214		No add-on drugs allowed		na	95.9	na	5.7	na	89.2
NORDIL	Diltiazem	5,410	Open^	ACEI then diuretic or α-blocker	5.0	na	77	na	44	na	50
	ß--blocker or diuretic	5,471		Both drugs then ACEI or α-blocker		na	93	na	47	na	49
STOP-2	Felodipine or isradipine	2,196	Open^	β-blocker	5.0	na	66.2	na	46†	na	35.7†
	Atenolol/metoprolol/pindolol or hydrochlorothiazide + amiloride	2,213		Combined diuretic + β-blocker		na	62.3	na	46†	na	33.6†
VHAS	Verapamil	707	DB/Open	Captopril	2.0	na	66.7	na	34.2	na	44.1
	Chlorthalidone	707		Captopril		na	65.0	na	38.4	na	38.8
ACE inhibitor vs. calcium antagonist											
ABCD (H)	Enalapril	235	DB	Metoprolol or hydrochlorothiazide[1]	5.3	na	35.6	na	>50%	na	na
	Nisoldipine	235		Metoprolol or hydrochlorothiazide[1]		na	42.7	na	>50%	na	na
ABCD (N)	Enalapril	246	DB	Metoprolol or hydrochlorothiazide[1]	5.3	na	Na	na	na	na	na
	Nisoldipine	234		Metoprolol or hydrochlorothiazide[1]		na	Na	na	na	na	na
ALLHAT	Lisinopril	9,054	DB	Atenolol or clonidine or reserpine	4.9	82.4	72.6	32.6	43.0	47.1	18.9
	Amlodipine	9,048		Atenolol or clonidine or reserpine	4.9	83.5	72.1	25.9	39.5	58.3	28.0
BENEDICT	Trandolapril	302	DB	Both groups: diuretics then α- or β-blockers, then minoxidil or CCBs	3.6	na	Na	na	64.1	na	na
	Verapamil	303				na	Na	na	62	na	na
JMIC-B	ACE inhibitor	822	Open^	α-blocker or β-blocker	3.0	na	76	na	34.1†	na	41.9†
	Nifedipine	828		α-blocker or β-blocker		na	81	na	31.1†	na	49.9†
STOP-2	Enalapril or lisinopril	2,205	Open^	Hydrochlorothiazide	5.0	na	61.3	na	46†	na	33.1†
	Felodipine or isradipine	2,196	Open^	β-blocker	5.0	na	66.2	na	46†	na	35.7†
Diuretic vs ß-blocker											
MRC1	Bendrofluazide	4,297	SB	Methyldopa	7	81†	62	18	29	63†	33
	Propanolol	4,403		Methyldopa or guanethidine		84†	59	10	22	74†	37
MRC2	Amiloride + hydrochlorothiazide	1,081	SB	Atenolol then nifedipine	5.8	na	52	na	38	na	<50%†
	Atenolol	1,102		Amiloride + hydrochlorothiazide then nifedipine		na	37	na	52	na	<37%†

[1] Recommended, but open to physician discretion
[2] Results at 2-year follow-up visit.
[3] Estimated from published report
na= not available; CCBs = dihydropyridine CCBs; ACEI = angiotensin converting enzyme inhibitors

APPENDIX FOUR

Additional trials included in meta-analysis of G-VR (chapter 3). VR = variance ratio; OR = odds ratio for stroke reported.

	Reference	Name in Analysis	VR	OR
1.	Nissen SE et al for the CAMELOT investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure. *JAMA* 2004; **292:** 2217	CAMELOT	X	X
2.	Liu et al. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients *J Hypertens* 2005; **23:** 2157	FEVER	X	X
3.	Dahlof et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359:** 995	LIFE	X	X
4.	Lithell et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; **21:** 875	SCOPE	X	X
5.	PATS et al. Post-stroke antihypertensive treatment study. A preliminary result. PATS Collaborating Group *Chin Med J* 1995; **108:** 710	PATS	X	X
6.	Amery et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet* 1985; **1:** 1349	EWPHE	X	X
7.	Mcfate-Smith et al. Treatment of mild hypertension: results of a ten-year intervention trial. *Circ Res* 1977; **40 S 1:** 98	USPHS	X	X
8.	ALLHAT investigators. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981	ALLHAT II	X	X
9.	Julius et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363:** 2022	VALUE	X	X
10.	SHEP et al. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group *JAMA* 1991; **265:** 3255	SHEP	X	X
11.	Dahlof et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) *Lancet* 1991; **338:** 1281	STOP I	X	X
12.	Asselbergs FW et al for the PREVEND-IT investigators. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation.* 2004; **110:** 2809-2816.	PREVEND-IT		X
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APPENDIX FIVE

Protocol version 4: 13/11/12

A study of the association between blood pressure variability, blood pressure control and clinical outcomes in patients with transient ischaemic attack or strokes

Alastair Webb, Jonathan Diesch, Peter M. Rothwell

Background

Blood pressure variability and stroke:

Blood pressure (BP), particularly systolic blood pressure (SBP), is the most powerful risk factor for ischemic stroke.[1,2,3] Lowering BP is highly effective in preventing stroke in both primary prevention[4] and in the medium- and long-term after a transient ischemic attack.[5]

We recently showed that patients with episodic hypertension have a high risk of vascular events,[6,7] that residual visit-to-visit variability in blood pressure (BP) on treatment has a poor prognosis despite good control of mean BP,[6,7] and that benefits of some antihypertensive drugs are due partly to reduced variability in SBP.[8,9] Variability in SBP is reduced by calcium channel blockers (CCBs), less so by diuretics and increased by beta-blockers, explaining class differences in effects on stroke risk in randomized controlled trials (RCTs).[8,9] Furthermore, variability of BP measurements are increased in patients with prior cerebrovascular disease.[10] Screening for hypertension based on a single measurement can be misleading and estimates of the prevalence of hypertension can be biased if appropriate correction for within-person variability is not made. Measurements obtained from 24-hour ambulatory BP monitoring can reduce the effects of short-term (daily) variation,[11] but there are also important medium-term (within weeks or months) components of variability in patients with a previous TIA or stroke.[10] There is some evidence that within-person variation in BP increases with age and tends to be high in patients with widespread atherosclerosis.[14] These groups are of particular clinical importance because they are at a high risk of stroke and coronary events.

Autonomic cardiovascular system and stroke:

BP regulation is maintained by the autonomic nervous system. One of the most important mechanisms in the regulation of the autonomic cardiovascular system is the baroreceptor reflex arc, which includes peripheral afferent (aortic and carotid baroreceptors) and efferent (vagal and sympathetic tone) as well as central mechanisms (brain stem and higher cerebral centers).[15,16] Baroreflex function, expressed as Baroreflex sensitivity (BRS), has been reported to be an important determinant of cardiac death after acute myocardial infarction.[17] There is also evidence of abnormal BRS in animal models of stroke[16,18] and in patients with chronic cerebrovascular diseases.[19,20] Furthermore it was found that BRS was impaired after acute stroke, and that poststroke patients with impaired BRS had a poor prognosis.[15,21] However, data about BRS in patients with TIA and minor strokes are lacking.

Blood pressure variability and autonomic cardiovascular system:

High BP variability might reflect an impairment of central control of the autonomic cardiovascular system. This can be tested by stimulation of the sympathetic nervous system. For example, BP and heart rate responses to a stress test (cold pressor test, CPT) in patients with a coronary artery disease were significantly larger than in matched controls.[22] Therefore the question arises, whether patients with minor strokes and TIA with high BP variability show a higher increase in their BP after CPT **or** mental arithmetic than patients without high BP variability. High sympathetic nervous system activity can raise the BP significantly. It is a well known phenomenon that in the acute phase after TIA or minor stroke BP is often high. Until now this so-called “post-stroke hypertension” has been assumed to be a physiological response to stroke, perhaps aimed at improving cerebral

perfusion. However, the hypothesis resulting from our recent work is that the BP rise precedes and is, in fact, in many cases the cause of the TIA or stroke rather than the consequence. Therefore patients with a high BP variability with occasionally high BP values might be at much higher risk of stroke in both the primary and secondary preventing settings.

Measuring short- and medium-term variability in BP requires many consecutive BP measurements over weeks and months. A simple and reliable tool - such as the measurement of BRS or the CPT - reflecting BP variability in short- and medium-term is lacking. These simple tests of autonomic cardiovascular function may help selecting patients at high risk for recurrent ischemic events and may therefore influence primary and secondary prevention strategies. Furthermore, showing that patients who display a rapid rise in BP during CPT have a higher risk of stroke at long-term follow-up would support the evidence, that high BP in patients with an acute TIA or stroke was the cause of the stroke and not vice versa.

Hypothesis and objectives

This project aims to test the hypothesis that patients with a TIA and stroke with high short- and medium-term BP variability have a more impaired autonomic function than patients with a low BP variability. Impaired autonomic function is defined as impaired cardiac BRS and as an excessive cardiovascular response to a stress test (CPT). Since arterial stiffness and vascular reactivity influence BP variability as well, arterial stiffness and vascular reactivity will also be assessed.

Primary Objective:

The primary objective of this study is to establish whether a link exists between short- and medium-term BP variability; furthermore we want to assess, whether there is a link between short- and medium-term BP variability and impaired autonomic cardiovascular function in patients with a TIA or minor stroke.

Secondary Objective:

The secondary objective is to test whether patients with a TIA or minor stroke with a high BP variability and and/or an impaired autonomic cardiovascular function have a greater risk of recurrent ischemic events during long-term follow-up than patients with a low BP variability and/or normal
autonomic cardiovascular function.

Study Design

Eligibility and Recruitment

500 participants will be identified from patients recruited to the Oxford Vascular Study with a suspected TIA or stroke. This study provides rapid assessment, investigation and treatment for nine GP practices in Oxfordshire (pop 91,500). Patients are seen at the West Wing Out-patients Department at the John Radcliffe Hospital if directly referred, usually in the first 24 hours after symptom onset, or are recruited following admission to hospital. All patients are followed-up after one month, six months, one year and five years. As part of the daily clinical practice, patients directly referred to the OXVASC clinic are currently measuring their BP with a monitor at home three times a day (morning, mid-morning and evening) during the first month after their event. Twenty-four-hours BP monitoring is also done as part of the clinical routine one month after the event.
Physiological assessments will be accomplished through close cooperation between the OXVASC Clinic (Prof Peter Rothwell and colleagues) and the Department of Cardiovascular Medicine, and will be performed in the new Cardiovascular Clinical

Research Facility at the JR Hospital, by Jonathan Diesch, the vascular scientist employed by the CCRF.

The eligibility criteria are as follows:
1. Recruited to the OXVASC study in the month after a TIA or ischaemic stroke.
2. Written informed consent.

The following patients will be excluded from the study:
1. Inability to give informed consent.
2. Recent myocardial infarction (in the last month) or unstable angina pectoris.
3. Severe cardiac heart failure (NYHA 3-4, EF<40%)
4. Bilateral severe stenosis of the carotid arteries prior to carotid endarterectomy.

The following patients will be exclude from CPT and mental arithmetic tests:
1. Very high blood pressure (>180/110 mmHg).

The following patients will be excluded from the analysis of baroreceptor sensitivity:
1. Patients with atrial fibrillation .
2. Patients with a history of severe diabetes mellitus.
3. Patients with an impaired renal function (creatinine >200 umol/L).
4. Patients with other conditions with autonomic failure (e.g.: Parkinson's disease)

The following patients will be excluded from the assessment of pulse wave velocity:
1. Severe (>50%) or recently symptomatic carotid stenosis on that side.

Assessing clinical and radiographic data

Clinical and radiological data and stroke aetiology are assessed in all patients with an ischemic stroke and transient ischemic attack in the ongoing OXVASC study.

Assessing short-term BP variability

24-hours BP monitoring will be assessed with the use of a Spacelabs recorder on the occasion of the one month follow-up visit. The monitor will record BP at 15-minute intervals during the day (7 am to 10 pm) and 30-minute intervals at night (10.01 pm to 6:59 am).

Assessing BP medium-term variability

BP values of all patients before their stroke or TIA recorded by the GP are collected within the OXVASC study. This will allow assessment of medium-term BP variability in the patients before their stroke.
Furthermore all patients referred to the OXVASC clinic are currently measuring their BP at home during the first month after stroke with a BP monitor as part of the usual care in OXVASC patients. This will allow assessing medium-term BP variability in the patients after their stroke.

Assessing cardiovascular physiological measures

The physiological measurements will be performed either on the day of the initial assessment in clinic, once carotid imaging has been performed, or on another occasion within six weeks after the index event, if recruited at or prior to the one month follow up visit. If the tests are performed after the day of the acute assessment, patients will be asked to abstain from smoking, alcohol, and all caffeinated products for at least 12 hours. The tests will be performed at least 2 hours after a light meal, in an evenly lit room kept at a constant

temperature between 22-22^{0}C. The patients will be asked to micturate, if they wish, before the study.

The following tests will be performed:

1. Testing spontaneous baroreflex sensitivity (BRS)[15]

Continuous ECG will be recorded and continuous BP will be assessed using a Finometer (BP monitor which allows continuous non-invasive assessment of finger arterial pressure). After a period of at least 15 minutes of rest and after achievement of a satisfactory BP signal from the monitor and the stabilization of BP at the same level, recordings will be performed for a 10 minutes. The outputs from the Finometer and simultaneous surface ECG recordings will be analysed to estimate the cardiac BRS using in-house analysis programs written in Matlab, according to both sequential[23] and spectral[15] methods.

2. Assessment of cardiovascular reactivity[24,25,26]

To test the reactivity of the baroreceptor arch to vasoconstriction as well as to vasodilatation, the following tests will be performed:

2.1. Vasoconstriction

Baroreceptor reactivity and central sympathetic response to vasoconstriction will be assessed using the cold pressor test according to Hines and Brown (Am Heart J 11:1–9, 1936). The cold pressor test is used to assess neural control of the cardiovascular system, which reflects cardiac sympathetic nerve activity. The test is based on the fact that immersion of a hand in ice-cold water causes a rise of BP which varies in different subjects. It is designed to measure the reactivity of the cardiovascular system to a standard stimulus. The technique adopted by Hines is as follows: Patients have to rest in the supine position until the BP has reached a steady basal level. The hand on the side opposite to the arm used to record the BP pressure is then immersed in water at a temperature of **0-**4^{0}C for one minute. BP and heart rate will be assessed during the immersion and until the pressure has fallen to its original basal level. The maximum increase of the systolic and diastolic BP above the basal level is taken as a measure to the size of the cold pressor response.

2.2 Mental Arithmetic

Blood pressure response to a purely internal sympathetic stimulus will be assessed through mental arithmetic. Patients will be asked to perform mental arithmetic aloud for two minutes, consisting of serially subtracting 29 from 1007, or if this is too difficult, serially subtracting 7 from 100. Blood pressure response will be assessed by the maximum increase in blood pressure from baseline.

2.3 Postural Blood Pressure

BP will be measured with the Finometer and using a standard “AND” oscillometric brachial BP manometer in the sitting, supine and standing positions. The minimum and maximum BP reached after transition from sitting to standing and lying to standing will be measured.

2. Assessment of arterial stiffness[27]

3.1 Augmentation index

Radial artery pulse waveforms will be recorded using a pressure tonometer and designated software as previously described (SphygmoCor, At-Cor Medical, Sydney, Australia).[28] Briefly, mean values of approximately 10 radial pulse waves will be used to generate a corresponding central aortic pressure waveform with a validated mathematical transfer function.[29] The software uses an algorithm to determine the aortic pressure waveform's inflection point which corresponds to the onset of the reflected wave returning from peripheral arteries, and divides the aortic pressure wave into an early and late systolic peak. Augmentation index (AI_x) quantifies augmentation of central aortic pressure (due to the reflected component of the pulse pressure waveform) and typically increases with age as the arteries become stiffer (or less compliant).[30] AI_x is calculated as the difference between the second (P2) and first systolic peak pressure (P1), expressed as percentage of the central pulse pressure (PP): AI_x (%) = ((P2-P1)/PP)*100. As heart rate influences AI_x, all values of AI_x will be corrected to 75 beats per minute as previously described.[31] Essentially, the faster the pulse wave returns from the periphery, the stiffer the arteries must be, and the higher the calculated augmentation index.
A minimum of 10 radial artery pulse waveforms are required by the software to calculate the AI_x and to also derive an operator index (indicating the quality and reproducibility of the arterial signal (SphygmoCor, At-Cor Medical, Sydney, Australia). Several estimates of AI_x will be performed on each occasion and the measurement with the highest operator index will be used for statistical analysis.

3.2 Aortic pulse wave velocity

Aortic arterial stiffness will be assessed by the gold standard technique of carotid-femoral pulse wave velocity. This requires recording of the pulse wave by applanation tonometry with the SphygmoCor device from both carotid and femoral arteries, and the speed of transmission between the two sites used to estimate the velocity of the pulse wave. This provides a measure of the stiffness of the central arteries.

4 Transcranial Doppler Ultrasound (TCD)

Dual channel, bilateral, monitoring TCD will be performed with a DiaMon 2MHz monitoring set acquired by the DWL Doppler Box, and MCA velocity will be acquired simultaneously with the Finometer continuous BP monitoring by an ADInstruments Powerlab acquisition system. This allows measurement of stiffness of the middle cerebral artery by pulse wave velocity,[32] and assessment of cerebrovascular reactivity / autoregulation in the face of perturbations in blood pressure. The gain of cerebrovascular reactivity will be measured as the change in MCA velocity per unit change in systolic and mean arterial pressure.

Potential risk

BP monitoring, assessment of aortic stiffness and BRS function consist of BP measurements, tonometry and ECG monitoring, none of which are harmful to patients. The cold pressor test has no greater effect on BP than MRI scans or multiple other tests, performed in patients with an ischemic stroke, and therefore does not expose patients to an additional risk.

Ethical considerations

The pulse wave analyses will be entirely non-invasive and take 15 minutes per session. There will be no adverse effects from the pulse wave analysis system.

Power Calculation

500 patients will be recruited over five years. Based on Years 1-7 of OXVASC, the two-year stroke risk (excluding the first 7-days) is 20%. Assuming a linear relation between the mainly continuous physiological parameters and stroke risk, and allowing for 15% mortality due to non-stroke causes, this will provide 80% power at the 95% level of significance to detect a two-fold increase in stroke risk across quintiles of each variable over two years. However, the risk relations that we have identified in our preceding studies of BP variability have often been considerably stronger (5-10-fold increases across deciles) and so we will perform two intermediate analyses after recruitment of 250 patients (mean follow-up = 6 months) and after 400 patients (mean follow-up = 10 months). Although leading to a slight reduction in statistical power, the use of intermediate analyses will prevent the study going on beyond a clear result.

Statistical Analysis

BP variability on home monitoring: Standard deviation (SD), coefficient variant (SD/mean) and variation independent of the mean BP will be evaluated.
Data analysis of baroreflex sensitivity testing (BRS): In-house programs written in Matlab will be used for the analysis of BRS according to the sequential and spectral methods, and correlated with the automatic calculation of BRS by the Westergren method by the proprietary Beatscope software provided with the Finometer.
Assessment of arterial stiffness – The SphygmoCor software provides automated analysis of PWV and augmentation index.
Assessment of reactivity of blood-pressure: The maximum increase of the systolic and diastolic BP above the basal level is taken as a measure of the size of the cold pressor response.
Subgroup analysis: Patients with a cardioembolic stroke and those with antihypertensive medication will be analyzed separately.
The statistical tests that we intend to use are logistic regression for clinical outcomes and multivariate linear regression for relating continuous physiological variables.

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APPENDIX SIX

A pilot study into the relationship between differences in variability in systolic blood pressure, blood pressure control mechanisms and cerebrovascular autoregulation

Ethics Ref:	**Southampton REC B – 11/SC/0415**
Date and Version No:	**07/09/2011 Version 1.0**
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Sponsor:	**University of Oxford**
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Signatures:	

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Summary
Differences in intra-individual variability in systolic blood pressure strongly predict the risk of stroke, independent of mean blood pressure. However, it is unclear which blood pressure control mechanisms are responsible for differences in variability in blood pressure and whether there are associated differences in cerebrovascular autoregulation which might explain effects on stroke risk. This study aims to assess the relationship between systemic blood pressure control mechanisms and cerebrovascular autoregulation in states of reduced or increased blood pressure variability. Drugs that reduce peripheral resistance reduce variability in blood pressure whilst beta-blockers increase peripheral resistance and increase variability in blood pressure. Using these medications to induce a physiological state with increased or decreased peripheral resistance and blood pressure variability allows measurement of the relationship between blood pressure control mechanisms and cerebrovascular autoregulation.
10 healthy men and women will undergo physiological tests and an MRI brain scan at baseline and following 48 hours (two doses) of 10mg of amlodipine and of 160mg propranolol LA (Inderal LA). These tests include ECG monitoring, non-invasive beat-to-beat blood pressure (Finometer), middle cerebral artery blood flow (by transcranial ultrasound, DWL DopplerBox), and radial, femoral and carotid applanation tonometry (SphygmoCor). They will then undergo brain MRI in states of hypocapnia, normocapnia and hypercapnia to measure cerebrovascular reactivity. These techniques enable measurement of central and peripheral arterial stiffness (aortic pulse wave velocity, middle cerebral artery pulse wave velocity and augmentation index respectively), spontaneous baroreceptor sensitivity, orthostatic blood pressure responses, responses to mild stress (mental arithmetic and cold pressor test) and measures of cerebrovascular autoregulation (breath holding index, spontaneous transfer gain of blood pressure, MRI perfusion). The tests will measure changes in physiological blood pressure control mechanisms and associated differences in cerebrovascular perfusion during treatment, and relate these to beat-to-beat and 24 hour variability in SBP.

Background
We recently demonstrated that increased visit-to-visit, within-visit and 24 hour variability in systolic blood pressure (SBP) are associated with an increased risk of stroke in 3 cohorts of patients with previous TIA or stroke and 2 cohorts of patients with hypertension, independent of mean SBP.[1, 2] Visit-to-visit variability in SBP is therefore a powerful new marker of stroke risk that is amenable to treatment with current antihypertensive agents, with resulting reductions in the risk of stroke. It has since been demonstrated that visit-to-visit variability is also predictive of overall mortality[3] and the risk of nephropathy in type 1 diabetes.[4] However, the physiological basis for differences in variability in SBP is unknown. Furthermore, it is possible that the relationship between variability in SBP and risk of stroke is dependent upon strongly correlated differences in cerebrovascular autoregulation rather than effects on systemic blood pressure. Drugs that cause peripheral vasodilation decrease both blood pressure variability and the risk of stroke, whilst drugs that increase peripheral resistance increase them.[5, 6]
This study is designed to assess the relationship between the mechanisms underlying the systemic control of blood pressure and cerebrovascular autoregulation in a physiological state known to be associated with a lower variability in blood pressure and risk of stroke (during treatment with amlodipine) and in a physiological state associated with an increased variability in blood pressure and the risk of stroke (during treatment with propranolol).

Physiological control of blood pressure
The primary aim of this study is to assess the relationship between changes in peripheral mechanisms controlling blood pressure and cerebrovascular autoregulation. We have previously demonstrated that the differing effects of antihypertensive drugs on variability in SBP and the risk of stroke are unlikely to be due to new-onset atrial fibrillation.[7] As this is the commonest cause of cardioembolic stroke, it is likely that the increase in stroke risk

associated with increased blood pressure variability is due either to direct blood pressure changes or associated changes in the cerebrovascular circulation. Increased variability in SBP could relate to any component of the blood pressure control system. This includes increased centrally-driven sympathetic responses to stressful external stimuli (increased cardiovascular reactivity), greater responses to direct environmental stimuli such as postural changes, or a reduced capacity to buffer changes in blood pressure through decreased arterial compliance (ie arterial stiffness) or reduced baroreceptor sensitivity. Increased cardiovascular reactivity has been shown to predict future hypertension and an increased risk of cardiovascular events.[8] This is consistent with findings that people with hostile personality traits are at an increased risk of cardiovascular events[9, 10] and that known triggers of stroke also cause marked elevations in blood pressure.[11] Many laboratory tests of cardiovascular reactivity have been devised. For this study, we have selected a purely internal stressor, mental arithmetic, and an external, mildly noxious stress test, the cold pressor test, which has previously been shown to be increased in patients with coronary artery disease and predict increased coronary reactivity.[12, 13] Postural blood pressure responses reflect both the effect of a gravitational challenge to blood pressure and the capacity of the body to buffer this. Both orthostatic hypertension and orthostatic hypotensive are predictive of future cardiovascular events.[14-16]
Two major arterial functions that buffer blood pressure changes in the short term are arterial stiffness and the baroreceptor reflex. Arterial stiffness can be measured in many ways and at many sites of the arterial system.[17] Central aortic stiffness is most commonly assessed by carotid-femoral pulse wave velocity[18] and has been shown to be strongly predictive of the risk of white matter disease[19] and lacunar stroke.[20] An alternative measurement, the augmentation index, assesses the effect of reflected pulse waves returning from the peripheral circulation and increasing the size of the forward travelling wave from the heart and has been shown to be predictive of future cardiovascular events in some studies.[21] Finally, the cerebral vessels are of particular interest regarding the subsequent risk of stroke but no study has yet assessed the prognostic significance of middle cerebral artery stiffness, although a technique for this purpose has recently been developed.[22]
Baroreceptors situated predominantly in the carotid bulb and aortic arch buffer acute changes in blood pressure, predominantly through modulating the autonomic control of cardiac output. Baroreceptor sensitivity is decreased post-stroke[23] and this predicts a worse outcome after stroke,[24] whilst animal experiments indicate a direct effect of calcium channel blockade on baroreceptor function.[25]

<u>Evidence for the effects of amlodipine and propranolol on variability in SBP</u>
The calcium channel blocker in this study will be amlodipine as it is the agent with the strongest evidence for significant effects on visit-to-visit variability in blood pressure[3] and stroke risk, is taken once a day and is well-tolerated. The beta-blocker will be propranolol as the typical non-selective beta-blocker in common use in neurological practice, including in patients at increased risk of stroke (ie migraine with aura and essential tremor). We have recently shown that non-selective beta-blockers are associated with a greater increase in visit-to-visit variability in SBP than selective beta-blockers[26] and are associated with greater increases in the risk of stroke. As such, it is likely to produce greater differences in variability in SBP and the physiological measurements, increasing the sensitivity of this study. A prospective cohort study is currently underway in patients with TIA or minor stroke (reference 08/H0606/124) to identify the relationship between differences in various physiological measures, variability in SBP and the subsequent risk of TIA, stroke or cognitive decline. However, this study includes patients with pre-existing cerebrovascular disease which has direct effects on both blood pressure variability and cerebrovascular autoregulation which could confound any measured relationships. Furthermore, detailed assessment of parenchymal cerebral perfusion and autoregulation by MRI is not feasible in a large cohort of patients under prospective surveillance due to the more prolonged and

complex imaging protocols required. Finally, any relationship between peripheral measures and cerebrovascular autoregulation in a cross-sectional study is likely to be confounded by multiple demographic measures or other variables that are not measured. In this study, participants will be compared with themselves, avoiding any confounding by inter-individual variation.

Hypothesis

Changes in peripheral mechanisms underlying the control of systemic blood pressure are strongly correlated with changes in cerebrovascular autoregulation.

Primary Objective:

Measure the correlation between changes in baroreceptor sensitivity, arterial stiffness and postural blood pressure control with changes in cerebrovascular autoregulation in healthy individuals in a state of increased blood pressure variability compared to decreased blood pressure variability.

Secondary Objectives:

1. Measure the direct correlation between changes in systemic blood pressure control mechanisms or cerebrovascular autoregulation with awake variability in systolic blood pressure in healthy individuals, in a state of increased blood pressure variability compared to decreased blood pressure variability.
2. Assess the degree of change in measured physiological variables in each state of blood pressure variability to guide power calculations for future studies.

Study Design

The study is a human-subject, laboratory and MRI-based experiment. This study will be performed in healthy volunteers to exclude the possibility of confounding due to coexistent conditions associated with differences in variability in blood pressure (ie heart failure, previous cerebrovascular disease, autonomic failure). It aims to recruit 10 volunteers over the next 6 months, with each volunteer participating for 3 weeks from the time of the registration visit. The sequence of administration of the two drugs will be randomised to nullify any medium-term effects of the medications after cessation.

Inclusion Criteria

1. Healthy men and women volunteers.
2. Aged 18-70.
3. Written informed consent.

Exclusion Criteria

1. Inability to provide informed consent, ie significant cognitive impairment (MMSE<23).
2. Established cardiovascular disease including previous diagnosis of myocardial infarction, angina, TIA, stroke, peripheral vascular disease, heart failure, cardiac valve disease, diabetes, familial hyperlipidaemia.
3. Other major organ disease likely to affect blood pressure: ie liver disease, renal impairment (creatinine >150 or eGFR<50), autonomic failure, Parkinson's disease.
4. Pregnancy.
5. Current treatment with antihypertensive agents or hypertension likely to require treatment (SBP>160 or DBP>100).

6. Conditions preventing accurate physiological testing: atrial fibrillation, Raynaud's syndrome, bilateral carotid stenosis (>50%) or haemodynamically significant vertebrobasilar stenosis, significant aortic valve disease.
7. Contraindication to treatment with calcium channel blockers or beta-blockers: asthma, bradycardia, previous adverse reaction.
8. Contraindication to MRI – cerebral aneurysm clip, pacemaker, cochlear implant, mechanical cardiac valve, coronary artery stent, potential iron debris in eyes.

Recruitment
Recruitment of healthy volunteers will be carried out in two ways: firstly by open advertisement of the study within University premises, and secondly by sending a letter and information sheet to people who have previously been control participants for the OXVASC study. Once a potential participant has contacted the study, a short telephone interview will be carried out to ensure that there are no obvious inclusion or exclusion criteria, and that the participant is aware of what the study will entail. Following this, arrangements will be made to meet the participant for a 30 minute registration and consent interview at the John Radcliffe Hospital.
All phases of recruitment will be performed by Dr Alastair Webb.

Study procedures
Once recruited to the study, participants will undergo a 30 minute registration interview by Dr Alastair Webb, entailing full informed consent and a brief medical interview and examination to identify any possible exclusion criteria. At the registration visit, appointment times will be agreed for three subsequent visits and physiological procedures.
Following the registration visit, each participant will be examined on three occasions with physiological testing and MRI. The first test will be performed on no medications. Following this visit, the participant will take either amlodipine 10mg or propranolol LA 160mg at 6am for 48 hours. On the second day at 6 hours post-dose (peak serum concentration) they will undergo 2 hours of physiological tests and an MRI scan. They will then take no further treatment for at least 1 week, after which they will take the other medication for 48hours, undergoing testing at 6 hours post-dose. At the end of each visit, patients will be fitted with a 24 hour blood pressure monitor to measure half hourly blood pressures during the daytime and hourly blood pressures overnight until the same time the next day.
Physiological tests will be performed at the Cardiovascular Clinical Research Facility at the John Radcliffe Hospital, in the morning following at least a 12 hour fast from a substantial meal and caffeinated drink, by Dr Alastair Webb.

Blood pressure measurement
Office blood pressure will be measured at each of the four visits with an automated 'AND' brachial blood pressure device with an appropriately sized cuff. 3 measurements will be taken from the non-dominant arm after 5 minutes of quiet rest in a sitting position. 3 measurements will also be taken from the dominant arm at the registration visit. 24-hour ambulatory BP monitoring will be assessed with the use of a Spacelabs recorder. The monitor will record BP at 30-minute intervals during the day (7 am to 10 pm) and 60-minute intervals at night (10.01 pm to 6:59 am).

Physiological Testing
The physiological measurements will be performed at each clinic visit except for the registration visit and take approximately 2 hours to perform. Participants will be asked to abstain from smoking, alcohol, and all caffeinated products for at least 12 hours. The tests will be performed at least 2 hours after a light meal. The patients will be asked to micturate, if they wish, before the study.
The following tests will be performed:

1. Testing spontaneous baroreflex sensitivity (BRS)

Continuous ECG will be recorded and continuous BP will be assessed using a Finometer (BP monitor which allows continuous non-invasive assessment of finger arterial pressure). After a period of at least 15 minutes of rest and after achievement of a satisfactory BP signal from the monitor and the stabilization of BP at the same level, recordings will be performed for a 10 minutes. The outputs from the Finometer and simultaneous surface ECG recordings will be analysed to estimate the cardiac BRS using in-house analysis programs written in Matlab, according to both sequential[27] and spectral[28] methods.

2. Assessment of cardiovascular reactivity

2.1. Cold Pressor Test

Baroreceptor reactivity and central sympathetic response to vasoconstriction will be assessed using the cold pressor test. The cold pressor test is used to assess neural control of the cardiovascular system, which reflects cardiac sympathetic nerve activity. The test is based on the fact that immersion of a hand in ice-cold water causes a rise of BP which varies in different subjects. It is designed to measure the reactivity of the cardiovascular system to a standard stimulus. The technique is as follows: Patients have to rest in the supine position until the BP has reached a steady basal level. The hand on the side opposite to the arm used to record the BP pressure is then immersed in water at a temperature of 0-4^0 Celsius for one minute. BP and heart rate will be assessed during the immersion and until the pressure has fallen to its original basal level. The maximum increase of the systolic and diastolic BP above the basal level is taken as a measure to the size of the cold pressor response.

2.2 Mental Arithmetic

Blood pressure response to a purely internal sympathetic stimulus will be assessed through mental arithmetic. Patients will be asked to perform mental arithmetic aloud for two minutes, consisting of serially subtracting 27 from 1005, or if this is too difficult, serially subtracting 7 from 100. Blood pressure response will be assessed by the maximum increase in blood pressure from baseline.

2.3 Postural Blood Pressure

BP will be measured with the Finometer and using a standard 'AND' oscillometric brachial BP manometer in the sitting, supine and standing positions. The minimum and maximum BP reached after transition from sitting to standing and lying to standing will be measured.

3. Assessment of arterial stiffness

3.1 Augmentation index

Radial artery pulse waveforms will be recorded using a pressure tonometer and designated software as previously described (SphygmoCor, At-Cor Medical, Sydney, Australia).[21] Briefly, mean values of approximately 10 radial pulse waves will be used to generate a corresponding central aortic pressure waveform with a validated mathematical transfer function. The software uses an algorithm to determine the aortic pressure waveform's inflection point which corresponds to the onset of the reflected wave returning from peripheral arteries, and divides the aortic pressure wave into an early and late systolic peak. Augmentation index (AI_x) quantifies augmentation of central aortic pressure (due to the reflected component of the pulse pressure waveform) and typically increases with age as the arteries become stiffer (or less compliant).[29] AI_x is calculated as the difference between the second (P2) and first systolic peak pressure (P1), expressed as percentage of the central pulse pressure (PP): AI_x (%) = ((P2-P1)/PP)*100. As heart rate influences AI_x, all values of AI_x will be corrected to 75 beats per minute as previously described. Essentially, the faster the pulse wave returns from the periphery, the stiffer the arteries must be, and the higher the calculated augmentation index.

3.2 Aortic pulse wave velocity

Aortic arterial stiffness will be assessed by the gold standard technique of carotid-femoral pulse wave velocity. This requires recording of the pulse wave by applanation tonometry with the SphygmoCor device from both carotid and femoral arteries, and the speed of transmission between the two sites used to estimate the velocity of the pulse wave. This provides a measure of the stiffness of the central arteries.

4 Transcranial Doppler Ultrasound (TCD)

Dual channel, bilateral, monitoring TCD will be performed with a DiaMon 2MHz monitoring set acquired by the DWL Doppler Box, and MCA velocity will be acquired simultaneously with the Finometer continuous BP monitoring by an ADInstruments Powerlab acquisition system. This allows measurement of stiffness of the middle cerebral artery by pulse wave velocity,[22] and assessment of cerebrovascular reactivity / autoregulation in the face of perturbations in blood pressure. The gain of cerebrovascular reactivity will be measured as the change in MCA velocity per unit change in systolic and mean arterial pressure.[30] Then, a 30 second breath hold will be performed to increase arterial pCO_2 and 20s of hyperventilation at 1 breath/second will be perfumed to decrease arterial pCO_2 to assess cerebrovascular reactivity.[31] During this phase of assessment, end-tidal CO_2 will be measured via nasal cannulae with the use of a capnograph (OXI-PULSE, Pulmolink).

MRI imaging

Participants will undergo 1 hour of MRI scanning, including approximately 15 minutes for preparation and a safety questionnaire. The scan will be performed in the AVIC 3T Siemens MRI scanner for approximately 45 minutes. During this period they will wear a saturation probe on a finger, an ECG monitor and nasal cannula to record carbon dioxide levels. During scanning they will be asked to breath regularly through their nose whilst a series of sequences are taken. During the scans they will be asked to lie still, and at times carry out respiratory manoeuvres including 3 periods of 30s breath-holding and three periods of controlled hyperventilation at 1 breath per second for 30s in random order. Instructions will be delivered to the patient by means of projected instructions on to a screen. Following this period of assessment, participants will wear a tight-fitting mask covering the lower half of the face to deliver a specified mixture of medical air and carbon dioxide (3-5%). A sequence measuring cerebral blood flow will be performed whilst breathing medical air alone and then whilst breathing a mixture of medical air and 3-5% carbon dioxide for 5 minutes.

Potential risks

Both medications used in this study have been used commonly for several decades in routine clinical practice, including in the treatment of hypertensive patients and in normotensive patients for other indications. They are both very well-tolerated, with limited side-effects and minimal or no evidence of significant risks associated with their use in otherwise healthy individuals.

Risk of side-effects: The most common side-effects of amlodipine include postural dizziness, ankle oedema, flushing and headache, and of propranolol include postural dizziness, cold extremities, sleep disturbance and impotence. Rare but more serious potential complications of treatment include symptomatic bradycardia and bronchospasm with propranolol and heart failure with amlodipine. In addition, there is a very low risk of idiosyncratic allergic reactions to either agent. To reduce the likelihood of serious complications, subjects at risk of these will be excluded: pregnant or breast-feeding women, known history of asthma, cardiac conduction disease (or strong family history of), predisposition to heart failure. Secondly, patients will be warned of the above possible side-effects prior to consenting to the study, and will be provided with a telephone number to contact the study investigators directly if they experience them, and if necessary will be reviewed immediately.

BP monitoring, cerebrovascular reactivity, assessment of aortic stiffness and BRS function consist of BP measurements, transcranial Doppler ultrasound, tonometry and ECG monitoring, none of which are harmful to patients. The cold pressor test and mental

arithmetic tests have no greater effect on BP than MRI scans or multiple other tests, performed in patients with an ischemic stroke, and therefore does not expose patients to an additional risk. The MRI scans will require no contrast agent and will not be performed in any participant with a potential contraindication to MRI, and therefore pose no additional risk to the participants.
MRI is a safe and non-invasive technique, which does not involve ionising radiation. Risks associated with the magnetic field will be removed by excluding potential participants with ferromagnetic objects in their bodies (e.g. metal implants, vessel clips, shrapnel injuries) or with implanted devices which may be damaged by the magnet (e.g. heart pacemakers). All people entering the scanner room are screened for such objects.
While most people do not experience discomfort in a MRI environment, the enclosed space of the scanner can potentially feel uncomfortable, especially for more elderly subjects. Discomfort from lying still for a long period of time will be minimised with comfortable padding and positioning. Whilst in the scanner, subjects would be able to use the alarm button if they wish to communicate with the operator or to interrupt the scanning.
People with a history of claustrophobia would be excluded from participation in the study. All participants would be introduced carefully to the scanner and allowed to leave at any stage, should they wish to do so. Once in the scanner, participants would be able to indicate immediately if they wish the scanning to cease by squeezing a bulb placed in their hands, or by requesting it verbally. As the MRI scanner is noisy, subjects would be given ear-plugs and acoustically shielded headphones to minimize the noise.
Carbon dioxide inhalation: This procedure is a very common respiratory physiology technique used to generate reflex respiratory responses and to maintain arterial CO2 levels constant in the face of changes in respiration. There are no serious risks associated with breathing CO2 in healthy individuals. When PCO2 is raised to more than 8kPa (a level that will not be reached in this study) common side effects include headache and lightheadedness. At much higher blood levels than employed here (~11kPa), there is a remote possibility of abnormal heart rhythms or increase in blood pressure. These side effects usually disappear within 1 minute of the removal of inspired CO2 and are highly unlikely to occur with the level of CO2 we propose to use.

Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events.*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to participant would be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was: 'related' – that is, it resulted from administration of any of the research procedures; and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs would be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form.

In addition, the CI will report any related and unexpected SAE's to the MHRA using the Yellow Card System. In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical research study or on request a safety report to the Ethics Committee. All related AEs that result in a patient's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs. It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the patient would undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

Statistical Analysis

BP variability on home monitoring: Standard deviation (SD), coefficient variant (SD/mean) and variation independent of the mean BP will be evaluated.

Data analysis of baroreflex sensitivity testing (BRS): In-house programs written in Matlab will be used for the analysis of BRS according to the sequential and spectral methods, and correlated with the automatic calculation of BRS by the Westergren method by the proprietary Beatscope software provided with the Finometer.

Assessment of arterial stiffness The SphygmoCor software provides automated analysis of PWV and augmentation index. Middle cerebral artery stiffness will be assessed by the time interval between the R-wave of the ECG to the foot of the pulse wave recorded by TCD, divided by the distance between the sternal notch and the temporal window.[22]

Assessment of blood-pressure reactivity: The maximum increase of the systolic and diastolic BP above the basal level is taken as a measure of the size of the cold pressor, orthostatic and mental arithmetic responses.

Assessment of TCD cerebrovascular reactivity: The breath-holding index will be used as the primary measure of cerebrovascular reactivity in TCD measures, calculated as the percentage increase in middle cerebral artery blood flow from rest divided by the time the breath was held.[32] This will be correlated with end-tidal CO_2 levels measured by expiration capnography via nasal cannulae. Secondly, the transfer gain function relating spontaneous changes in blood pressure with changes in middle cerebral artery blood flow will be calculated.[30]

MRI imaging: MRI imaging will be analysed to exclude the presence of white matter disease and intracranial arterial stenosis. Secondly, whole brain perfusion and regional perfusion will be measured on ASL and VASO-GRASE sequences at rest, during hyperventilation and during inhalation of 3-5% carbon dioxide mixed with medical air using specially written, in-house software in MATLAB as described previously.[33]

The statistical tests that we intend to use are multivariate linear regression for relating continuous physiological variables and t-tests or ANOVA for direct group comparisons.

Power Calculation

This is a pilot study to assess the relationship between two sets of continuously varying physiological measures within individuals. As such, no clear prior data exists upon which an

accurate power calculation can be derived. Rather, the results of this study will be used to derive more accurate power calculations for further research.

Patient Reimbursement

For completing the study, patients will be reimbursed at £200 for the entire study. This is calculated according to time contributed to the study (at £5 per hour) plus reimbursement for discomfort:

Study Component	No.	Time per session	Cost per session	Total
Travel to hospital	4		£10	£40
Clinic appointment	1	1hr	£5	£5
Physiology Study	3	2hr	£10	£30
MRI scan	3	1hr	£5	£15
24 hr ABPM	3	n/a	£20	£60
Medication		n/a	£50	£50
Total				£200

Funding

The cost of the physiological tests, reimbursement and consumables will be met from an MRC Clinical Fellowship awarded to Alastair Webb (HMCRTA0). Cost of MRI scanning will be reimbursed from the BRC project grant awarded to the Stroke Prevention Research Unit under Prof Rothwell. These grants are administered by the University of Oxford.

Insurance and Indemnity

Negligent harm:
The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor.

Non-negligent harm:
The University has arrangements in place to provide for non-negligent harm arising from participation in the study for which the University is the Research Sponsor.

Publication Policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was Funded by the Oxford Biomedical Research Council and a Medical Research Council Clinical Fellowship. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Conflict of Interest

There are no declared conflicts of interest for any author.

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APPENDIX SEVEN

A physiological study to determine relationships between changes in variability in systolic blood pressure, arterial stiffness, aortic blood pressure and cerebrovascular pulsatility

Ethics Ref: **13/SC/0245 Oxfordshire REC A**
Date and Version No: **22/04/2013 Version 1.0**

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Sponsor: **University of Oxford**
Funders: **Oxford Biomedical Research Centre / Medical Research Council**

Signatures:

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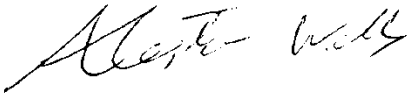
Chief Investigator



Dr AJS Webb
Clinical Fellow

Contents

MENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1	17/02/2013	A Webb	Original Version

SYNOPSIS

Study Title	A physiological study to determine relationships between changes in variability in systolic blood pressure, arterial stiffness, aortic blood pressure and cerebrovascular pulsatility
Internal ref. no.	n/a
Study Design	A human-subject, laboratory and clinic-based experiment to determine relationships between changes in physiological variables.
Study Participants	Patients with acute TIA or minor stroke, already recruited to the Oxford Vascular Study
Number of Participants	50
Planned Study Period	20 Months
Primary Objective	To measure the relationship between changes in arterial stiffness, aortic blood pressure and cerebral pulsatility with changes in home blood pressure variability in hypertensive individuals with recent cerebrovascular disease.
Secondary Objectives	To measure the relationship between changes in arterial stiffness, aortic blood pressure and cerebral pulsatility with changes in ambulatory blood pressure variability in hypertensive individuals with recent cerebrovascular disease. To measure the association between cerebral pulsatility and both home and ambulatory blood pressure variability, independent of central aortic measures
Intervention (s)	Standard treatment of hypertension with amlodipine or perindopril, as per national guidelines. Choice of treatment by random allocation.

ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
AE	Adverse Event
AIx	Augmentation index
ARB	Angiotensin receptor blocker
CCB	Calcium channel blocker
CI	Chief Investigator

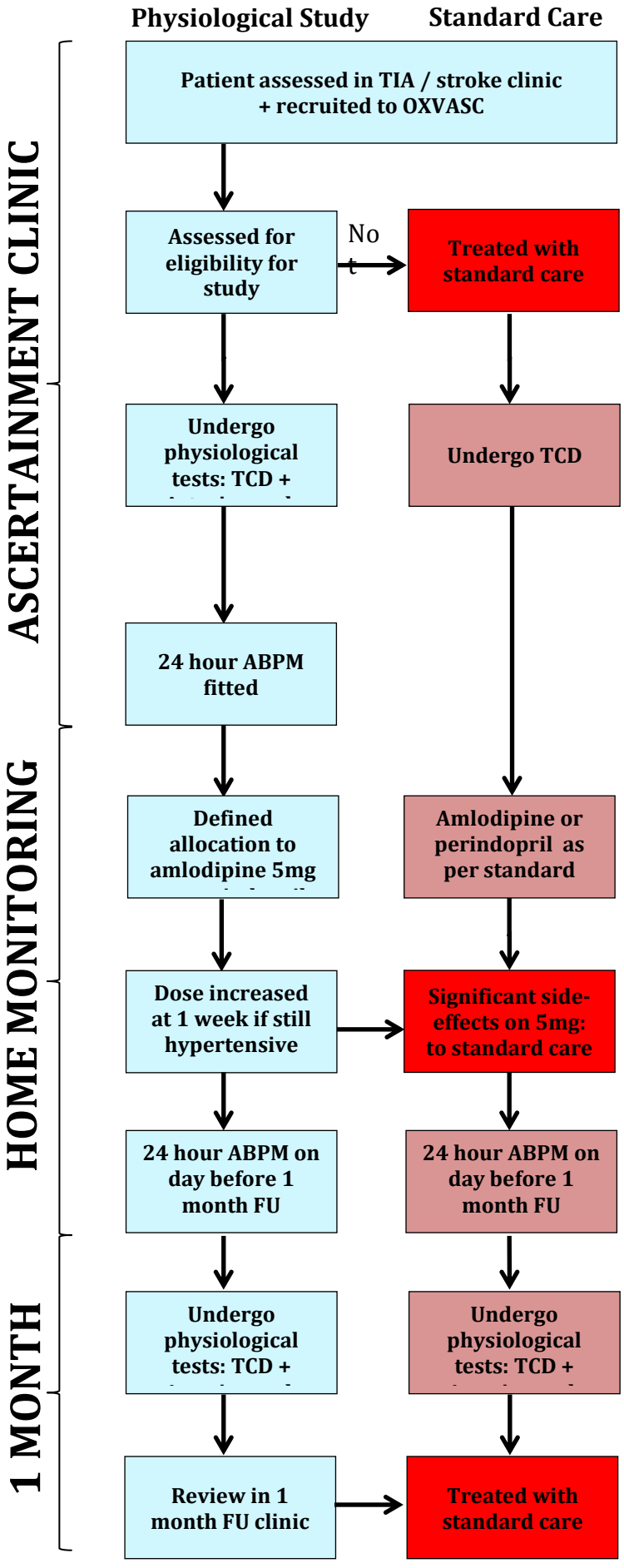
DBP	Diastolic blood pressure
GP	General practitioner
MRI	Magnetic resonance imaging
NRES	National Research Ethics Service
OXVASC	Oxford Vascular Study
REC	Research Ethics Committee
SAE	Serious adverse event
SBP	Systolic blood pressure
TIA	Transient ischaemic attack
TCD	Transcranial Doppler ultrasound

Summary

Differences in intra-individual variability in systolic blood pressure (SBP) strongly predict the risk of stroke, independent of mean blood pressure. Cerebral pulsatility is also strongly related to the occurrence of both recurrent stroke and chronic ischaemic pathology in the white matter of the brain (leukoaraiosis), and is dependent upon increased aortic stiffness and aortic pulsatility. Intra-individual variability in SBP, cerebral pulsatility and central aortic haemodynamics may represent different components of a single pathological vascular phenotype, but observational associations between these measures are strongly confounded by age and coexistent pathology. However, different classes of antihypertensive drugs have well-established effects on BP variability, with reductions in BP variability with calcium channel blockers and increases with ACE inhibitors, allowing us to test whether changes in BP variability are directly associated with changes in the other parameters, implying a common phenotype. Having completed a pilot study in 10 healthy volunteers with intact physiological adaptive mechanisms, this study is designed as a physiological study within an ongoing observational BP monitoring study in hypertensive patients with recent cerebrovascular disease. We aim to test whether changes in BP variability in this patient group are associated with corresponding changes in aortic BP, aortic stiffness and cerebral pulsatility.

Participants will be recruited from the observational BP-monitoring cohort within the population-based Oxford Vascular Study. As part of this study, hypertensive patients presenting to the TIA and minor stroke clinic are normally treated with either amlodipine or a perindopril-based regimen following their initial assessment, as part of standard care. They have a transcranial Doppler ultrasound examination at baseline and one month, then perform Bluetooth, telemetric home blood pressure monitoring (3 readings, 3 times daily) for at least 1 month, with a 24 hour ambulatory blood pressure monitor at the 1 month follow-up appointment. As part of this physiological study, participants will undergo additional measures of central aortic blood pressure and aortic stiffness (Arteriograph) at the initial assessment and 1 month follow up clinic in the Cardiovascular Clinical Research Facilities' Physiological Laboratory, in addition to transcranial Doppler ultrasound measures of cerebral blood flow velocity and cerebral arterial pulsatility (DWL Doppler Box) performed as part of OXVASC. In addition, they will have a 24 hour ambulatory blood pressure monitor fitted at the initial assessment. Following this, 25 participants in each group, stratified by age and gender, will be given amlodipine 5mg or perindopril arginine 5mg to induce appropriate changes in BP variability, with random allocation to facilitate unbiased comparisons of physiological associations (in accordance with CAMARADES recommendations for experimental stroke studies). The primary outcome will be the association between percentage change in BP variability on home blood pressure monitoring with percentage change in cerebral pulsatility, aortic stiffness and aortic blood pressure.

Physiology study design



Design: Physiological laboratory + clinic-based study with use of known effects of antihypertensive drugs to alter BP variability (as NIMP).

Measures: Cerebral pulsatility (TCD), arterial stiffness and Aortic BP (arteriograph), BP variability – home and ambulatory

Endpoint: Relationship between changes in BP variability + changes in cerebral pulsatility, aortic BP and arterial stiffness

Inclusion Criteria

1. Men and women with a recent cerebrovascular event assessed in the TIA and minor stroke clinic of the Oxford Vascular Study.[14]
2. Consenting participants in the Oxford Vascular Study.
3. Aged ≥18 years.
4. Written informed consent.
5. Able to perform home blood pressure monitoring.
6. BP >140/90 in clinic

Exclusion Criteria

1. Unable or unwilling to provide informed consent, including an individual, who, in the opinion of the investigator may be unable to comply with the requirements of the protocol.
2. Recent non-cerebrovascular cardiovascular event: myocardial infarction, unstable angina, peripheral vascular disease or new heart failure.
3. Major organ disease likely to affect blood pressure or physiological indices: liver disease, renal impairment (creatinine >150 or eGFR<50), autonomic failure, Parkinson's disease, prosthetic cardiac valve.
4. Pregnancy.
5. Current treatment with ACE inhibitor, angiotensin-receptor blocker or calcium channel blocker.
6. Clinical need for treatment with either ACEi or CCBs: heart failure or renal failure.
7. Atrial fibrillation.
8. Contraindication to treatment with calcium channel blockers or ACE inhibitors: heart failure, previous adverse reaction, bilateral carotid stenosis (>70%) or haemodynamically significant end-artery or posterior circulation stenosis.

We recently demonstrated that increased medium term visit-to-visit variability in systolic blood pressure (SBP) is associated with an increased risk of stroke in 3 cohorts of patients with previous TIA or stroke and 2 cohorts of patients with hypertension, independent of mean SBP.[1, 2] Further studies have also demonstrated associations with total mortality,[3] vascular mortality,[4] cerebral white matter disease (leaukoaraiosis)[5, 6] and cognitive dysfunction[7]. The association between medium-term variability and stroke can also be measured on day-to-day home blood pressure monitoring,[8] and more weakly with 24 hour ABPM.[1] However, the physiological basis for the association between blood pressure variability and stroke risk remains unclear with no published studies directly measuring the relationship between changes in medium-term blood pressure variability and changes in cerebral perfusion or systemic BP-related physiological indices.

A number of recent studies have demonstrated a relationship between cerebral pulsatility and both recurrent stroke[9] and cerebral white matter disease,[10] but the physiological determinants of cerebral pulsatility and leukoaraiosis are unclear. However, our recent study[11] in 100 patients with TIA or minor stroke demonstrated a strong relationship between central aortic stiffness, aortic blood pressure, cerebral pulsatility and the resulting severity of leukoaraiosis on MRI, providing a pathophysiological explanation for the relationship between cerebral pulsatility with leukoaraiosis, in which increased central aortic stiffness results in both increased aortic pulsatility and increased transmission of the pulsatile arterial waveform to the cerebral circulation. The exposure of the small vessels of the brain to increased pulsatility then results in vessel rarefraction, leukoaraiosis and an increased risk of stroke.

A possible explanation for the association between increased blood pressure variability and stroke risk is that increased blood pressure variability, arterial stiffness and cerebral pulsatility represent different facets of the same hypertension-related vascular phenotype. These measures are all strongly related to age and therefore any associations in an observational study are strongly confounded by age and gender. A less confounded method of investigating the potential relationship between arterial stiffness, cerebral pulsatility and blood pressure variability is to pharmacologically increase one measure and determine if there are strongly associated effects on the potentially associated measures. It is now well established that different antihypertensive medications reduce blood pressure variability. In the ASCOT-BPLA study, a calcium channel blocker (amlodipine) reduced blood pressure variability compared to a beta-blocker based regimen,[12] explaining the unexplained difference in stroke risk between the two arms. In addition, our meta-analysis of all published trials demonstrated that there is a significant reduction in both blood pressure variability and stroke risk in patients treated with calcium channels blockers compared to either beta-blockers or angiotensin converting enzyme inhibitors (ACEi).[13]

We recently carried out a pilot physiological study in 10 healthy volunteers to determine the feasibility of treatment with an antihypertensive agent to induce a reduction in blood pressure variability (amlodipine) compared to an agent to increase blood pressure variability (propranolol) in order to investigate the relationship between central aortic blood pressure and cerebral pulsatility (REC: 11/SC/0415). There were no serious adverse events with either treatment and the test procedures were both reliable and tolerable, however there was limited power in this small study to investigate these relationships due to its size and the efficient vascular adaptation in young individuals with healthy cerebral circulations. Furthermore, this study did not assess medium-term blood pressure variability, which is more strongly associated with stroke risk than ambulatory blood pressure variability. Therefore, we aim to test the hypothesis that induced changes in blood pressure variability are associated with changes in cerebral pulsatility and central aortic blood pressure in a larger population of patients with TIA or minor stroke who already require initiation of antihypertensive treatments.

This study will be carried out as a physiological substudy of the observational BP-monitoring cohort within the Oxford vascular study (OXVASC OREC A: 05/Q1604/70). Within this study, patients are recruited at the time of their initial assessment with a TIA or minor stroke, when they also undergo a transcranial Doppler study. They undergo 1 month

of telemetric Bluetooth home blood pressure monitoring followed by 24 hour ambulatory blood pressure monitoring and a physiological assessment at one month including a repeat transcranial Doppler ultrasound and measure of arterial measures with the Arteriograph. During the home monitoring period, they are actively treated for hypertension according to current guidelines with the specific antihypertensive agent chosen by the treating physician according to standard care, with the commonest agents prescribed being either perindopril arginine (an ACE inhibitor) or amlodipine (a calcium channel blocker).
Therefore, this study will measure relationships between changes in aortic stiffness, central aortic blood pressure, cerebral pulsatility, 24 hour ambulatory blood pressure variability and home blood pressure variability between ascertainment to the OXVASC study and the one month follow-up visit. Differences in blood pressure variability between individuals will result from allocation to either amlodipine or perindopril arginine, in accordance with standard care and current guidelines, but with equal numbers of participants allocated each drug.

Primary Objective:
Is there a relationship between changes in arterial stiffness, aortic blood pressure and cerebral pulsatility with changes in home blood pressure variability in hypertensive individuals with recent cerebrovascular disease?

Secondary Objectives:
3. Is there a relationship between changes in arterial stiffness, aortic blood pressure and cerebral pulsatility with changes in ambulatory blood pressure variability in hypertensive individuals with recent cerebrovascular disease?
4. Is there an association between cerebral pulsatility and both home and ambulatory blood pressure variability, independent of central aortic measures?

Endpoints
1. SBP variability on home and ambulatory blood pressure monitoring
2. Aortic SBP, DBP and pulse pressure
3. Aortic pulse wave velocity
4. Middle cerebral artery pulsatility – Gosling's pulsatility index

Study Design

The study is a human-subject, laboratory and clinic-based experiment to determine relationships between changes in physiological variables, resulting from established effects of commonly used antihypertensive medications. Physiological testing will be performed in 50 hypertensive participants with cerebrovascular disease, before and after 1 month of home blood pressure monitoring.

Inclusion Criteria
4. Men and women with a recent cerebrovascular event assessed in the TIA and minor stroke clinic of the Oxford Vascular Study.[14]
5. Consenting participants in the Oxford Vascular Study.
6. Aged ≥18 years.
7. Written informed consent.
8. Able to perform home blood pressure monitoring.
9. BP >140/90 in clinic

Exclusion Criteria
1. Unable or unwilling to provide informed consent, including an individual, who, in the opinion of the investigator may be unable to comply with the requirements of the protocol.

2. Recent non-cerebrovascular cardiovascular event: myocardial infarction, unstable angina, peripheral vascular disease or new heart failure.
3. Major organ disease likely to affect blood pressure or physiological indices: liver disease, renal impairment (creatinine >150 or eGFR<50), autonomic failure, Parkinson's disease, prosthetic cardiac valve.
4. Pregnancy.
5. Current treatment with ACE inhibitor, angiotensin-receptor blocker or calcium channel blocker.
6. Clinical need for treatment with either ACEi or CCBs: heart failure or renal failure.
7. Atrial fibrillation.
8. Contraindication to treatment with calcium channel blockers or ACE inhibitors: heart failure, previous adverse reaction, bilateral carotid stenosis (>70%) or haemodynamically significant end-artery or posterior circulation stenosis.

Recruitment

Participants will be recruited from the TIA and minor stroke assessment clinic of the Oxford Vascular Study, at the time of ascertainment to OXVASC study and following informed consent. All patients with a new TIA or minor stroke within the OXVASC study area are referred to this assessment clinic by local GP practices who participate in the OXVASC study, as part of their clinical care following a TIA or non-disabling stroke. All consecutive patients fulfilling the inclusion and exclusion criteria will be offered the opportunity to participate, with the Clinical Fellow Responsible for the clinic identifying appropriate participants.

Withdrawal

Participants will provide formal consent for use of their data, and any participant will be entitled to withdraw from the study at any stage, and may withdraw consent for the use of any or all information gathered as part of this study. They will be asked if we can use all data gathered up to the point of withdrawal, but they will be entitled to withdraw consent to the use of this data.

Study procedures

Study Summary

Participants will be recruited from the TIA and minor stroke clinic associated with the population-based, observational Oxford Vascular Study (OXVASC). The OXVASC population consists of about 92,000 individuals registered with 100 primary-care physicians in nine practices in Oxfordshire, UK, with very high ascertainment of cerebrovascular events through multiple overlapping methods of ascertainment.[15] All patients requiring treatment for probable TIA or stroke undergo a standardised medical history and examination by the stroke physician or neurologist in the clinic, ECG and routine blood tests, with face-to-face follow up at 1, 3, 6, 12 and 60 months. When not contraindicated, patients then undergo a stroke protocol MRI brain and contrast-enhanced MRA of the extracranial brain-supplying arteries during the assessment clinic, with the remaining patients having a CT-brain and either a carotid Doppler ultrasound or CT-angiogram. The majority of patients with TIA and minor stroke also undergo transcranial Doppler ultrasound in the acute clinic. Participants to this study perform home blood pressure monitoring with a Bluetooth-enabled, telemetric home blood pressure monitor, 3 times a day, taking three readings at each sitting for at least one month. Treatment is initiated either at the assessment clinic or after 1 week of home blood pressure readings if indicated according to national guidelines. Choice of antihypertensive agent is left to the treating physician, but in accordance with guidelines most patients are treated with either a perindopril-based

treatment or an amlodipine-based regimen as standard care, with titration of drug dose, or addition of a second agent, after 1 week of further home blood pressure monitoring. At the one month face-to-face follow-up, all patients then undergo a 24 hour ambulatory blood pressure monitor to assess for adequate blood pressure control and a repeat physiological assessment including transcranial Doppler ultrasound and Arteriograph.

Participants fulfilling the eligibility criteria for this physiological study (see above), will have exactly the same clinical care and diagnostic investigations as all patients presenting to the OXVASC clinic, and will perform the same blood pressure monitoring procedures. In addition to the transcranial Doppler ultrasound performed in the acute clinic as part of OXVASC, they will also have arterial measures taken with the Arteriograph, adding approximately 5 minutes to the initial assessment clinic. This will measure central aortic blood pressure and aortic stiffness.[16, 17] Cerebral pulsatility and other cerebrovascular haemodynamic parameters will be measured by transcranial Doppler ultrasound (DWL Doppler Box).[11] In addition to the tests carried out as part of OXVASC, participants will also undergo ambulatory blood pressure monitoring for the subsequent 24 hours, which will be fitted during the acute clinic. As in the overall OXVASC study, participants who are hypertensive in the assessment clinic will start antihypertensive treatment as soon as is feasible. However, rather than allowing a free choice of antihypertensive agent, equal numbers of participants will be allocated to one of two drugs, where either drug is equally acceptable according to guidelines and standard care: perindopril arginine 5mg or amlodipine 5mg, with titration of the dose of each agent to 10mg after 1 week, unless normotension has been achieved. Drug choice will be randomly allocated to facilitate unbiased comparisons of physiological associations, in accordance with CAMARADES recommendations for experimental stroke studies. At the one month follow-up visit, the physiological tests and a 24 hour ambulatory blood pressure monitor will be repeated. If normotension has been achieved at 1 month, then participants will stop home blood pressure monitoring, but if they are still hypertensive they will continue with home blood pressure monitoring as part of the OXVASC study, with selection of antihypertensive medication at the physician's discretion. Throughout the study, all participants will have an open access telephone number to contact during working hours.

The physiological tests (transcranial Doppler ultrasound and Arteriograph measures) will be performed during the assessment clinic in Neurosciences Outpatients and at the one month follow up clinic in the Cardiovascular Clinical Research Facility at the John Radcliffe Hospital, either by Neurology Research Fellows (LL / MT) or by the senior vascular scientist (JD). Telemetric home blood pressure and treatment is monitored as part of OXVASC by Stroke Research Fellows (NL / AW).

Blood pressure measurement

Office blood pressure will be measured at baseline and follow up with an automated 'AND' brachial blood pressure device with an appropriately sized cuff. 3 measurements will be taken from the non-dominant arm after 5 minutes of quiet rest in a sitting position.

Home blood pressure will be measured by all participants. Readings will be performed in sets of three measurements, three times daily (on waking, mid-morning and before sleep) with a Bluetooth-enabled, regularly-calibrated, telemetric BP monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT. Participants will be asked to relax in a chair for 5 minutes before performing readings in the non-dominant arm, or the arm with the higher reading if the mean SBP differed by >20mmHg between arms, and are trained and assessed at doing so at the assessment clinic. Anonymised measures are transmitted by Bluetooth radio to a mobile phone, for secure transmission to a server hosting a password-protected website for daily review and download of readings (t+ Medical, Abingdon, UK).

At baseline and the 1 month follow-up visit, ambulatory blood pressure monitoring (ABPM) will be performed with an A&D TM-2430 monitor in the non-dominant arm, fitted by a trained study nurse, at 30 minutes intervals during the day and 60 minute intervals at night. During a reading, participants will be asked to sit down and refrain from excessive activity if possible and are asked to keep a diary of the day. Participants are instructed in how to

operate the monitor, and to switch the monitor off. Currently ABPM is only performed at 1 month as part of OXVASC.

Physiological Testing

The physiological measurements will be performed at each clinic visit and take approximately 30 minutes to perform. Currently, transcranial Doppler ultrasound is performed at both ascertainment and 1 month, whilst Arteriograph measures are only performed at 1 month. All tests will be performed after at least 5 minutes of supine rest. The following tests will be performed:

Central Aortic Blood Pressure / Aortic Pulse Wave Velocity

Central aortic blood pressure and aortic pulse wave velocity will be determined with an Arteriograph.[16, 17] This records brachial arterial waveforms with a blood pressure cuff inflated to 35mmHg supra-systolic pressure for 6-8 seconds. This procedure is very similar to a normal blood pressure measurement and exposes the participants to no additional discomfort or risk. The recorded waveforms are then automatically analysed to derive central aortic blood pressure via a proprietary transfer function. Aortic pulse wave velocity is estimated from the interval between the forward travelling aortic waveform and its reflection from the aortic bifurcation, both waves being recordable at the brachial artery. This time period is divided by the aortic length, estimated by the symphisis-sternal notch length. Augmentation index (AI_x) quantifies augmentation of central aortic pressure (due to the reflected component of the pressure waveform) and typically increases with age as the arteries become stiffer (or less compliant).[18] AI_x is calculated as the difference between the second (P2) and first systolic peak pressure (P1), expressed as percentage of the central pulse pressure (PP): AI_x (%) = ((P2-P1)/PP)*100.

Transcranial Doppler Ultrasound (TCD)

TCD will be performed with a DiaMon 2MHz hand held probe, with spectra acquired by a DWL Doppler Box to a dedicated laptop. The M1 segment of the middle cerebral artery will be identified bilaterally via a trans-temporal bone window (anterior to the ear and above the zygoma). The M1 segment will be identified between 50-60mm depth as the segment of the artery with blood flow towards the probe, slightly superficial to a site of bifurcation into another vessel with flow away from the probe (the anterior cerebral artery), with blood flow towards the probe extending for at least 1cm within the skull. The peak, trough and mean blood flow velocities will be derived from the wave form envelope. From these measures Gosling's pulsatility index will be derived as the primary measure of cerebral pulsatility.[11]

Blood Pressure Treatment

Participants will be eligible for the study if they are hypertensive in clinic (>140/90 mmHg). Furthermore, they must not be on an ACEi or CCB and must not have a specific clinical indication for or contraindication to one of these drugs (see above). Participants on other antihypertensive medications except for renin-angiotensin receptor antagonists are eligible.

Treatment will be initiated as for the overall OXVASC study, in which drugs are openly prescribed by the study physician in the clinic, or else a prescription is sent via the post after a telephone consultation. In accordance with CAMARADES recommendations for experimental stroke studies, drug allocation will be carried out by randomised allocation, stratified by age and gender, by the Stroke Prevention Unit statistician (ZM), who will be blinded to clinical details except for age and gender. Participants will be allocated to either perindopril arginine 5mg or amlodipine 5mg, with titration to 10mg of each drug if normotension (mean <130/80) is not achieved after 1 week of home monitoring. As for the OXVASC study, the patient's GP will be informed regarding the prescribed treatment.

Participants will continue on the higher dose of the drug (or the lower dose if normotensive at 1 week) until the one month clinic appointment. However, in the case of significant side-effects on the lower dose of the drug requiring its cessation, or excessively low BP (20% of readings <90/60mmHg), then the drug will be stopped and the patient will be excluded from the physiologically substudy at that point. However, they will then continue monitoring as

part of the overall OXVASC study. If the blood pressure remains excessively high and further treatment is clinically indicated prior to one month (mean or 50% of readings >160/100 or frequent readings >180/110), then the addition of indapamide 2.5mg will be recommended unless contraindicated. If at one month the patient is still hypertensive (BP >130/80) then the patient will continue to monitor as part of the overall OXVASC study, with antihypertensive treatment at the physician's discretion.

Randomisation
Random allocation will be performed stratified by age (into <50, 50-65, 65-80 and >80 groups) and gender. The allocation procedure will be performed by a random computerised allocation method using in-house software, carried out by members of the Stroke Prevention Research Unit who are blinded to clinical data.

Summary of additional procedures
As part of this study, most procedures are already carried out within the Oxford vascular study. No additional visits to the hospital will be required for the study, but a study nurse will make one additional visit to the participant's home to retrieve the 24 hour blood pressure monitor. In addition to the standard procedures carried out as part of OXVASC, participants will also undergo measurement of arterial stiffness with the Arteriograph at baseline, and an additional 24 ambulatory blood pressure monitor. Finally, choice of antihypertensive for participants will be determined by computer-assisted randomisation between amlodipine and perindopril, as opposed to the choice being determined by the treating physician. No other procedures or interventions in addition to those performed as part of OXVASC are required.

Potential risks and Adverse Events
Both medications used in this study are recommended as part of national guidelines for use in this patient group for the indications stated in this study, without a definitive preference for either agent. They are both very well-tolerated, with limited side-effects and an overall net benefit for use in this patient group.[19]
Risk of side-effects: The most common side-effects of amlodipine include postural dizziness, ankle oedema, flushing and headache. The most common side-effects of perindopril include postural dizziness, dry cough and sleep disturbance. Rare but more serious potential complications of treatment include heart failure with amlodipine and renal impairment or angioedema with perindopril arginine. In addition, there is a very low risk of idiosyncratic allergic reactions to either agent. To reduce the likelihood of serious complications, subjects at risk of heart failure or renal failure will be excluded. Secondly, participants will be warned of the above possible side-effects prior to consenting to the study, and will be provided with a telephone number to contact the study investigators directly if they experience them, and if necessary will be reviewed immediately.
BP monitoring, cerebrovascular pulsatility and assessment of aortic stiffness and central aortic blood pressure consist of standard BP measurement methods and transcranial Doppler ultrasound, neither of which pose any additional risk to participants.

Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,

- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events.*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to participant would be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was: 'related' – that is, it resulted from administration of any of the research procedures; and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs would be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form. Only events occurring during the first month of treatment, prior to the 1 month follow up clinic will be deemed eligible to be SAEs. In addition, the CI will report any related and unexpected SAE's to the MHRA using the Yellow Card System and to the Sponsor.

Confidentiality and Data Protection

All participants will be participants of the Oxford Vascular Study and will be allocated a unique ID number associated with this study. Their full clinical details are retained as part of the OXVASC study within the premises of the Stroke Prevention Research Unit, except when required as part of the patient's clinical care. Any further use of data for analysis both within the unit or outside of the unit will use data only identifiable by this unique ID number and date of birth. Responsible members of the University of Oxford or the Oxford University Hospitals NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

Research data will be stored on the University of Oxford Network, and physiological data is acquired with the use of laptops for both transcranial doppler ultrasound and Arteriograph measures. These password-protected laptops are retained within the Laboratory. Finally, all participants in OXVASC have a paper file, also retained in secure storage within the University Department of Clinical Neurosciences.

As part of the ongoing Oxford Vascular Study, telemetric Bluetooth-enabled home blood pressure monitoring involves the transmission of encrypted and anonymised blood pressure readings over a data-only mobile telephone connection. Also as part of OXVASC, patients provide details of personal contact information, and 24 hour ambulatory blood pressure machines are often fitted or collected at an individuals home.

Statistical Analysis

BP variability on monitoring: The 2nd two readings of each set of three readings will be averaged to determine the point estimate of blood pressure at each time of day. The standard deviation (SD), coefficient of variation (SD/mean) and residual coefficient of variation about a 3 day moving average will be calculated for the first seven days compared to the last 7 days of home monitoring, for all measures and at each time of day. The same

indices will be determined for the awake and asleep periods of ambulatory blood pressure monitoring.

Assessment of arterial stiffness: The Arteriograph provides automated analysis of aortic pulse wave velocity, central aortic BP and augmentation index. Middle cerebral artery TCD measures will be determined from measurement with the proprietary QL software.
The primary analysis for this study will be a general linear model to determine predictors of the percentage change in home BP variability from baseline to follow-up. Independent predictors will include change in cerebral pulsatility, central aortic pulse pressure and aortic stiffness and drug allocation, with and without interaction terms between drug allocation and the other three primary indices, individually and in a combined model. Models will be analysed both unadjusted and adjusted for age, gender and significant cardiovascular risk factors. Secondary analyses will be paired analyses comparing baseline and follow readings for each of the four primary measures (BP variability, cerebral pulsatility, aortic blood pressure and aortic stiffness), by drug class allocation.

Power Calculation
No evidence for the relationship between home BP variability and the physiological parameters in this study has been published, so no accurate power calculation can be determined based upon BP variability. However, the association between central aortic pulse pressure and cerebral pulsatility, (the physiological measures most likely to be related to BP variability) was measured in our previous study.[11] To have 80% power of replicating this association in each of the groups assigned a specific drug would require 25 participants per group at a 0.05 level of significance.

Funding
This study will be funded through the Oxford Biomedical Research Centre and via a Clinical Research Training Fellowship award to AW

Insurance and Indemnity
Negligent harm:
The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor.
NHS indemnity operates in respect of the clinical treatment which is provided.

Non-negligent harm:
The University has arrangements in place to provide for non-negligent harm arising from participation in the study for which the University is the Research Sponsor.

Publication Policy
The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was Funded by the Oxford Biomedical Research Council and a Medical Research Council Clinical Fellowship. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Participants are continued to be followed-up for 10 years as part of the Oxford Vascular Study. Any participants in this Physiological Study will therefore be informed of the results at the appropriate follow-up.

Conflict of Interest
There are no declared conflicts of interest for any author.

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