BLOOD PRESSURE VARIABILITY FOLLOWING ISCHAEMIC STROKE

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Abstract

Variability in blood pressure (BP) may influence ischaemic stroke outcomes in addition to mean BP. However, how best to measure BP variability (BPV) and whether different measurements are equivalent is unknown, as is whether treatment can reduce BPV. This thesis aimed to investigate relationships between BP and BPV measurements from different devices in patients with ischaemic cerebrovascular disease, relationships between BPV and stroke severity, and whether antihypertensive medications can reduce BPV.

Three trials that recruited patients following an ischaemic cerebrovascular event provided data. Correlations and limits of agreement between mean BP and BPV from different measurement devices were assessed. Relationships between baseline BPV and stroke severity were investigated, along with differences in baseline BPV in those treated with calcium channel blockers (CCB) or renin-angiotensin system inhibitors. A feasibility trial was developed to compare the effects of these medication classes on reduction of BPV post stroke.

BP from daytime ambulatory monitoring was significantly lower than home BP monitoring and BPV values from different devices were unrelated. There was an inverse relationship between baseline BPV and stroke severity, with BPV increased in lacunar infarction. There was no difference in baseline BPV with the medication regimens specified above. Recruitment to the feasibility trial was insufficient due to patient ineligibility, but a reduction in BPV over three month follow-up was demonstrated.

In patients with ischaemic cerebrovascular disease, BP and BPV recorded using different devices are not equivalent. Work to standardise BPV measurement and establish if any method is clinically superior is required. Treatment to reduce BPV may particularly benefit certain stroke patients, yet establishing that it is possible to target BPV, and doing so improves outcomes, is prerequisite. The feasibility trial in this thesis requires modification to be scaled up, but a definitive trial could be successful if recruitment were improved.

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List of Abbreviations

95% CI	95% Confidence interval
AAMI	Association for the Advancement of Medical Instruments
ABPM	Ambulatory blood pressure measurement
ACCESS	Acute Candesartan Cilexitil Therapy in Stroke Survivors (trial)
ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AHA	American Heart Association
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (trial)
ARB	Angiotensin receptor blocker
ARV	Average real variability
ASA	American Stroke Association
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm
ASV	Average successive variation
ATACH-2	Antihypertensive Treatment of Acute Cerebral Hemorrhage (trial, second)
BHS	British Hypertension Society
BMI	Body mass index
BP	Blood pressure
BPV	Blood pressure variability
BRS	Baroreceptor sensitivity
CATIS	China Antihypertensive Trial in Acute Ischemic Stroke
CBF	Cerebral blood flow
CBPM	Clinic blood pressure measurement
CCB	Calcium channel blocker
c-fPWV	Carotid-femoral pulse wave velocity
CHHIPS	Controlling Hypertension and Hypotension Immediately Post-Stroke (trial)
CT	Computed tomography

CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
END	Early neurological deterioration
ENOS	Efficacy of Nitric Oxide in Stroke (trial)
ESH	European Society of Hypertension
ESPS-1	European Stroke Prevention Study
GP	General Practitioner
GTN	Glyceryl trinitrate
HBPM	Home blood pressure measurement
HDFP	Hypertension Detection and Follow-up Program(trial)
HOMED-BP	Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (trial)
HR	Hazard ratio
HRV	Heart rate variability
ICH	Intracerebral haemorrhage
ICH-ADAPT	Intracerebral Haemorrhage Acutely Decreasing Arterial Pressure Trial
IHD	Ischaemic heart disease
INTERACT	Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (first)
INTERACT-2	Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (second)
IST-3	Third International Stroke Trial
LACS	Lacunar stroke
LIFE	Losartan Intervention For Endpoint reduction in hypertension (trial)
MAP	Mean arterial pressure
MH	Masked hypertension
MI	Myocardial infarction
MiND-B	Motor Neuron Disease Behavioural Instrument
MMD	Maximum-minimum difference
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council (trial)
MRI	Magnetic resonance imaging

mRS	Modified Rankin score
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NNUH	Norfolk and Norwich University Hospital
OCSP	Oxford Community Stroke Project classification
OR	Odds ratio
PACS	Partial anterior circulation stroke
PATS	Post-stroke Antihypertensive Treatment Study
POCS	Posterior circulation stroke
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
RCT	Randomised controlled trial
RR	Relative risk
SBP	Systolic blood pressure
SCAST	Scandinavian Candesartan Acute Stroke Trial
SD	Standard deviation
SHEP	Systolic Hypertension in the Elderly Program(trial)
SITS-ISTR	Safe Implementation of Thrombolysis in Stroke – International Stroke Thrombolysis Register
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes (trial)
TACS	Total anterior circulation stroke
TIA	Transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VA	Veterans Association
VIM	Variation independent of the mean
WCH	White coat hypertension
WHO	World Health Organisation
X-CELLENT	Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (trial)

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1 Introduction

Stroke is an important health issue both globally and in the UK [1, 2]. The last 20-30 years have seen several major advances in stroke care, such as the creation of specialist stroke units and the development of acute reperfusion treatment strategies [3-5]. However, in spite of these developments stroke remains a major cause of morbidity and mortality [2, 6]. Raised blood pressure (BP) is recognised to be one of the major modifiable risk factors for stroke, with extensive evidence demonstrating that treatment aimed at reducing BP confers a reduced risk of both first episode and recurrent stroke [7, 8]. Furthermore, it is suggested that the relationship between BP and cardiovascular risk is linear (at least to a lower threshold of 115/75mmHg) [9], but with regard to stroke the relationship may not be this straightforward.

Raised BP (>140/90mmHg) is frequently demonstrated in the hours to days following a cerebrovascular event [10], yet usually falls without specific intervention in the subsequent days to weeks [11]. The exact mechanism underlying this observation is uncertain and it is likely a multifactorial process. Interestingly, trials that have investigated intervening to reduce BP in the acute phase of ischaemic stroke have not demonstrated any benefit from such intervention in terms of mortality or stroke recovery, with limited data suggesting that doing so may be harmful [11]. This observation may relate to one of the proposed mechanisms underlying the rise in BP seen in acute stroke. Cerebral autoregulation allows the adjustment of cerebral blood flow (CBF) to match metabolic demand [12]. However, cerebral autoregulation is dysfunctional following stroke [13], leading to an increased dependence on systemic BP for the maintenance of adequate CBF. In this context it could be hypothesised that rapid changes in systemic BP levels (i.e. BP variability (BPV)), rather than simply the absolute BP level, may be the most important factor.

There is a growing body of evidence examining the prognostic importance of BPV, with the majority of data suggesting that increased BPV is an independent risk factor for cardiovascular death, coronary heart disease events, and stroke events in addition to mean BP [14]. Further work focusing on BPV following ischaemic stroke indicates associations between increased BPV and both adverse stroke outcomes [15], and the

risk of stroke recurrence [16]. However, there is inconsistency in the approach to defining BPV in the literature due to variability being measured over different timescales and calculated using multiple techniques [17]. This inconsistency is underscored by a lack of data directly comparing different measures of BPV and uncertainty regarding which is most relevant. Furthermore, much of the evidence regarding the clinical importance of BPV in relation to stroke risk and outcomes has come from post hoc analysis of existing trial data. Whilst some of this evidence suggests that it may be possible and desirable to reduce BPV in patients with stroke, this has not been adequately investigated. Consequently, the role of BPV in acute stroke and secondary prevention is a subject of current interest and debate.

The first part of this thesis will concentrate on the measurement of BPV using different techniques, and the relationships between these different techniques and durations of BP recording, in patients with a recent cerebrovascular event. In chapter four, different out-of-office BP measurement techniques will be compared for their equivalence. Chapter five will then go on to investigate differences in variability from beat-to-beat BP measurements compared with other short and medium-term variability measures. The second part of the thesis will investigate the potential of BPV as a therapeutic target following an ischaemic cerebrovascular event. In chapter six the relationships between BPV and stroke severity will be investigated and whether any subgroup of stroke patients in particular might benefit from treatment intended to reduce BPV will be discussed. Chapters seven and eight will then explore if there are differences in the effect on BPV between commonly used antihypertensive medication classes, the former using a cross-sectional analysis of trial data and the latter presenting a feasibility trial comparing two different antihypertensive medication classes.

2 Background

2.1 Stroke

2.1.1 Definition

Stroke is defined as the presence of rapidly developing focal neurological dysfunction of presumed vascular origin [18-20]. This incorporates events due to cerebral infarction (which account for over 80% of strokes), primary intracerebral haemorrhage (ICH), and subarachnoid haemorrhage [18, 21]. Historically, the definition has also included reference to symptom duration. The World Health Organisation (WHO) definition, widely used for the last 40 years, states that symptoms should persist for over 24 hours or result in death to qualify as stroke [20], with episodes of focal neurological deficit resolving before 24 hours traditionally being classified as transient ischaemic attack (TIA) [22, 23]. However, the increased use of neuroimaging in the investigation of acute stroke and TIA has challenged this notion. Firstly, although non-contrast computed tomography (CT) is highly sensitive for detecting acute haemorrhage, up to 60% of patients with cerebral infarction will have no acute ischaemic changes on imaging in the first few hours after onset [24]. Secondly, between 30-50% of patients whose symptoms resolve within 24 hours will have evidence of restricted diffusion lesions consistent with acute infarction on magnetic resonance imaging (MRI) [25]. Consequently, revised 'tissue-based' classifications of both stroke and TIA have been proposed. They define TIA as a transient episode of neurological dysfunction of vascular origin without any acute abnormality on neuroimaging [18, 23, 25], whereas stroke is an acute focal neurological deficit with radiological evidence of acute infarction or non-traumatic haemorrhage consistent with the symptoms, or a clear clinical syndrome of infarction without acutely abnormal imaging [24]. Modern definitions also acknowledge that stroke and TIA can affect the spinal cord or retina as well as cerebral tissue.

2.1.2 Epidemiology

Cerebrovascular disease is a major global health issue. Statistics from the WHO show that in 2008 30% of deaths worldwide were attributable to cardiovascular disease, of which a third were caused by cerebrovascular disease [1]. In the UK stroke is the fourth most common cause of death, accounting for 7% of deaths annually [2], with a reported age-standardised incidence of 115-160 events per 100,000 population per year [2, 26]. Over 1.2 million people are living with the effects of stroke and over 50% of stroke survivors remain dependent on others for assistance with their activities of daily living after discharge from hospital [2, 19], making it the third leading cause of disability [6]. Consequently, stroke represents a significant burden to the UK economy costing around £1.7 billion per annum to the National Health Service (NHS) directly, with additional costs, for example of lost productivity, meaning that the overall cost is nearer to £9 billion annually [2].

The epidemiology of stroke in the UK has changed in the last 40-50 years. A study of stroke incidence in Oxfordshire between 1981 and 2004 demonstrated a decline in age-specific incidence in the region of 30% [26]. However, this reduction may have plateaued, with the 2010 Global Burden of Disease Study indicating a slower decline of approximately 20% in the 20 years since 1990 and little change from 2005 to 2010 [27]. This change in incidence reflects significant reductions in major cardiovascular risk factors in the population, such as smoking rates and hypertension, driven by improvements in primary cardiovascular preventative treatments [6, 26]. Stroke mortality has also decreased, falling by around 45% from 1990 to 2013, and this is due in part to the reduced incidence [6]. However, it is also due to significant improvements in acute stroke care, including the introduction of specialist 'stroke units' for the provision of multidisciplinary care and rehabilitation [3], faster access to specialist stroke physician and therapist assessments [28], and the introduction of reperfusion therapies for acute ischaemic stroke (initially thrombolysis and more recently mechanical thrombectomy) [4, 5]. In contrast, as more people are surviving stroke, the disease prevalence has increased by around 30% during this period [27].

The successful impact of advances in acute care and primary prevention strategies are mirrored by changes in secondary prevention. Data from the Oxfordshire incidence study indicates that in stroke patients with previous TIA significantly greater proportions were on secondary prevention treatment in 2004 compared to 1981. This includes antihypertensives (around 60% compared to 35%), antiplatelets (around 60% compared to 5%), and lipid-lowering medication (around 35% compared to 0%) [26]. Estimates of the risk of recurrent stroke are lower in more recent cohorts compared to those from over 20 years ago and, whilst this may in part be attributable to methodological issues such as the definition of recurrent events, it also demonstrates the efficacy of more widespread secondary prevention [29]. Nevertheless, recurrent events remain common, with the risk of stroke in the three months following a TIA approaching 20% and roughly a 25% cumulative risk of recurrent stroke in the five years following a first event [2, 29]. Furthermore, recurrent events tend to be more severe, with a mortality rate nearly double that of first events and an increased risk of poor functional outcome at 90 days [30, 31]. As a result of this, and the fact that the reperfusion therapies are not viable for all patients with acute stroke (around 10% of patients in the UK receive thrombolysis [21, 28]), there remains room for improvement in the treatment and prevention of stroke and a need for further research to drive this improvement.

2.1.3 Pathophysiology

In cases of cerebral infarction there is vessel obstruction leading to reduced blood flow which lasts sufficiently long to cause irreversible damage. Multiple mechanisms can lead to the obstruction and can be divided according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (**Table 1**) [32]. Interruption of the blood supply results in insufficient oxygen and glucose delivery required for cell metabolism. This triggers a cascade of events, including cell membrane disruption characterised by potassium efflux and calcium influx, release of glutamate and other toxic substances (e.g. free radicals), inflammation with cytotoxic oedema, localised acidosis, and ultimately cell necrosis [33, 34]. There may be additional early or late cell damage secondary to apoptotic mechanisms triggered by inflammatory cytokines [33]. The degree of damage is dependent on the level of reduction in blood flow, with the

Table 1: Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of acute ischaemic stroke [32].

Classification	**Criteria**
Large artery atherosclerosis	Clinical findings of a cortical, brainstem, or cerebellar deficit. Normal neuroimaging/imaging showing a lesion >1.5cm in diameter consistent with symptoms. Evidence of occlusion in pre-cerebral arteries (e.g. carotid stenosis).
Cardio-embolism	As above with evidence of a high-risk source of cardio-embolism, such as atrial fibrillation or left ventricular thrombus.
Small artery occlusion (lacunar)	Clinical lacunar syndrome. Normal neuroimaging/imaging showing a subcortical lesion <1.5cm in diameter. No evidence of large vessel or cardio-embolic disease. Supported by a history of hypertension or diabetes.
Other determined cause	Other confirmed abnormality on testing, such as vasculitis or hypercoagulable state.
Undetermined cause	One of the following: • two or more causes identified; • no cause identified; • incomplete investigation.

lowest flow found in the infarcted core (which is irreversibly damaged) and higher (but still abnormal) flows in the surrounding tissue known as the ischaemic penumbra [35]. Collateral blood supply to the penumbra contributes to blood flow to this area and cells within this region, despite being dysfunctional, remain viable for a short period. Salvage of the ischaemic penumbra by restoring perfusion is a key aim in the acute treatment of ischaemic stroke.

The mechanism in ICH differs to ischaemic stroke. The most common cause of acute bleeding is rupture of a small vessel lipohyalinotic aneurysm secondary to chronic hypertensive vascular damage [34, 36, 37]. Other potential causes include, but are not limited to, chronic vascular damage due to cerebral amyloid angiopathy, structural pathologies like arteriovenous malformation, cavernous haemangioma, or saccular aneurysm, and the use of anticoagulant medications [37]. Following the acute bleed there is a similar inflammatory and cytotoxic cascade as in ischaemic stroke, but the mechanical impact of tissue oedema and the developing haematoma is probably the greater source of neuronal damage. Whether there is salvageable penumbral tissue in ICH is debated [37]. Currently the immediate goals of treatment are to arrest the bleeding and reduce haematoma expansion.

2.2 The Relationship between Stroke and Blood Pressure

2.2.1 Historical Aspects

Hypertension has been recognised as a risk factor for cardiovascular disease for almost 100 years, yet the medical community did not immediately accept the necessity of its treatment. Shortly after the development of the sphygmomanometer in the late 19th century American insurance companies began including BP measurement in their assessments [38]. By the mid-1920's they had published reports that linked above average BP values with an increased risk of death. In 1928 the term 'malignant hypertension' was coined for a syndrome of very high BP (>200/100mmHg) and retinopathy which was noted to lead to death within months from heart failure, stroke or kidney failure unless treatment to lower BP was instigated [39]. However, it would

be another 30 years before attitudes to the treatment of so-called 'benign hypertension' would comprehensively shift. A key event in this process was the discovery of chlorothiazide in the late 1950's [40]. This was the first effective oral antihypertensive not hampered by excessive side effects and its discovery started to shift the risk-benefit balance in favour of treatment. The second key event was the publication, beginning with reports from the Framingham Heart Study [41], of robust observational data demonstrating a strong correlation between raised BP and subsequent complications such as heart disease, stroke, and kidney failure.

2.2.2 Primary Prevention - Observational Studies

The observational evidence linking hypertension to cardiovascular disease is now substantial and the consistency of the evidence strongly suggests a causal relationship. Pooled analysis of the data, amounting to over 400,000 participants with an average follow-up period of 10 years, demonstrated that in patients with no previous history of cardiovascular disease the relationship between BP and cardiovascular risk is direct, continuous and linear [9]. Further pooled analysis incorporating additional data amounting to nearly one million participants corroborated this [42]. The relationship is stronger for stroke than ischaemic heart disease (IHD) or other vascular disease, with a reduction in BP of 10/5mmHg conveying a reduction in first ever stroke risk of approximately 30% [9, 43]. Although it has been demonstrated that this is not consistent across age groups, with larger hazard ratios (HR) for raised BP seen in patients under 60 years old compared to those over 80 years old [42], the greater incidence of stroke in older age groups means that the absolute benefit of lowering BP in these patients is at least similar, if not greater [43]. Interestingly, there does not appear to be a threshold at which lower BP is not associated with lower cardiovascular risk, although data for BP below 115/75mmHg is limited [9, 42, 43].

2.2.3 Primary Prevention - Randomised Controlled Trials (RCT)

Building on the observational evidence, multiple large and robust RCT have confirmed that BP reduction results in a decreased primary cardiovascular risk, in particular

stroke risk. Two of the earliest landmark RCT were the Veterans Association (VA) Co-operative Study and the Hypertension Detection and Follow-up Program (HDFP) study [44]. The VA Co-operative Study was the first randomised, placebo controlled, double blind trial investigating the treatment of hypertension. 143 men with diastolic BP (DBP) between 115-129mmHg and 380 men with DBP between 90-114mmHg were randomised to treatment with hydrochlorothiazide (plus reserpine and hydralazine added stepwise if necessary) or placebo [45, 46]. For the group with severe hypertension the trial was terminated early [45]. After two years follow-up BP in the treatment group fell by 43/29.7mmHg and there were only two recorded severe complications compared to no change in BP and 27 severe complications in the placebo group. The results for the group with mild-moderate hypertension after a total of five years follow-up were also positive, but more modest [46]. These results were subsequently corroborated by the HDFP study which randomised 10,500 patients with DBP between 90-104 mmHg to stepped care or treatment as usual [47]. The stepped care group received standardised treatment (diuretic plus reserpine, hydralazine and guanethedine added in sequence if necessary) to lower DBP to <90mmHg. Deaths from cardiovascular disease were 26% lower in the intervention group, demonstrating the benefit of treating patients with mild-moderate diastolic hypertension. The Systolic Hypertension in the Elderly Program (SHEP) trial addressed the question of the importance of isolated raised systolic BP (SBP) [48]. In this study 4736 patients with SBP >160mmHg but DBP <90mmHg were randomised to treatment (chlorthalidone ± atenolol) or placebo. Although some patients in the placebo group also received antihypertensive therapy with other agents during the trial, over the five-year follow-up there was a greater reduction in SBP and a 36% lower risk of stroke in the intervention group. Systematic review of the major RCT confirms that lowering BP is beneficial for reducing the risk of primary cardiovascular disease, especially stroke (**Tables 2-3**) [7, 43, 49]. Furthermore, it is likely that BP reduction is the important factor irrespective of the particular therapy used to achieve it [43, 49], although whether antihypertensive medicines really are equivalent in relation to stroke will be discussed further in this thesis.

Table 2: Risk of stroke in selected randomised controlled trials evaluating antihypertensive medications vs. placebo [43].

Study	Treatment Arm		Placebo Arm		Relative Risk ([RR] 95% confidence interval (CI))
	Events	Total	Events	Total	
ACTION	82	3825	108	3840	0.63 (0.37 to 1.09)
ACTIVE 1	379	4518	411	4498	0.71 (0.43 to 1.19)
ADVANCE	215	5569	218	5571	0.96 (0.69 to 1.35)
ANBPS	13	1721	22	1706	0.59 (0.30 to 1.16)
Coope	20	419	39	465	0.57 (0.34 to 0.96)
EUROPA	98	6110	102	6108	0.92 (0.53 to 1.60)
EWPHE	32	416	48	424	0.68 (0.44 to 1.04)
FEVER	177	4841	251	4870	0.41 (0.23 to 0.71)
HDFP	102	5485	158	5455	0.64 (0.50 to 0.82)
HYVET	51	1933	69	1912	0.79 (0.62 to 1.00)
MRC older	101	2183	134	2213	0.76 (0.59 to 0.98)
MRC young	60	8700	109	8654	0.55 (0.40 to 0.75)
NAVIGATOR	105	4631	132	4675	0.43 (0.17 to 1.08)
PREVENT	5	417	5	408	0.98 (0.29 to 3.35)
SHEP	105	2365	162	2371	0.65 (0.51 to 0.83)
STOP H	30	812	55	815	0.55 (0.35 to 0.85)
Syst-China	45	1253	59	1141	0.63 (0.41 to 0.97)
Syst-Eur	47	2398	77	2297	0.58 (0.41 to 0.84)
TRANSCEND	112	2954	136	2972	0.63 (0.33 to 1.18)
VA	6	254	23	257	0.26 (0.11 to 0.64)

Table 3: Relative risk of stroke per 10mmHg reduction in systolic blood pressure in selected randomised controlled trials evaluating intensive vs. less intensive blood pressure targets [7].

Study	**Intensive BP Target Arm**		**Control Arm**		**Relative Risk (95% CI)**
	Events	Total	Events	Total	
ABCD-H	9	237	9	233	0.97 (0.21 to 4.35)
ACCORD	36	2362	62	2371	0.69 (0.52 to 0.92)
BBB	8	1064	11	1064	0.75 (0.33 to 1.71)
HOT	200	12,526	94	6264	1.22 (0.56 to 2.64)
JATOS	52	2212	49	2206	1.06 (0.71 to 1.58)
SPRINT	62	4678	70	4683	0.91 (0.70 to 1.19)
VALISH	16	1545	23	1534	0.49 (0.15 to 1.60)

BP denotes blood pressure; 95% CI, 95% confidence interval.

2.2.4 Secondary Prevention

It is reported that 50-60% of strokes can be attributed to uncontrolled hypertension, making this the most important modifiable risk factor for cerebrovascular disease [49, 50]. So far I have concentrated on the primary prevention of stroke, but given that there are over 20,000 recurrent strokes annually in the UK lowering BP should also improve secondary prevention [18, 21]. This view is supported by observational data that shows an association between higher BP in the 12 months post-stroke and a greater risk of recurrence, and conversely that antihypertensive treatment is associated with lower rates of recurrence [50]. Fewer RCT have investigated BP lowering for secondary prevention, but both the Post-stroke Antihypertensive Treatment Study (PATS) and the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) demonstrated a reduced risk of recurrent stroke in the region of 30% with intervention compared to placebo [51, 52]. A recent meta-analysis of secondary prevention RCT confirmed these reports (**Table 4 and Figure 1**) and also demonstrated that intensive BP lowering is beneficial for secondary prevention [8]. Patients were stratified according to the achieved level of SBP (<130mmHg, 130-140mmHg, or >140mmHg) and DBP (<85mmHg, 85-90mmHg, or >90mmHg). The risk of recurrent stroke was smallest for those in the lowest categories of SBP and DBP, linearly increasing with achieved BP level. This analysis supports the findings of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial which was a dedicated RCT designed to assess the impact of intensive BP lowering on recurrent events after lacunar stroke in 3020 patients [53]. SPS3 reported a trend towards reduced rates of recurrent stroke in the group treated to target SBP <130mmHg, indicating that intensive BP lowering for secondary prevention is likely to be beneficial (**Figure 2**).

2.2.5 Current Guidelines

It is clear that treatment to lower BP has a beneficial effect on stroke risk (**Figure 3**) and this is reflected in guidelines, with some advocating intensive treatment to a target BP of <130/80mmHg [18, 54]. However, this is not a consensus recommendation. For example, the American Stroke Association (ASA) and the

Table 4: Risk of recurrent stroke in trials of antihypertensive medication vs. placebo. Data adapted from the meta-analysis by Katsanos et al. 2017 [8].

Study	**Treatment Arm**		**Placebo Arm**		**Risk Ratio (95% CI)**
	Events	Total	Events	Total	
Carter et al.	7	49	11	48	0.62 (0.26 to 1.47
Dutch TIA	52	732	62	741	0.85 (0.60 to 1.21
HOPE	13	500	23	513	0.58 (0.30 to 1.13)
HSCSG	37	233	42	219	0.83 (0.55 to 1.24)
Liu et al.	67	762	147	758	0.45 (0.35 to 0.59)
Marti Masso and Lozano	20	170	18	94	0.61 (0.34 to 1.10)
PATS	159	2841	217	2824	0.73 (0.60 to 0.89)
PRoFESS	880	10146	934	10186	0.95 (0.87 to 1.03)
PROGRESS	307	3051	420	3054	0.73 (0.64 to 0.84)
SCOPE	5	97	14	97	0.36 (0.13 to 0.95)
TEST	74	372	69	348	1.00 (0.75 to 1.35)
Total	**1621**	**18953**	**1957**	**18882**	**0.73 (0.62 to 0.87)**

95% CI denotes 95% confidence interval.

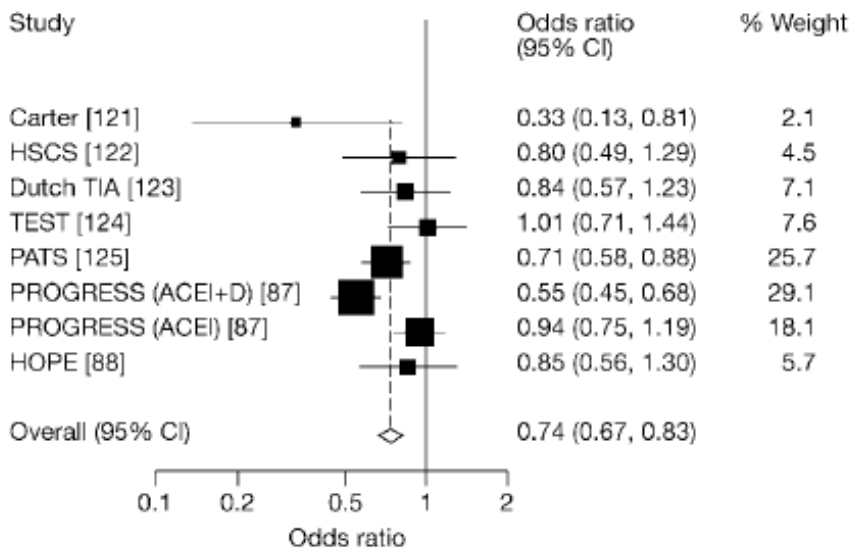

Figure 1: Meta-analysis of the effects of antihypertensive therapy following stroke on the risk of fatal and non-fatal recurrence [10].

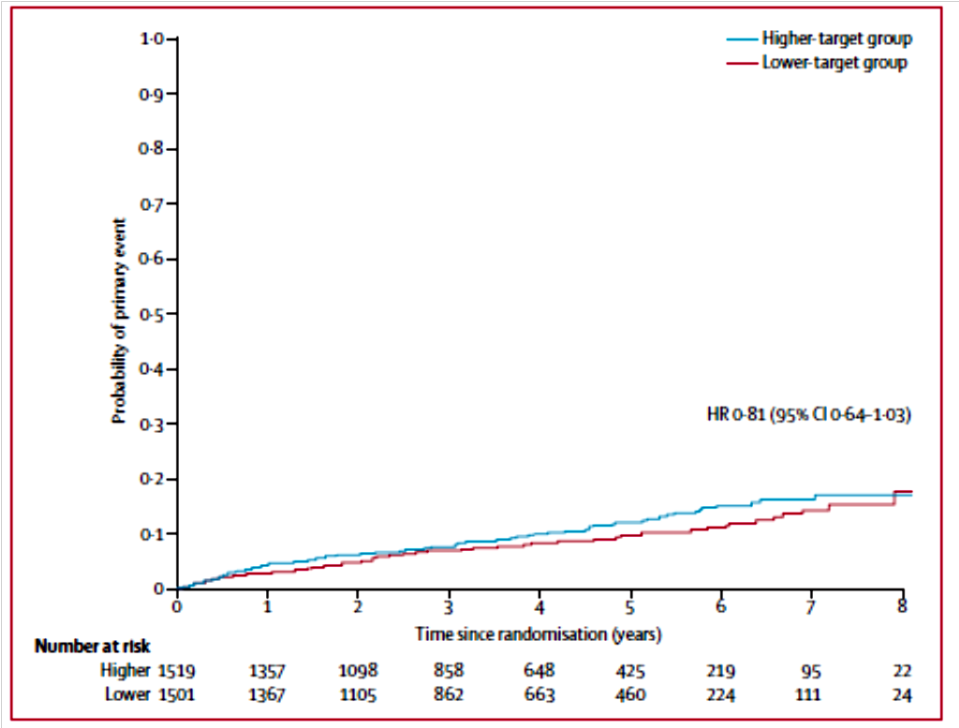

Figure 2: Probability of recurrent stroke, myocardial infarction (MI), or vascular death after randomisation in the intensive blood pressure target and standard blood pressure target arms of SPS3 [53].

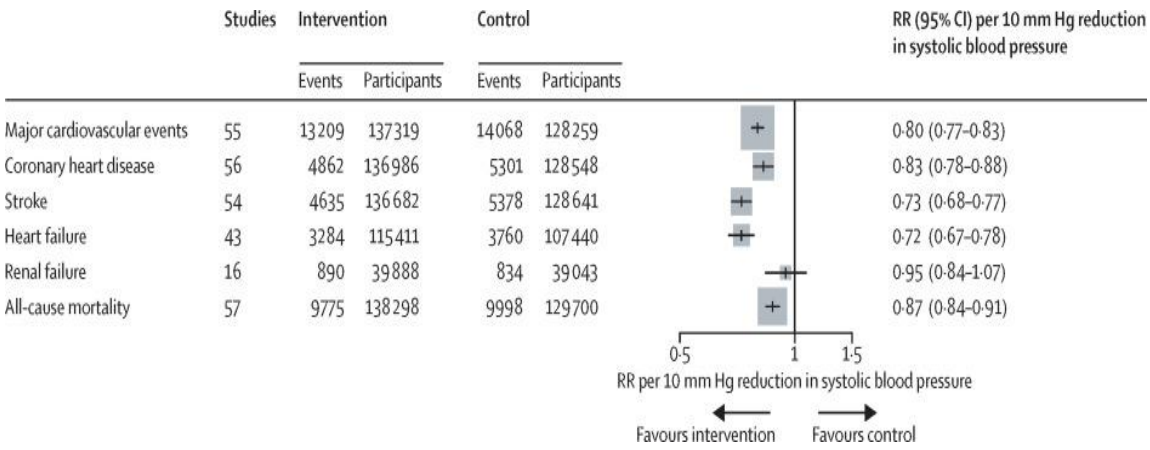

Figure 3: Standardised effects of a 10mmHg reduction in systolic blood pressure on cardiovascular outcomes incorporating data from primary and secondary prevention trials, and trials of intensive blood pressure lowering. Adapted from Ettehad et al. 2016 [7]. RR denotes relative risk; 95% CI, 95% confidence interval.

European Society of Hypertension (ESH) are more cautious. Firstly, they note that trials drawing conclusions about intensive BP targets have not always successfully lowered BP beyond standard recommendations [55]. However, this criticism is not true of more recent trials, including SPS3 and the Systolic Blood Pressure Intervention Trial (SPRINT), which both achieved their pre-stated intensive BP reduction, and successfully showed an associated reduction in cardiovascular events and mortality [53, 56]. Secondly, the ASA and ESH cite a post-hoc analysis of PROGRESS which suggested that the effectiveness of secondary prevention diminished in line with baseline BP level, such that participants with baseline SBP <120mmHg gained no additional benefit from antihypertensive therapy [55, 57]. However, a meta-analysis of the benefit of antihypertensive treatment stratified by baseline BP level, incorporating a mixture of low and high-risk hypertensive subjects, contradicts this position [58]. This uncertainty relates to the debate about whether the relationship between BP and secondary stroke risk is linear or 'J' shaped, the latter implying that overly aggressive BP reduction could be harmful [59]. This idea has some logical basis given that autoregulatory mechanisms to maintain organ perfusion have both a lower and higher functional limit and that these limits can shift in the presence of chronic vascular disease [60, 61]. Further research into these issues is required and dedicated ongoing trials, such as the Stroke in Hypertension Optimal Treatment trial (ESH-CHL-SHOT [62]), should help to establish the optimum BP target for secondary stroke prevention.

2.3 Blood Pressure in the Acute Phase of Stroke

2.3.1 The Acute Hypertensive Response

It is common for patients with an acute stroke (either infarct or ICH) to have BP >140/90mmHg, with between 60-84% of acute stroke patients found to have BP above this threshold within 24 hours of symptom onset [10, 63, 64]. Similar rates are reported for patients with acute TIA [65]. Only around half of these patients will be known to have hypertension prior to their cerebrovascular event [10, 11], leading to the hypothesis that there is an 'acute hypertensive response' related to stroke and TIA. Whilst the natural history of raised BP in TIA has not been reported, observational data

in stroke patients demonstrates that this acutely raised BP can decline without specific treatment from around 24 hours to 14 days post-event [11, 63, 66]. This suggests a possible stroke specific cause for the observed pattern. Multiple potential mechanisms have been suggested, including haematoma expansion in ICH, cerebral oedema and raised intracranial pressure, autonomic dysfunction, and abnormal cerebral autoregulation [11, 13, 63, 67, 68]. Perhaps the most important of these in ischaemic stroke is the latter. As a consequence of disordered cerebral autoregulation, CBF becomes dependent on systemic BP and therefore raised BP may be necessary to maintain perfusion of the ischaemic penumbra, with low BP potentially causing cerebral hypoperfusion and infarct expansion. This idea is supported by a meta-analysis of observational studies investigating the prognostic impact of raised BP in acute stroke that demonstrated raised BP is associated with worse outcomes (either death or dependency) [69]. Retrospective review of data from the International Stroke Trial corroborated this conclusion and additionally showed that low BP is also a poor prognostic factor [70]. Consequently, the management of BP in the acute phase of stroke is of clinical interest as appropriate therapeutic intervention could potentially improve outcomes for stroke survivors.

2.3.2 Management in Patients Receiving Thrombolysis

For patients who receive thrombolysis raised BP can increase the risk of haemorrhage as a treatment complication. Retrospective review of the Third International Stroke Trial (IST-3) data showed that a higher baseline BP was associated with an increased risk of any early adverse event with an odds ratio (OR) of 1.05 (95% CI 1.01 to 1.09, p=0.01) [71]. This was primarily driven by an increased risk of symptomatic ICH (OR 1.10 [95% CI 1.02 to 1.19, p=0.01]), which was the only other statistically significant association. Similarly, retrospective review of the Safe Implementation of Thrombolysis in Stroke – International Stroke Thrombolysis Register (SITS-ISTR) found that increased BP (measured at baseline, 2 hours post-onset and 24 hours post-onset) was linearly associated with an increased risk of symptomatic ICH. Furthermore, they reported a ‘U’ shaped relationship between BP level and mortality and 3 month independence [64]. As a result of this it is accepted that BP should be lowered to ≤185/110mmHg (the upper BP threshold required for inclusion in the first National Institute of Neurological

Disorders and Stroke (NINDS) trial) prior to administering thrombolysis and this is recommended in stroke guidelines [18, 19, 57]. However, whether to lower BP in patients not eligible for thrombolysis, and if so to what target level, is controversial.

2.3.3 Management in Patients not Receiving Thrombolysis

Interestingly, in their review of IST-3 Berge et al. observed that receiving BP lowering treatment in the first 24 hours after randomisation to thrombolysis or control resulted in a reduced risk of poor functional outcome at six months, irrespective of whether the patient received alteplase or placebo (OR 0.78 [95% CI 0.65-0.93, p=0.007]) [71]. The decision to give BP lowering treatment was according to local protocols. Participants receiving antihypertensives had a higher mean baseline SBP (159.7mmHg compared to 152.5mmHg), but after 24 hours mean SBP in the groups had converged (147.8 mmHg with treatment and 144.1mmHg without). BP lowering treatment was also not associated with the development of early neurological deterioration (END) or early recurrent ischaemic stroke. However, these findings have not been replicated in RCT specifically designed to investigate the effect of lowering BP in the acute phase of ischaemic stroke (**Table 5**).

Of the large dedicated trials the Acute Candesartan Cilexitil Therapy in Stroke Survivors (ACCESS) trial was the first, enrolling patients with ischaemic stroke and BP >200/110mmHg within 6-24 hours after admission (or >180/105mmHg 24-36 hours after admission) [72]. The trial was stopped early due to an increased mortality rate at 12 months in the placebo group. However, BP was not significantly lowered by the intervention compared to control and mortality at 12 months was a secondary outcome. Neither of the pre-specified primary outcomes (mortality or functional status at three months) were reported, partly due to the recognition that the Barthel Index was not a suitable measure of functional outcome. In the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) trial 179 patients with any stroke and SBP >160mmHg were randomised within 36 hours of symptom onset to labetalol, lisinopril or placebo [66]. There was no difference in the primary outcome of death or dependency (defined as a modified Rankin score (mRS) >3) at 14 days (RR 1.03 [95% CI 0.80 to 1.33, p=0.82]) despite a definite reduction in SBP (21mmHg with intervention

Table 5: Summary of main published trials of blood pressure lowering treatment in acute ischaemic stroke. Outcome figures presented are mean (standard deviation (SD)) or risk (95% CI).

Trial	N	Intervention	Control	Treatment duration	ICH eligible	Outcome
Bath 2000 [73]	37	GTN patch within 5 days of onset	Placebo	12 days	Yes	Day 1 BP reduction: 13.0/5.2mmHg with intervention
ACCESS 2003 [72]	339	Candesartan, commenced 24-36 hours after onset	Placebo	7 days	No	Barthel index at 3 months: 87.0 (22.9) vs. 88.9 (19.9)
Eames 2005 [74]	37	Bendroflumethiazide within 96 hours of onset	Placebo	7 days	No	BP at 7 days: No significant differences
Eveson 2007 [75]	40	Lisinopril within 24 hours of onset	Placebo	14 days	No	Change in NIHSS[1] at 14 days: No significant differences
CHHIPS 2009 [66]	179	Labetalol or Lisinopril within 36 hours of onset	Placebo	14 days	Yes	mRS ≥4 at 2 weeks RR 1.03 (0.80 to 1.33)*
PRoFESS 2009 [76]	1360	Telmisartan within 72 hours of onset	Placebo	2.5 years	No	mRS at 30 days: OR 1.03 (0.84 to 1.26)
SCAST 2011 [77]	2029	Candesartan within 30 hours of onset	Placebo	7 days	Yes	a) death/recurrent stroke or MI: HR 1.09 (0.84 to 1.41)

						b) mRS at 6 months: OR 1.13 (0.97 to 1.32)
CATIS 2013 [78]	4071	Any treatment within 48 hours of onset to achieve BP <140/90mmHg	Not treated	14 days	No	mRS ≥3 at 14 days or hospital discharge: OR 1.00 (0.88 to 1.14)
RIGHT 2013 [79]	41	GTN patch within 4 hours of onset	No GTN	Single dose	Yes	Difference in SBP at 2 hours: -18 (30) mmHg with intervention
ENOS 2014 [80]	4011	GTN patch within 48 hours of onset	No GTN	7 days	Yes	mRS at 90 days: OR 1.01 (0.91 to 1.13)

[1]National Institutes of Health Stroke Scale (NIHSS)

*combined active treatment groups vs. placebo

BP denotes blood pressure; ICH, intracerebral haemorrhage; GTN, Glyceryl trinitrate; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin score; MI, myocardial infarction; SBP, systolic blood pressure.

vs. 11mmHg with placebo, p=0.04), though the trial did not meet its recruitment target. The Scandinavian Candesartan Acute Stroke Trial (SCAST) employed a similar study design to ACCESS, but with a lower threshold BP for inclusion [77]. Two thousand twenty-nine patients with any stroke within 30 hours of symptom onset and with SBP >140mmHg were randomised to candesartan or placebo. After seven days of treatment mean BP in the intervention group was 5/2mmHg lower. However, this difference was not sustained at the six month outcome point, nor was there any difference in composite vascular death/non-fatal myocardial infarction (MI)/non-fatal stroke (HR 1.09 [95% CI 0.84 to 1.41, p=0.52]). In fact there was a non-significant trend towards better six month functional outcome with placebo (OR 1.17 [95% CI 1.00 to 1.38, p=0.048]). The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) investigated an intensive BP target rather than a specified treatment [78], enrolling 4071 ischaemic stroke patients with SBP 140-220mmHg within 48 hours of onset. Those in the intervention arm had a greater BP reduction in the first 24 hours with the difference sustained at seven days. Despite this, there was no difference in the primary outcome of death or disability (mRS ≥3) at 14 days, nor was there any difference at three months. Finally, the Efficacy of Nitric Oxide in Stroke (ENOS) trial investigated glyceryl trinitrate (GTN) as the therapeutic agent [80]. GTN is a nitric oxide donor which, as well as having BP lowering properties, may be neuroprotective and inhibit apoptosis, thereby reducing ischaemic damage. The trial enrolled 4011 patients with any stroke within 48 hours of symptom onset and randomised them to transdermal GTN or placebo. As with other trials there was a greater BP reduction with intervention but this did not translate to a difference in functional outcome (assessed as the distribution of mRS at 90 days). Systematic review of these and additional studies, including a total of 17,011 patients, has confirmed the findings of the individual trials [11].

Overall, there is no evidence of benefit for lowering BP in hyperacute ischaemic stroke and the data from SCAST suggests it may actually be harmful to do so. However, this may relate to methodological factors, specifically the timing of treatment initiation. Whilst subgroup analysis in CATIS suggested a possible improvement in functional outcome in those who commenced treatment >24 hours after symptom onset [78],

several trials have shown the opposite. In SCAST there was a non-significant finding that those who received treatment <6 hours after symptom onset had an improved functional outcome [77]. This was also reported as a statistically significant finding in ENOS, where it was a pre-specified secondary outcome [80]. Furthermore, a pilot trial for transdermal GTN administered within four hours of stroke onset reported a one point favourable shift in mRS at 3 months in the intervention group [79]. Although the trial was not powered for this outcome it is a potentially important finding that is being further investigated [81]. It is also interesting to note that larger BP reductions have been achieved with earlier treatment initiation (mean reduction -16.0/-15.0mmHg for patients receiving pre-hospital treatment compared to -7.3/-4.9mmHg for those commencing treatment >48 hours after onset) and this may underlie the differences in reported outcomes [11].

2.3.4 Management in Patients with Intracerebral Haemorrhage

It is also hypothesised that stroke subtype may be a relevant factor in the acute treatment of raised BP. Hypertension is the major risk factor for primary ICH. Chronic hypertension is associated with degenerative changes to penetrating arterioles that can lead to vessel rupture and haemorrhage, such as lypohyalinosis and Bouchard aneurysm formation [36, 37]. Two theories about the risk related to BP immediately following ICH have been proposed. Firstly, raised BP may inhibit haemostasis and propagate haematoma expansion. Secondly, as in ischaemic stroke, there may be a peri-haematomal penumbra that is vulnerable to low BP [82]. The first theory is supported by the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) which showed less haematoma expansion 24 hours after symptom onset with intensive management of BP (target of SBP <140mmHg) compared to standard management (target SBP of <180mmHg) [83]. However, the idea of a vulnerable peri-haematomal penumbra is not supported by data from the Intracerebral Haemorrhage Acutely Decreasing Arterial Pressure Trial (ICH-ADAPT). Using CT perfusion imaging this trial demonstrated that relative CBF in the peri-haematomal region is not reduced with intensive BP reduction (SBP <150mmHg) compared to standard management (SBP <180mmHg) [84]. Trials of intensive vs. standard BP reduction in acute primary ICH are summarised in **Table 6**.

Table 6: Summary of published trials of intensive blood pressure reduction compared to standard blood pressure lowering (according to guideline recommendations) in acute intracerebral haemorrhage.

Trial	N	Recruitment window	SBP targets (mmHg)*	Primary outcome	Result
Koch 2008 [85]	42	<8 hours	<110 vs. 110-130	END (NIHSS drop ≥2 within 48 hours)	No significant difference
INTERACT 2008 [83]	404	<6 hours	<140 vs. <180	Haematoma growth at 24 hours	13.7% vs. 36.3% (p=0.04)
ICH-ADAPT 2013 [84]	75	<24 hours	<150 vs. <180	Perihaematoma relative CBF at 2 hours	0.86 vs. 0.89 (p=0.18)
INTERACT-2 2013 [86]	2839	<6 hours	<140 vs. <180	mRS ≥3 at 3 months	OR 0.87 (0.75 to 1.01), p=0.06
ATACH-2 2016 [87]	1000	<4.5 hours	110-139 vs. 140-179	mRS ≥4 at 3 months	RR 1.04 (95% CI 0.85 to 1.27), p=0.72

*Mean arterial pressure (MAP) in Koch, SBP all other trials

SBP denotes systolic blood pressure; END, early neurological deterioration; NIHSS, National Institutes of Health Stroke Scale; CBF, cerebral blood flow; mRS, modified Rankin score; OR, odds ratio; RR, relative risk; 95% CI, 95% confidence interval.

The two major trials (The second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT-2) and the second Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-2)) both failed to show a benefit to morbidity and mortality (defined as mRS ≥3 or ≥4 respectively) at three months with intensive BP lowering compared to standard management [86, 87]. However, in a pre-specified secondary outcome, INTERACT-2 did demonstrate a significant favourable shift in mRS with intensive BP lowering, suggesting a benefit in terms of functional outcome for survivors (OR 0.87 [95% CI 0.77 to 1.00, p=0.04]) [86].

2.3.5 Guideline Recommendations

Current stroke guidelines reflect the uncertainty in the evidence base. For ischaemic stroke the recommendations for patients receiving thrombolysis have already been described, but for all other patients it is felt that BP lowering treatment should only be started in the first 24 hours after stroke onset if there is a hypertensive emergency with organ damage [18, 19, 57]. Only the ASA specifically mentions an upper BP threshold (220/120mmHg) [57]. For patients with ICH it is felt to be safe, and possibly beneficial, to aim for intensive BP reduction to a target SBP <140mmHg, provided that treatment can be instigated within six hours [18, 88]. Rather than the lack of evidence being related to the timing of initiation of treatment, an alternative explanation may be that it is not just the absolute BP level that matters in the acute phase of stroke. This will be discussed further in subsequent sections of this thesis where I will consider the concept of BPV and its relationship with stroke outcomes.

2.4 Blood Pressure Monitoring

2.4.1 Office Measurement

Controlling BP for primary and secondary stroke prevention relies on being able to accurately measure BP levels and establishing at what level BP treatment is of benefit. Whilst distinguishing normotension and hypertension with a specific threshold value is somewhat arbitrary due to the normal distribution of BP within the population and the continuous relationship between BP and cardiovascular risk, such categorisations are clinically useful. Based on the evidence from major trials SBP >140mmHg and/or DBP >90mmHg has traditionally been accepted as the point at which treatment benefits significantly outweigh any risks. However, the 2017 American Heart Association (AHA) guidelines recommend a lower threshold, citing recent evidence from observational studies demonstrating increased risks of stroke and coronary heart disease at BP levels between 120-139/80-89mmHg [54]. Currently recommended threshold values for clinic and out-of-office BP measurement methods are presented in **Tables 7-8**.

Traditionally BP measurement has been undertaken using a manual sphygmomanometer, referred to as 'office' or 'clinic' BP measurement (CBPM) [89]. To ascertain the patient's 'usual' BP repeated measurements on separate occasions are recommended as this mitigates against the natural variation in BP attributable to factors like change in circadian rhythm or seasonal variation [90]. CBPM is more complex than it may appear and its fallibility is recognised. Limitations include poor technique (e.g. not allowing the patient to rest several minutes before measuring, incorrect cuff size, not positioning the arm level with the heart), taking single measurements (often due to time constraints), observer bias, and observer terminal digit preference [89]. Furthermore, CBPM may not accurately represent the 'usual' BP in some patients. White coat hypertension (WCH) exists when the patient's office BP is consistent with a diagnosis of hypertension, yet their out-of-office BP is within the normal range. Conversely, masked hypertension (MH) is where office BP is within the normal range yet out-of-office BP is consistent with a diagnosis of hypertension. Neither of these phenomena can be identified by CBPM alone and both are important

Table 7: Definitions of normotension and hypertension based on clinic blood pressure measurement from current guidelines [54, 91, 92]. Blood pressure category is defined according to the highest value, whether systolic or diastolic.

	NICE (2011)		ESH (2018)		AHA (2017)	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Normal	<140	<90	<130	<85	<120	<80
High normal	-	-	130-139	85-89	120-129	<80
Grade 1 hypertension	≥140	≥90	140-159	90-99	130-139	80-89
Grade 2 hypertension	≥160	≥100	160-179	100-109	140-159	90-99
Grade 3 hypertension	≥180	≥110	≥180	≥110	≥160	≥100

SBP denotes systolic blood pressure; DBP, diastolic blood pressure; NICE, National Institute for Health and Care Excellence; ESH, European Society of Hypertension; AHA, American Hypertension Association.

Table 8: Threshold values for grade 1 hypertension based on out-of-office blood pressure measurements from current guidelines [54, 91, 92].

	NICE (2011)	ESH (2018)	AHA (2017)*
Home measurement	≥135/85mmHg	≥135/85mmHg	≥130/80mmHg
Daytime ABPM	≥135/85mmHg	≥135/85mmHg	≥130/80mmHg
Night-time ABPM	-	≥120/70mmHg	≥110/65mmHg
24 hour ABPM	-	≥130/80mmHg	≥125/75mmHg

*AHA guidelines also provide out-of-office measurement threshold values for each grade of hypertension

ABPM denotes ambulatory blood pressure measurement; NICE, National Institute for Health and Care Excellence; ESH, European Society of Hypertension; AHA, American Hypertension Association.

as they can lead to over-treatment and under-treatment respectively [93]. Consequently, modern hypertension guidelines recommend the additional use of out-of-office BP measurement to improve diagnostic accuracy and for the monitoring of treatment response [54, 91, 92].

2.4.2 Beat-to-beat Measurement

Continuous (beat-to-beat) BP measurements in the clinic/lab are also possible over short periods. Non-invasive methods that measure the finger arterial pressure waveform using a cuff with built-in plethysmograph have been available since the 1980's, with available validated devices including the Finometer (Finapres®), Portapres®, and the Task Force® Monitor [94-96]. Evaluation of these devices has shown that they are sufficiently accurate (**Table 9**), although the standard deviation (SD) of SBP with the Finapres® is higher than the Association for the Advancement of Medical Instruments' (AAMI) acceptable limit of 8mmHg, so they may lack the required precision for assessment of isolated BP levels. The Finapres®, in comparison with invasive arterial measurements, has also been shown to accurately track sudden changes in BP and measure variability (defined as SD or spectral analysis) in recordings up to 30 minutes long [95, 97], with the Task Force Monitor® being validated against the Finapres® for assessment of BPV [96]. Consequently, non-invasive beat-to-beat measurement has become established in clinical practice for the assessment of syncope and in research for the investigation of BPV [98-101].

Table 9: Accuracy (mean difference (SD)) of blood pressure measurements with the Finapres® and the Task Force Monitor® [95, 96]. The Finapres® has been compared to both invasive and non-invasive methods and weighted average values are presented. The Task Force Monitor® has only been compared against non-invasive devices.

	Finapres®	**Task Force Monitor®**
SBP	-1.3 ± 9.0 mmHg	-1.8 ± 7.6 mmHg
DBP	-2.0 ± 5.1 mmHg	-1.8 ± 6.4 mmHg

SD denotes standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

2.4.3 Out-of-Office Measurement

For out-of-office BP measurement UK guidelines recommend the use of ambulatory BP measurement (ABPM) as the first-line method [91]. ABPM involves the use of an automated BP monitor, usually over 24 hours, programmed to measure BP at set time intervals. The recommended measurement interval varies [54, 91, 92], but to ensure the minimum required 14 daytime and seven night-time readings the maximum frequency should probably be every 30 minutes [89]. A major advantage of ABPM is that night-time measurements are obtained. BP normally falls by around 10-20% at night. Those who do not display this pattern are labelled “non-dippers”, this status being associated with increased target organ damage and an increased risk of cardiovascular events, coronary heart disease, stroke, and death [102, 103]. Indeed, night-time BP values and patterns may relate more closely to the risk of cardiovascular events than daytime values [104], though not all studies support this [105]. The other major advantage of ABPM is that a more accurate ‘usual’ BP is obtained as measurements are taken during the patient’s normal activities away from the clinic environment, an increased number of measurements are obtained, and technical limitations like observer bias/terminal digit preference are eliminated. These factors reduce the influence of natural variation in BP measurements and improve the reproducibility of the data. Research has shown that this translates to improved prediction of cardiovascular risk and a better correlation with target organ damage than CBPM [105-107]. Unfortunately, ABPM is significantly more expensive due to the equipment cost and the need for supporting software to interpret the data. Its interpretation also requires some additional expertise. Perhaps most importantly though, not all patients are able to tolerate ABPM and this can limit its practical use.

An alternative to ABPM is home BP measurement (HBPM) (also referred to as self-BP measurement), which has become a viable alternative method with the development of cheaper, more accurate semi-automated monitors [89]. HBPM is recommended alongside ABPM in guidelines for the diagnosis and monitoring of hypertension [54, 91, 92]. With this technique the patient measures their own BP at home, commonly being instructed to take two measurements in the morning and two in the evening for at

least three, but preferably seven consecutive days [92]. The mean of all measurements, excluding those from day one to allow for acclimatisation, can then be used. Like ABPM, HBPM provides an increased number of measurements and can identify both WCH and MH. Although it does not provide night-time measurements and can be susceptible to some of the same observer bias as CBPM, HBPM is probably more tolerable than ABPM and therefore may be more practical for monitoring long-term control. It is reported that HBPM correlates at least as well as ABPM with cardiovascular risk and target organ damage and also out-performs CBPM in this respect [106, 108, 109].

2.4.4 Comparisons of Office and Out-of-Office Measurements

It is known that out-of-office BP levels are not identical to office levels when contemporaneous measurements are taken in the same subjects. At a CBPM of 140/90mmHg the equivalent daytime ABPM value is on average 4/3mmHg lower, though this difference increases as BP rises [110]. The current diagnostic threshold for daytime ABPM from European guidelines is 135/85mmHg (**Table 8**) [91, 92]. The threshold for HBPM is considered equivalent to daytime ABPM, but it should be noted that this has not been as thoroughly investigated [93, 111]. In fact, available data regarding their comparison shows inconsistent differences between them (**Table 10**), some of which is attributable to methodological factors, such as the age of study participants [112-114]. In terms of diagnosing hypertension, agreement between the methods has been reported as between 59% and 82% [115, 116]. When ABPM is used as the reference standard, HBPM provides increased sensitivity but reduced specificity compared to CBPM (CBPM with threshold >140/90mmHg mean sensitivity 74.6% [95% CI 60.7% to 84.8%] and specificity 74.6% [95% CI 47.9% to 90.4%], HBPM with threshold >135/85mmHg mean sensitivity 85.7% [95% CI 78.0% to 91.0%] and specificity 62.4% [95% CI 48.0% to 75.0%]) [122]. It is possible that CBPM, HBPM and ABPM are not interchangeable methods of measuring BP and this will be discussed further in a later chapter of this thesis.

Table 10: Studies taking contemporaneous blood pressure values from clinic, ambulatory, and home measurements for comparison. Mean values for each method are presented.

Study	**N**	**Mean CBPM (mmHg)**	**Mean ABPM (mmHg)†**	**Mean HBPM (mmHg)**
Denolle 1995 [117]	16	156/91	131/89	128/87
Juhanoja 2016 [118]	461	132.8/85.2	138.4/85.1	130.0/85.2
Larkin 1998 [119]	65	127.8/82.7	132.8/81.9	131.4/80.0
Mancia 1995 [120]	1438	127.4/82.3	123.0/78.7	119.2/74.7
Nasothimiou 2012* [116]	44	152/86	138/80	144/81
Nunan 2015 [121]	203	145.0/92.0	133.6/82.6	141.1/87.0
Sega 1997 [112]	248	147.7/82.9	127.6/77.0	138.2/78.0
Stergiou 2000 [115]	133	143.2/93.0	139.3/91.1	138.7/89.3

*patients with clinic resistant hypertension (defined as average CBPM ≥140/90mmHg from two visits while on stable treatment with ≥3 antihypertensive drugs for ≥4 weeks.

†daytime ABPM values reported with the exception of Denolle et al. and Larkin et al. who reported 24 hour ABPM values.

CBPM denotes clinic blood pressure measurement; ABPM, ambulatory blood pressure measurement; HBPM, home blood pressure measurement.

2.5 Blood Pressure Variability

2.5.1 Concept

Hypertension diagnosis and monitoring has traditionally been based on CBPM with a manual sphygmomanometer [89]. It has already been noted that, for an individual, BP readings obtained using this method will not be exactly the same on separate occasions, with some of this difference attributable to natural variation. Factors that contribute to this over the short-term include the circadian rhythm (most people's BP is 10-20% lower at night-time) [102, 103, 122], emotional state, behavioural stimuli (e.g. caffeine, exercise, smoking), homeostatic mechanisms (e.g. the renin-angiotensin system) and the autonomic nervous system [90, 122]. Longer-term fluctuations may be attributable to seasonal variation and may also relate to inadequacies in measurement technique, changes to antihypertensive treatment, or poor adherence to antihypertensive treatment regimens [90, 122]. However, patients may also experience 'episodic hypertension' whereby, similar to WCH or MH, recorded BP may sometimes be within the normal range and sometimes be raised. For example, in 150 patients with a recent stroke who were not on antihypertensive treatment prior to their cerebrovascular event, 87% of patients had at least one recorded SBP >160mmHg and 69% had at least two recorded SBP's <130mmHg in the 10 years preceding their stroke [26]. Hypertension guidelines recommend that multiple CBPM are taken over several visits to try and establish an individual's 'usual BP' before diagnosing them with hypertension, and that CBPM should be corroborated using out-of-office measurements [54, 91, 92]. However, recent expert opinion has suggested that this variability may be more than just a barrier to establishing an individual's 'usual BP'. Rather, there is evidence that it is a reproducible measurement that provides information about cardiovascular risk [17, 123-125].

Much of the recent interest in BPV stems from a review article by Rothwell which highlighted several observations not fully explained by the currently accepted concept of 'usual BP' (particularly in relation to stroke) and which suggest that there may be additional important factors [126]. One of those factors may be BPV. For example, the

predictive value of mean SBP for stroke falls with increasing age despite the fact that stroke incidence increases with age and elderly patients benefit from antihypertensive treatment. Furthermore, the benefit seen with BP reduction may be greater than expected given the level of risk predicted by mean SBP. Secondly, conditions such as WCH, MH, and episodic hypertension, which imply that at least sometimes an individual's BP is 'normal' yet is also subject to increased variability [127], are associated with an increased risk of stroke. Similarly, BP surges seen in the morning as part of the usual circadian BP rhythm, or associated with conditions like postural hypertension and hypotension, are predictive of stroke but are not associated with mean SBP. Finally, data from trials of antihypertensive medications indicates that, despite similar reductions in mean BP, not all classes of medications convey an equal reduction in stroke risk.

2.5.2 Practical Aspects

Variability can be derived from any of the BP recording methods previously described, provided multiple BP measurements are obtained. The main difference between BP measurement methods is that they allow the quantification of BPV over different timescales according to the gap between measurements. Very short-term variability (over seconds to minutes) can be obtained from beat-to-beat BP monitoring. Short-term variability (over minutes to hours) can be obtained from ABPM or repeated CBPM within a single encounter. Medium-term variability (over days to weeks) is best assessed using HBPM, but could also be derived from repeated CBPM on consecutive days. Finally long-term variability (over months to years), also referred to as visit-to-visit variability, is usually calculated from repeated CBPM over separate visits, but could also be obtained from repeated sets of ABPM or HBPM over time.

Not only can BPV data come from different BP measurement methods over varying timescales, it can also be calculated in a number of different ways (**Table 11**). SD is a

Table 11: Statistical measures that can be applied to a set of blood pressure measurements to derive average values and variability data.

Measure	Abbreviation	Description
Mean		The sum of all recorded values divided by the number of measurements.
Standard deviation	SD	The square root of the mean of the squared difference of all values in the set from the overall mean value.
Coefficient of variation	CV	The standard deviation of a set of recordings divided by the mean value and multiplied by 100.
Variation independent of the mean	VIM	The standard deviation of a set of recordings divided by the mean raised to the power "x". The value "x" is derived by fitting a curve (SD = mean^x multiplied by a constant) to a plot of SD against mean values.
Maximum-minimum difference	MMD	The maximum recorded blood pressure minus the minimum recorded blood pressure.
Peak value		The maximum recorded blood pressure minus the mean value of a set of recordings.
Trough value		The mean blood pressure from a set of recordings minus the minimum recorded value.
Average successive variation	ASV	The mean value of the squared difference in blood pressure between successive measurements.
Average real variability	ARV	The mean value of the absolute difference in blood pressure between successive measurements.

common statistical method of describing variance in a dataset and is the most frequently quoted method of presenting BPV [128]. However, its use for demonstrating BPV may be limited. For example, when applied to 24 hour ABPM recordings SD may just represent the natural variation between daytime and night-time BP. This can be overcome by using weighted SD, which takes account of the greater number of readings acquired during waking hours [129], but a more intractable issue may be that because SD is statistically related to the mean value it may not provide useful information over and above mean BP [130, 131]. One approach to remove the influence of the mean value is to use the coefficient of variation (CV). A more statistically sophisticated method is variation independent of the mean (VIM), which employs curve fitting techniques to derive a population specific value which removes the influence of mean BP [131]. The maximum-minimum difference (MMD) is another simple measure of BP range, describing the maximal change within a recording. Peak and trough values can also be used to capture variation in terms of BP spikes. Finally, average successive variation (ASV) and average real variability (ARV) are methods of deriving variability that account for the time sequence of BP recordings within a set. Both may be particularly applicable to data from 24 hour ABPM as they avoid the difficulty in accounting for day-night differences that may be encountered with the other indices described [132].

2.5.3 The Prognostic Value of Blood Pressure Variability

Rothwell's group has published a body of work relating to BPV to complement his review article. Other contemporaneous publications include a study demonstrating that BPV is a reproducible phenomenon and two papers re-examining the data from several RCT [17, 131, 133]. The first of these re-examinations analysed data from the UK-TIA trial and three other cohorts designed to validate its findings (European Stroke Prevention Study (ESPS-1), Dutch TIA, and Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)). This analysis demonstrated that visit-to-visit variability of SBP (adjusted for mean BP) was a stronger predictor of future stroke than mean BP (**Table 12**) [131].

Table 12: Systolic blood pressure parameters and their predictive value for stroke (HR with 95% CI for the top vs. bottom decile of each parameter) in four cohorts of patients with TIA and minor stroke [131].

	UK-TIA	ESPS-1	Dutch TIA	ASCOT-BPLA	
				Atenolol arm	Amlodipine arm
N	1324	1247	3150	1012	999
Mean	3.63 (2.41 to 5.48)	1.89 (0.96 to 3.71)	2.34 (1.41 to 3.89)	1.81 (0.89 to 3.67)	0.94 (0.36 to 2.42)
SD*	4.84 (3.03 to 7.74)	1.78 (1.12 to 2.62)	3.35 (1.63 to 6.87)	4.29 (1.78 to 10.36)	4.39 (1.68 to 11.50)
CV*	3.82 (2.54 to 5.73)	2.22 (1.52 to 3.22)	3.41 (1.62 to 7.19)	3.51 (1.56 to 7.93)	3.25 (1.32 to 8.00)
VIM*	3.27 (2.06 to 5.21)	1.86 (1.28 to 2.69)	1.83 (0.76 to 4.39)	3.96 (1.66 to 9.43)	3.57 (1.38 to 9.19)

*Adjusted for mean SBP

HR denotes hazard ratio; 95% CI, 95% confidence interval; TIA, transient ischaemic attack; SD, standard deviation; CV, coefficient of variation; VIM, variation independent of the mean.

Variability from ABPM was also predictive of future stroke independent of mean BP, but less so than visit-to-visit variability. The second analysed data from the ASCOT-BPLA and Medical Research Council (MRC) trials to investigate the differential effects of antihypertensive medication classes on stroke risk, showing that the difference in stroke risk may be accounted for by differences in BPV [133]. In the wake of these publications other groups have sought to replicate and extend these findings. Studies relating to the prognostic value of BPV will be summarised here and the relationship between BPV and antihypertensive drug classes will be revisited.

2.5.4 Markers of Organ Damage

Various studies have reported positive associations between BPV and markers of damage to the kidneys, brain, and heart. Regarding renal damage, short-term BPV is positively associated with the presence of microalbuminuria and proteinuria in patients with hypertension [134-136]. Regarding the brain, short-term and long-term BPV are both associated with increased signs of cerebrovascular small vessel disease on neuroimaging [137, 138], with long-term variability also positively associated with the presence of cerebral micro-haemorrhages [138]. This may translate into an association with cognitive impairment and dementia as increased BPV has been linked to worse scores on cognitive screening in cross-sectional and longitudinal analyses [139-146]. Finally, in terms of cardiac organ damage the evidence is inconsistent with varying reports about the relationship between BPV and left ventricular mass [134, 136, 147].

2.5.5 Cardiovascular Events and Mortality

Several studies have questioned the finding of Rothwell's group that BPV is an independent cardiovascular risk factor, with post-hoc review of at least three large datasets suggesting that increased BPV does not provide prognostic information over that of mean BP levels [148-150]. Analysis of a general population cohort demonstrated that baseline BPV, defined as the between-visit VIM from two visits with a 2-4 week interval, did not predict all-cause mortality, cardiovascular events, or stroke

events over a median follow-up of 12 years (HR 1.00 [95% CI 0.91-1.10], 1.05 [0.96-1.15], 1.13 [0.88-1.46] respectively) [148]. In a second general cohort, variability derived as the root mean square error (an estimate of variation around a regression line for BP values recorded over time), from a minimum of six visits over two years, did not predict all-cause mortality over a median follow-up of 12.9 years (HR for the top quartile of variability 1.09 [95% CI 0.95-1.25]) [149]. Finally, in a post-hoc analysis of the Syst-Eur trial, increased VIM of systolic visit-to-visit variability, from visits every three months over two years, did not predict all-cause mortality, combined fatal and non-fatal cardiovascular events, or stroke events after adjustment for mean BP (HR per one SD increase in variability 0.95 [95 % CI 0.82-1.10], 0.92 [0.80-1.05], 1.03 [0.83-1.27] respectively) [150]. However, analysis of the US Veteran's database, which represents the largest reported cohort (N=2,865,157), supports Rothwell et al. Over a median follow-up of eight years the HR for total mortality, coronary heart disease events, and stroke events were all incrementally higher with quartiles of SD of systolic visit-to-visit variability (e.g. HR for all-cause mortality in the top quartile 1.80 [95% CI 1.78-1.82]) [151]. Several meta-analyses also demonstrate that long-term BPV is an independent cardiovascular risk factor, predicting all-cause mortality, cardiovascular mortality, incident cardiovascular events, and stroke events (**Figure 4**) [14, 128, 152, 153]. Although there is less data regarding medium and short-term variability, both are probably also independent risk factors for all-cause mortality [128].

2.5.6 Potential Inconsistencies

A criticism of studies reporting that increased BPV is an independent cardiovascular risk factor is that they have enrolled populations with a higher baseline cardiovascular risk and therefore the results may not be generally applicable. Whilst it is true that the negative studies described in the previous section are either based on general population cohorts or patients with hypertension but no additional cardiovascular disease, the impact of study population heterogeneity may not be significant. This is because when the predictive value of increased visit-to-visit variability was assessed in groups stratified by baseline cardiovascular risk according to European guidelines it

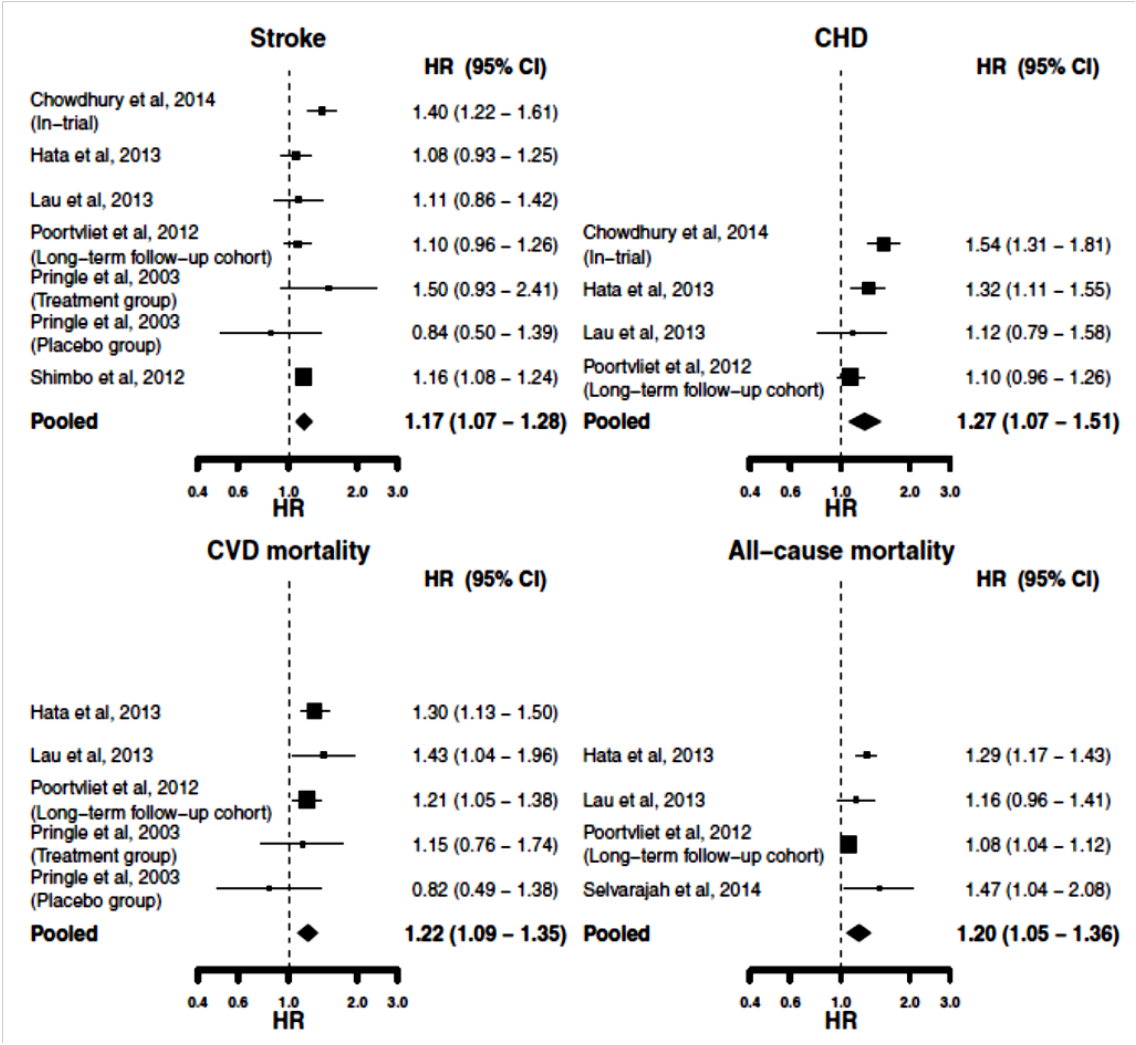

Figure 4: Forest plots showing the association of visit-to-visit systolic blood pressure variability (as standard deviation) with outcomes [14]. HR denotes hazard ratio; 95% CI, 95% confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease.

was found that increased variability predicted cardiovascular events irrespective of baseline risk [154]. Other methodological issues may go further towards explaining some of the inconsistency in the evidence. Presently there is no consensus as to the optimum way to derive BPV [90, 155, 156], therefore, studies have used different approaches in terms of BP measurement protocols and have defined variability with a multitude of statistical methods. The latter may be less important because, although it can inhibit direct comparisons of data, for visit-to-visit variability from repeated clinic BP measurements BPV values from different indices are strongly correlated [157]. However, with reference to the former, BP measurement protocols have not only differed in terms of the BP measurement method used, but also with respect to the number and timing of measurements obtained. For example, HBPM has not always been undertaken for the same number of consecutive days and visit-to-visit variability may be taken from different numbers of visits spread over variable study durations. These aspects of BP measurement have been shown to influence BPV values when calculated as SD [130]. Although perhaps not relevant to short-term variability from ABPM, medium-term variability is influenced by the number of consecutive days on which BP is measured and the number of readings per day, with two sets of duplicate measurements for three consecutive days probably the minimum required to assess variability [158]. Similarly, the number of visits used influences visit-to-visit variability [159]. It is not clear if this also applies to other BPV indices, but the predictive value of BPV from several metrics increases with the number of BP measurements available [131], with one study suggesting that a minimum of four visits are necessary to calculate visit-to-visit variability with sufficient accuracy [123]. At least two of the previously described negative trials are likely to have been influenced by the BP measurements obtained. In the study by Schutte et al. between-visit variability was calculated from just two visits with 2-4 weeks between them [148]. Gao et al. retrospectively collected clinic BP data and so, whilst there was no standardised protocol, it is likely that only a single BP measurement was obtained at each visit [149].

In addition to the fact that measurement factors may influence BPV values and their prognostic relevance, there is evidence that variability values from different measurement methods are not strongly related. Correlations between 24 hour ABPM

variability and repeated CBPM variability in hypertensive patients (either untreated or on stable therapy) are either weak or non-significant [157, 160], as are correlations between beat-to-beat BPV and variability from 24 hour ABPM and HBPM [134]. Considering that natural BPV over different timescales has different influencing factors the same may be true for pathological BPV. Consequently, BPV as it is currently understood and discussed in the literature may not be a singular concept and the same pathological processes may not be elucidated by all measures of variability.

Finally, in addition to these potential methodological issues, interpretation of the data is inhibited by the lack of established 'normal' values for BPV. Some studies have demonstrated increased variability in the study population compared to control subjects [13, 100, 161], but data to suggest how much of a difference is significant is limited. Two studies reporting long-term variability as CV found different levels of variability that may explain their inconsistent findings. Rothwell et al. reported average CV of SBP values of 9% and found a positive association between visit-to-visit variability and risk of recurrent stroke [131]. In contrast, Veloudi et al. found that increased visit-to-visit variability was not associated with target organ damage, but they reported average CV of SBP values of 7% [147]. This difference is in keeping with the findings from the only study that has attempted to establish BPV thresholds using outcome data [162]. In a general population cohort followed-up for approximately 10 years, participants were separated into deciles of BPV, with variability calculated as CV from HBPM conducted over four consecutive days. The risk of cardiovascular events and mortality was increased for those participants with CV of SBP >11%, suggesting that this may be a threshold value. Clearly further research is needed to establish the limits of 'natural' variability in order to properly establish the relevance of pathological BPV.

2.6 Pathological Mechanisms Underlying Blood Pressure Variability

2.6.1 Arterial Stiffness

At present the pathophysiological mechanisms underlying BPV are undetermined. Several factors have been associated with BPV, but the majority of studies have been cross-sectional and so unable to prove a causal relationship. Perhaps most frequently discussed is the association between BPV and arterial stiffness. BP is not consistent throughout the arterial system. Although DBP and mean arterial pressure (MAP) remain relatively unchanged from the aorta to the peripheries, SBP increases with the distance from the heart. This is because peripheral arteries are less elastic than the aorta resulting in so-called “amplification” of BP [163]. Two theories are often cited to explain this. The pulse wave model hypothesises that the arterial pressure waveform is a composite of a forward travelling wave generated by left ventricular contraction and a reflected wave generated by tapering of arterial size and the associated reduction in arterial wall compliance [164]. The reflected wave augments systolic pressure with the effect diminishing as it travels further back towards the central vessels. The Windkessel model proposes that the elastic properties of the central arteries allows them to act as a reservoir that fills in systole and empties in diastole [165]. This elasticity buffers some of the pressure generated by left ventricular contraction and the buffering effect diminishes further down the arterial tree. Increased arterial stiffness can theoretically both reduce the capacity of central arteries to act as a buffer and increase the amplification of BP by enhancing the reflected wave, which in turn can increase BP and its variability. Several markers of arterial stiffness are measurable, with the gold standard considered to be carotid-femoral pulse wave velocity (c-fPWV) [166]. Studies show that increased short and long-term BPV are both positively correlated with reduced aortic distensibility in general adult populations [167, 168]. In hypertensive adults they are also positively correlated with c-fPWV [136, 169, 170]. Similarly, increased long-term BPV both predicts and is predicted by increased brachial-ankle pulse wave velocity [171, 172]. Whether change in BPV correlates with change in arterial stiffness is unclear with two studies reporting same directional change in BPV and arterial stiffness over time [173, 174], but another finding no association [147]. Furthermore, increased BPV may be associated with endothelial

dysfunction [175]. Therefore, whether increased arterial stiffness causes increased BPV or vice versa, or whether both influence each other in a vicious circle remains to be elucidated.

2.6.2 Autonomic Dysfunction and Cardiac Baroreceptors

Another potential mechanism underlying BPV is autonomic dysfunction. It is known that syndromes characterised by abnormal BP changes, such as postural hypotension, can be associated with conditions that can cause dysautonomia, such as Parkinson's disease and Diabetes Mellitus. Short-term BPV from 24 hour ABPM is increased in diabetic hypertensive patients compared to non-diabetic hypertensives suggesting that this may be another clinical manifestation of diabetic autonomic neuropathy [176]. The BP volatility associated with autonomic dysfunction could be mediated by impairment of cardiac baroreceptors, which are a major determinant of short-term BP regulation [177-179]. Cardiac baroreceptors are stretch receptors, stimulated by changes in BP, located in the carotid sinus, aortic arch, and right atrium. Afferent signals to the central nervous system, via the glossopharyngeal and vagus nerves, are co-ordinated in the nucleus tractus solitaries, but multiple other central areas are involved in processing. Efferent sympathetic and parasympathetic outputs modulate heart rate, cardiac output, and peripheral vascular tone resulting in homeostatic alteration of BP. Baroreflex failure can result in a number of syndromes characterised by BP fluctuations, such as volatile hypertension and malignant vagotonia [178, 180]. Damage anywhere along the baroreceptor feedback pathway can potentially result in reduced baroreceptor function or baroreflex failure, including, for example, damage to central processing areas by stroke [181, 182]. Consequently, reduced baroreceptor sensitivity (BRS) may be particularly relevant to increased BPV post-stroke.

2.7 Blood Pressure Variability Post Stroke

2.7.1 Short and Medium-term Variability

The evidence suggests that in hypertensive individuals longer-term BPV, and to a lesser extent shorter-term, is predictive of cardiovascular events and mortality, with the strongest prognostic relationship possibly between increased BPV and stroke risk. This may also suggest a prognostic relationship with recurrent stroke. Additionally, given the theoretical link between central nervous system damage, BRS dysfunction, and BPV described in the previous section, increased BPV post-stroke may have an impact on outcomes. Furthermore, if we consider that cerebral autoregulation is disrupted in acute stroke [13, 183], resulting in CBF becoming dependent on systemic BP, then this question becomes more pertinent. In theory, if cerebral autoregulation is unable to maintain CBF within the normal limits (i.e. MAP 60-150mmHg [12]), then any increases in systemic BPV could result in cerebral hypo or hyper-perfusion. The consequences of the former could be tissue hypoxia, particularly in the under-perfused ischaemic penumbra, and infarct expansion. The consequences of the latter could be additional endothelial damage and blood-brain barrier disruption leading to secondary haemorrhage and/or cerebral oedema. Several studies have attempted to address these gaps in the knowledge base.

Studies of the impact of BPV post-stroke have investigated variability in different phases following the cerebrovascular event. In these studies the hyper-acute phase has generally been defined as the first 24 hours after symptom onset, the acute phase as days 1-3 or 1-7 post-event, and the subacute phase as beyond one week. Studies show that increased systolic BPV measured over hours in both the hyper-acute and acute phases after ischaemic stroke is associated with an increased risk of haemorrhagic transformation in patients receiving thrombolysis [184-186]. Increased day-to-day systolic variability over the first three days post-event is also associated with an increased risk of haemorrhagic transformation in patients not receiving thrombolysis [187]. Furthermore, increased systolic BPV measured over hours during the same period after ischaemic stroke is associated with an increased risk of END [188, 189]. In terms of stroke recovery there is no evidence to show that increased

variability in the hyper-acute and acute phases is related to early functional outcome (defined as two weeks post event) [190]. However, with a few exceptions [98, 191, 192], studies investigating the impact of increased systolic variability on functional outcome after three months show that increased variability is associated with an increased risk of poor outcome (**Table 13**). Meta-analysis of seven studies reinforces these positive findings, indicating that BPV within the first 72 hours after stroke onset affects outcomes (OR per 10mmHg increase in SD of SBP 1.2 [95% CI 1.1-1.3, p=0.0004]) [15]. There is also emerging evidence that increased variability from HBPM in the three months post-event is associated with an increased risk of stroke recurrence [16], and one study has also reported an increased risk of post-stroke cognitive impairment at 12 months [193].

2.7.2 Beat-to-Beat Variability

The majority of studies have utilised multiple ward BP measurements to derive BPV, thereby investigating short or medium-term variability. Beat-to-beat variability has not been extensively studied, but there is evidence to show that in patients with ischaemic stroke SD of SBP is increased in the first 72 hours post-event compared to control subjects [100]. Whilst the SD of beat-to-beat SBP was not associated with long-term outcome or stroke subtype (according to the Oxford Community Stroke Project (OCSP) classification) in the study by Dawson et al., the SD of beat-to-beat DBP was related to the risk of poor functional outcome in this cohort (OR 1.33 [95% CI 1.1-1.7, p<0.03]) [98]. Furthermore, in a study from the OXVASC database both SD and CV of beat-to-beat SBP recorded within six weeks of a cerebrovascular event (TIA, ischaemic stroke, or ICH) was predictive of recurrent stroke [200]. This suggests that, whilst the current evidence is limited, very short-term BPV post-stroke may be relevant to stroke recovery as well as long-term cardiovascular health.

Table 13: Summary of studies investigating the impact of increased blood pressure variability on outcomes after stroke.

Study	N	Patient Cohort	BP measurement method	BPV index*	Outcome	OR (95%CI)†	P value
Yong 2008 [184]	793	Ischaemic stroke within 6 hours of onset, thrombolysis vs. placebo (post-hoc analysis of ECASS-II)	Ward BP as per protocol (x37 over 24 hours)	ASV SBP	Functional independence at 3 months (mRS 0-1)	Thrombolysed: 0.57 (0.35-0.92) Placebo: 0.41 (0.22-0.76)	Not reported
Endo 2013 [194]	527	Ischaemic stroke receiving thrombolysis (Samurai registry)	Ward BP as per standard treatment (x7 over 24 hours)	MMD SBP	Functional independence at 3 months (mRS 0-1)	0.88 (0.77-0.99)	<0.05
Liu 2016 [185]	461	Ischaemic stroke receiving thrombolysis	Ward BP as per standard treatment (x1 per hour for 24 hours)	ASV SBP	Functional independence at 3 months (mRS 0-1)	0.25 (0.14-0.45)	<0.05
Kellert 2017 [186]	16,434	Ischaemic stroke receiving thrombolysis (SITS database)	Ward BP as per standard treatment (minimum x3 over 24 hours)	ASV SBP	Functional independence at 3 months (mRS 0-2)	0.94 (0.90-0.98)	0.002
Bennett 2018 [195]	182	Ischaemic stroke receiving thrombectomy	Ward BP as per standard treatment (x38 over 24 hours)	ASV SBP	Ordinal shift in mRS after 3 months	2.63 (1.47-4.70)	0.001
Chung 2018 (hyper-acute phase) [196]	386	ICH within 2 hours of onset (post-hoc analysis of FAST-MAG)	Ward BP as per protocol (x6 0-6 hours after onset)	CV SBP	Functional independence at 3 months (mRS 0-2)	Top quintile of BPV: 4.78 (2.00-11.40)	<0.001
Chung 2018 (acute phase) [196]	386	ICH within 2 hours of onset (post-hoc analysis of FAST-MAG)	Ward BP as per protocol (x11 0-24 hours after onset)	CV SBP	Functional independence at 3 months (mRS 0-2)	Top quintile of BPV: 4.97 (1.93-12.84)	<0.001

Zhang 2018 [192]	542	Ischaemic stroke admitted within 24 hours of onset	24 hour ABPM (set to measure BP at 2 hourly intervals)	CV SBP	Poor functional outcome at 3 months (mRS ≥3)	CV ≥ median value: 1.07 (0.71-1.59)	Not reported
De Havenon 2016 [197]	215	Anterior circulation ischaemic stroke	Ward BP as per standard treatment (median 34 measures over 120 hours)	CV SBP	Ordinal shift in mRS after 3 months per 10mmHg increase	3.16 (1.25-7.94)	0.02
Wang 2017 [198]	873	Ischaemic stroke admitted within 24 hours of onset	Ward BP as per standard treatment (x6 per day for 7 days)	CV SBP	Poor functional outcome at 3 months (mRS ≥2)	Top quintile of BPV: 2.02 (1.52-2.53)	0.001
Fukuda 2015 (acute phase) [199]	2566	First ischaemic stroke admitted within 24 hours of onset (Fukuoka stroke registry)	Ward BP as per standard treatment (x3 days 1-3 post onset)	CV SBP	Poor functional outcome at 3 months (mRS ≥3)	Top quartile of BPV: 0.91 (0.66-1.24)	0.54
Fukuda 2015 (subacute phase) [199]	2566	First ischaemic stroke admitted within 24 hours of onset (Fukuoka stroke registry)	Ward BP as per standard treatment (x1 days 4-10 post onset)	CV SBP	Poor functional outcome at 3 months (mRS ≥3)	Top quartile of BPV: 1.63 (1.20-2.22)	0.002
Dawson 2000 [98]	92	Ischaemic stroke within 10 days of onset	Beat-to-beat BP for 10 minutes	SD SBP	Poor functional outcome at 3 months (mRS ≥3)	1.07 (0.9-1.2)	0.29

*For studies reporting multiple BPV indices the largest effect is presented.

[†]Adjusted for confounding variables, including baseline BP and NIHSS.

BP denotes blood pressure; BPV, blood pressure variability; OR, odds ratio; 95% CI, 95% confidence interval; ASV, average successive variation; SBP, systolic blood pressure; mRS, modified Rankin score; MMD, maximum-minimum difference; ICH, intracerebral haemorrhage; CV, coefficient of variation; ABPM, ambulatory blood pressure measurement; SD, standard deviation.

2.7.3 Limitations of the Evidence

As with studies on the prognostic relevance of BPV to the risk of cardiovascular events discussed previously, some of the inconsistencies in the evidence for the impact of BPV post-stroke probably relate to methodological issues. For example, the method of BP measurement used, the number of measurements obtained, and the timescale encompassing and between measurements. In particular, the timing of measurements in relation to stroke onset may be important, with studies suggesting that increased variability may naturally decrease to a degree after the acute phase, similar to the pattern seen with mean BP described in section 3.1 [100, 189]. The degree of variability observed in different studies may also explain differences in reported outcomes. For example, in their negative study Tziomalos et al. observed a CV of SBP of 6% in the first 72 hours after admission, whereas Chung et al. found a CV of SBP of 11% to be associated with END and Wang et al. found a CV of SBP >11% to be associated with poor three month outcome [188, 191, 198]. Again, this is in keeping with the limited data regarding BPV threshold values [162]. Of course, interpretation of the evidence should be done in the context of its strengths and weaknesses. With that in mind, it should be noted that the majority of these studies have been either post-hoc analyses of trial data, or retrospective reviews of registry data or unselected secondary care cohorts. A major limitation of these designs is that BP measurements have not necessarily been standardised and, where they have, have not necessarily been designed to adequately capture variability. It could be argued that this is advantageous as it represents “real world” data, but further research based on specifically designed prospective trials would undoubtedly be beneficial to further investigate the impact of BPV post-stroke. Having said that, the available evidence (which includes a small but robust meta-analysis) is certainly intriguing and invites the question as to whether BPV might be a therapeutic target in addition to mean BP.

2.8 Differential effects of Antihypertensive Medication Classes on Blood Pressure Variability

2.8.1 Studies on Long-term Variability

As alluded to in section 2.5.3, evidence suggests that not all antihypertensive medications are equal with respect to their effect on stroke risk reduction, and these differential effects may be class effects. One potential explanation for this is that not all antihypertensive medications have an equal effect on BPV as suggested by Rothwell et al. in their post-hoc analysis of the ASCOT-BPLA and MRC trials (**Table 14**) [133]. In both of these trials there was an unexpected difference in stroke risk between the treatment arms (calcium channel blocker (CCB) vs. beta blocker in ASCOT-BPLA and thiazide diuretic vs. beta blocker in MRC), with both suggesting an increased stroke risk in the beta blocker arm. In ASCOT-BPLA visit-to-visit variability was greater in those treated with a beta blocker compared to a CCB. Moreover, this difference was able to account for the difference in stroke risk, whereas the between-group difference in mean BP was not. In MRC the findings were similar, with increased visit-to-visit variability in the beta blocker arm, but no effect on visit-to-visit variability seen in the thiazide diuretic arm.

Rothwell et al. have also performed a systematic review, incorporating 398 antihypertensive trials, to further explore the potential effects of different medication classes on BPV [201]. As individual BPV data was not routinely reported interindividual variance (the variance within the whole treatment group) was assessed as a surrogate. The review found that visit-to-visit variability of SBP was reduced by CCB, and to a lesser extent non-loop diuretics, but was increased by beta blockers and drugs inhibiting the renin-angiotensin system. The greatest increase in variability was seen in those treated with beta blockers. Furthermore, in keeping with their previous findings, increased BPV in this analysis was associated with an increased risk of stroke.

Table 14: Visit-to-visit variability of systolic blood pressure by treatment arm from the ASCOT-BPLA and MRC studies. Data presented are mean (SD) [133].

	ASCOT-BPLA		**MRC**	
	Atenolol arm	Amlodipine arm	Atenolol arm	Diuretic arm
Mean (mmHg)	141.8 (13.0)	139.1 (11.1)	156.6 (12.1)	151.2 (12.1)
SD (mmHg)	13.42 (5.77)	10.99 (4.79)	14.38 (5.34)	11.64 (4.39)
CV (%)	9.41 (3.78)	7.87 (3.23)	9.18 (3.33)	7.69 (2.77)
VIM (units)	13.13 (5.21)	11.14 (4.52)	14.55 (5.31)	11.98 (4.38)
ASV (mmHg)	13.79 (6.50)	11.28 (5.32)	14.71 (5.65)	12.40 (5.09)

SD denotes standard deviation; CV, coefficient of variation; VIM, variation independent of the mean; ASV, average successive variation.

Further work looking at visit-to-visit variability with individual patient data has been conducted in the wake of this systematic review. A post-hoc analysis of ALLHAT was able to compare angiotensin converting enzyme inhibitors (ACEI), CCB and thiazide-like diuretics. Systolic visit-to-visit variability (defined as SD, ARV, and SD independent of the mean (a statistically similar method to VIM)) was significantly increased with ACEI compared to both other medication classes [202]. Similarly, in a retrospective review of a large primary care database Smith et al. were able to assess the impact of all major antihypertensive classes on visit-to-visit variability, finding that variability was reduced with non-loop diuretics and CCB, but increased with beta blockers and ACEI or angiotensin receptor blockers (ARB) [203]. In contrast, in a substudy of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, which compared losartan with atenolol, it was reported that there was no significant difference in systolic visit-to-visit variability between the treatment arms [204]. However, the majority of participants in this study took other antihypertensive medications in addition to their investigational product, with most taking a CCB. Also, variability was only defined as SD. Both of these factors could have confounded the results.

When considering long-term BPV, it would be reasonable to suggest that the degree of variability could be influenced by factors other than medication effects. One such factor could be medication adherence, which is known to be problematic in patients with hypertension [205, 206]. Two studies have investigated the impact of medication adherence on visit-to-visit variability. Although both are post-hoc analyses and data on adherence was self-reported, both found that whilst poor adherence was associated with increased visit-to-visit variability, it was not able to account for the link between increased BPV and increased cardiovascular risk [207, 208].

2.8.2 Studies on Short-term Variability

A few studies have investigated the effect of different antihypertensive medication classes on short-term BPV, measured either with ABPM or HBPM. In a small study of valsartan vs. amlodipine daytime systolic BPV from ABPM (defined as SD and CV) was increased with the former compared to the latter [209]. Similarly, in a post-hoc

subgroup analysis of the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) study, after three months treatment with candesartan, amlodipine, or indapamide, BP was reduced in all groups whereas BPV (defined as ARV) was only reduced in the amlodipine and indapamide groups [210]. Another study reported on the SD of 24 hour ABPM in a larger cohort, observing that systolic variability was increased with beta blockers, decreased with both CCB and thiazide-like diuretics, but not affected by renin-angiotensin inhibitors [211]. Post-hoc analysis of the Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) study measured the impact of CCB or renin-angiotensin inhibitors on the variability of HBPM two to four weeks after treatment initiation [212]. No difference was reported between the two groups, but the study was limited as only a small number of BP measurements were obtained (one in the morning and one in the evening for five days). Finally, in the only study to focus on a population with cerebrovascular disease, Webb et al. investigated the impact on variability of HBPM of antihypertensive medication changes (either dose increases or medication additions) in patients with a recent ischaemic stroke [213]. They reported that the addition or increase in dose of a CCB or diuretic reduced BPV compared to the same changes using an ACEI.

2.8.3 Studies on Combination Therapy

Given that many patients with hypertension will require multiple medications to achieve good BP control [214-216], whether these apparent class effects persist when antihypertensive therapies are combined could be of clinical relevance. Again, Rothwell and colleagues have examined this question, conducting a systematic review of 97 trials [217]. As with their previous systematic review interindividual BPV was used as a surrogate measure of individual BPV. The results were in keeping with the data regarding antihypertensive monotherapy, with systolic BPV being reduced by the addition of a CCB to the antihypertensive regimen, and less so by the addition of a diuretic, but increased by the addition of a beta blocker. In the same systematic review they also analysed trials comparing high and low doses of the same antihypertensive

class, finding that higher doses of CCB further reduced BPV, with the opposite for beta blockers, and no difference for other antihypertensive classes.

2.8.4 Potential Explanations for Antihypertensive Class Effects on Blood Pressure Variability

The various classes of BP lowering medications exert their antihypertensive effects via different mechanisms and consideration of these mechanisms may provide some theoretical explanation of their effects on BPV. Dihydropyridine CCB (e.g. amlodipine) cause smooth muscle relaxation, which leads to peripheral vascular dilatation and a reduction in peripheral vascular resistance [133, 211]. Thiazide-like diuretics reduce peripheral vascular resistance via increased excretion of sodium and water, but also have vasodilatory effects, with the latter more likely to be the mechanism for long-term BP reduction [218, 219]. Both of these medication classes could consequently increase arterial compliance, which may reduce arterial stiffness and BPV. Notably, concurrent reductions in c-fPWV and BPV have been demonstrated with CCB therapy [220], though whether there is a causal link is unproven. Conversely, beta blockers primarily exert their antihypertensive effect through negative chronotropic activity, with less cardio-selective agents causing peripheral vasoconstriction, meaning they could be expected to have the opposite effect on arterial stiffness and, as a result, BPV [133, 211]. Finally, ACEI and ARB lower BP by inhibiting aldosterone release, altering sodium and water excretion, with relatively little effect on peripheral vascular tone.

Caution must be taken in interpreting the available evidence as the majority has been generated from post-hoc analyses of trials of antihypertensive medications that were designed to assess the medication's effects on overall BP, not BPV [221]. These trials are heterogeneous in terms of the particular medications studied, length of follow-up, and methods of BP measurement among other things, which could confound any further analysis. It should also be noted that interindividual BPV is a surrogate marker, although it is reported that within-individual BPV accounts for up to 40-60% of the variability within a group [131, 133]. Having said that, the weight of evidence is compelling and, as previously stated, warrants further investigation with dedicated primary trials. Findings to date suggest that available antihypertensive medications

may have an effect on BPV as well as overall BP and so theoretically these treatments could be used to target BPV therapeutically. Furthermore, given the apparent impact of BPV in acute ischaemic stroke this patient group could potentially benefit from such treatment. The final part of this thesis will be concerned with a feasibility RCT investigating the reduction of BPV in acute ischaemic stroke.

3 Methodology

This chapter describes the general materials and methods in this thesis. Any chapter specific methodology, including methods for statistical analysis, are described in that chapter.

3.1 Trials Contributing Data to this Thesis

Data for this thesis have been generated from four clinical trials, each of which is summarised, including my involvement. All trials were registered (ISRCTN registry) and full details are freely available online. The protocols for SERVED Memory and CAARBS have been published, as have the main findings from TEST-BP [222-224].

3.1.1 Trial of the Effectiveness and cost effectiveness of Self-monitoring and Treatment of Blood Pressure in secondary prevention following stroke or TIA (TEST-BP) (http://www.isrctn.com/ISRCTN86192648)

TEST-BP was an RCT investigating the benefit of HBPM, with and without guided self-management of antihypertensive treatment, in patients with a recent stroke or TIA. I was directly involved in participant follow-up, data management, and data analysis for this trial. Participants were adults (>18 years old) who had experienced a TIA, ischaemic stroke or primary ICH of mild/moderate severity (defined as National Institutes of Health Stroke Scale (NIHSS) score <15), who needed antihypertensive therapy for secondary stroke prevention (at the discretion of their clinician but based on UK guidelines), and were willing to self-monitor their own BP and adjust their treatment with study team clinician guidance if necessary. Exclusion criteria were a history of atrial fibrillation (AF), life expectancy less than six months due to terminal illness or end-stage chronic disease, diagnosed dementia or cognitive impairment, and not currently receiving or expected to commence antihypertensive therapy. Enhanced CBPM was undertaken as part of the screening procedure.

Participants were recruited from the inpatient and outpatient stroke services at the Norfolk and Norwich University Hospital (NNUH) between 72 hours and 12 weeks after the qualifying cerebrovascular event. At enrolment they were randomised in a 1:1:1 ratio to one of three study arms: treatment as usual (standard BP management by their General Practitioner (GP)), self-monitoring only (HBPM with treatment decisions managed by their GP), or self-monitoring and self-management (HBPM with telemonitoring of results to the trial team and self-managed treatment, guided by the trial clinician). Study measurements, including 24 hour ABPM and beat-to-beat BP measurements, were taken at baseline and after a follow-up period of six months. Participants in the HBPM intervention groups performed self-monitoring at six weeks, three months, and five months post-randomisation.

The main aim of the trial was to determine whether HBPM with or without guided self-management of BP treatment resulted in lower BP levels and better control than usual care in hypertensive patients with a recent stroke or TIA. The primary outcome measure was difference in ambulatory SBP at six months, with 48 participants per group required to detect a difference in mean daytime ambulatory SBP of 6mmHg, with a power of 0.8 at the 5% significance level, assuming SD of 10.3mmHg for daytime ABPM [225].

3.1.2 Feasibility study of Screening and Enhanced Risk management for Vascular Event related Decline in Memory (SERVED Memory)

(http://www.isrctn.com/ISRCTN42688361)

SERVED Memory was a feasibility RCT investigating the impact of enhanced monitoring and target driven treatment of vascular risk factors on post-stroke cognitive impairment. My roles in this trial included participant recruitment, data acquisition at baseline and follow-up, data management, and data analysis. Participants were adults (>18 years old) with a clinically or radiologically confirmed TIA or stroke (infarct or primary ICH), recruited within eight weeks of the qualifying cerebrovascular event. Patients were excluded if they had a formal diagnosis of dementia documented in their past medical history, a life expectancy less than one year, and if they did not wish, or

were unable to complete a cognitive screening test (Montreal Cognitive Assessment (MoCA)).

Participants were recruited from the inpatient and outpatient stroke services at NNUH. At enrolment they were stratified according to their baseline MoCA score and placed into one of three study arms. Patients with normal cognition (defined as MoCA ≥26) were allocated to an observational group [226]. This group received standard care, did not undergo any enhanced monitoring of their vascular risk factors, and had repeat cognitive screening after 12 months with the aim of providing data about the natural history of the development of post-stroke cognitive impairment. Patients with a MoCA score consistent with mild cognitive impairment (defined as MoCA 20-25 [226, 227]) were randomised in a 1:1 ratio to a control group or intervention group. Both groups underwent enhanced vascular risk factor measurement at baseline and after 12 months follow-up. Vascular risk factors targeted included BP (assessed with enhanced CBPM, 24 hour ABPM, and beat-to-beat BP measurement) and serum cholesterol in all individuals. Where applicable control of diabetes (assessed with serum HbA1C), and adequacy of anticoagulation (being prescribed a direct oral anticoagulant, or INR 2.5-3.0 if on warfarin) and heart rate control (target 60-80 beats per minute) in participants with AF were also targeted. In the interim the control group received usual care with no intervention by the study team, whereas those in the intervention group saw the trial team at three monthly intervals for additional risk factor assessment, with results and recommendations for interventions if necessary from these visits being passed to their GP for action. Patients with a MoCA score <20 were excluded from the trial.

The primary objective of the study was to determine the feasibility of recruiting patients with signs of early cognitive decline, but no dementia, into the trial and to assess adherence to the proposed intervention. The trial also aimed to provide data about the incidence of post-stroke cognitive impairment, the potential benefit of the intervention in terms of preventing cognitive decline, and help inform the necessary sample size for a future potentially definitive trial.

3.1.3 Blood Pressure Variability – definition, natural history, and prognosis following acute stroke (BPV observational study) (http://www.isrctn.com/ISRCTN86821598)

The BPV observational study was a prospective cohort study to investigate BPV in patients with an acute stroke/TIA. In this trial I participated in patient recruitment, follow-up, and data management. The cohort comprised adult patients with an acute stroke/TIA recruited within 48 hours of symptom onset. Patients with pre-event mRS >3, life expectancy <3 months, AF, and those required to take a beta blocker were excluded.

Participants were recruited from the inpatient and outpatient stroke services at NNUH and Leicester Royal Infirmary, and the outpatient stroke services at the John Radcliffe Hospital in Oxford. Alongside the collection of clinical data, baseline BP was measured using multiple methods (beat-to-beat BP, enhanced CBPM, 24 hour ABPM) to provide data on BPV over various timeframes. Participants were then followed-up at five points over 12 months, either by telephone (providing outcome data only), or in person (with BP measurements being repeated on these occasions). The main aims of the trial were to describe the natural history of BPV after stroke/TIA, determine the optimal measurement method for both patients and clinicians/researchers, and provide data relating to the prognostic relevance of BPV after stroke/TIA.

3.1.4 A Calcium channel or Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker Regime to reduce Blood pressure variability in acute ischaemic Stroke (CAARBS): a feasibility trial (http://www.isrctn.com/ISRCTN10853487)

CAARBS was an open label, feasibility RCT investigating the effect of two classes of standard antihypertensive medications on BPV in patients with ischaemic stroke or TIA. I was involved in the design and setup of this trial, including writing the protocol and gaining regulatory approvals, and acted as trial co-ordinator. At the NNUH site I also undertook participant recruitment and data acquisition. Finally, I was responsible for data management and was involved in the data analysis for this trial. Participants were adults with a first episode TIA or mild/moderate ischaemic stroke (NIHSS <10) who also required antihypertensive therapy for secondary stroke prevention (in

accordance with current guidelines [18]). Full inclusion and exclusion criteria are detailed in **Table 15**.

Participants were recruited from the inpatient and outpatient stroke services at NNUH and Leicester Royal Infirmary, and the outpatient stroke services at the John Radcliffe Hospital in Oxford. At enrolment, they were randomised using a computer generated protocol with block design in a 1:1 ratio, to treatment with a dihydropyridine CCB or an ACEI/ARB, with the choice of medication from within the randomly allocated class at the discretion of the treating clinician. Follow-up data were obtained at three weeks and three months post-randomisation. Titration of antihypertensive medication to try and achieve secondary prevention target BP was allowed during follow-up, including the use of additional antihypertensive medications provided they were not of the class from the opposite intervention arm.

The primary objectives of the trial were the assessment of feasibility and safety. This included recruitment and retention rates, compliance with trial treatment and BP measurements, and differences in adverse event rates between the trial arms. The exploratory primary outcome measure was three month mRS, with pre-specified exploratory secondary outcome measures including early (three week) and late (three month) differences in mean BP and BPV, and late differences in cognition (assessed using a cognitive battery including MoCA, Albert's line test, and the Motor Neuron Disease Behavioural Instrument (MiND-B)).

3.2 Consent

All participants chose to take part in the research trials of their own volition. Eligible patients were provided with a participant information sheet relevant to the trial for which they were being considered. After having the opportunity to read the information sheet and ask questions about the trial, those who were willing to take

Table 15: Inclusion and exclusion criteria for CAARBS.

Inclusion criteria	**Exclusion criteria**
Age >18 years old	Known contra-indication to proposed investigational medical products
First-ever clinically definite TIA or ischaemic stroke (NIHSS<10)	Definite indication for a specific antihypertensive
BP >130/80mmHg	Pre-event mRS >3
Within 72 hours of symptom onset	Life expectancy <3 months
Able to comply with antihypertensive treatment and BP measurements	Atrial fibrillation
	Unable to take oral medication
	Participation in another investigational drug trial
	Currently, or planning to become pregnant

TIA denotes transient ischaemic attack; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; mRS, modified Rankin score.

part provided written informed consent before any study specific procedures were conducted. Proxy consent was not used in any of the trials.

3.3 Regulatory Approvals

All of the trials received ethical approval prior to commencement:

- TEST-BP was approved by the Research Ethics Committee East of England – Norfolk (REC No. 11/EE/0147);
- SERVED Memory was approved by the East of England Cambridge Research Ethics Committee (REC No. 15/EE/0061);
- BPV observational study was approved by the London – South East Research Ethics Committee (REC No. 13/LO/0979);
- CAARBS was approved by the London – Central Research Ethics Committee (REC No. 17/LO/1427).

CAARBS was also approved by the Medicines and Healthcare products Regulatory Agency (EudraCT number 2017-002560-41) prior to receiving full Health Research Authority approval. Local approval was provided by the relevant Research and Development Office at all sites involved in the trials prior to their commencement.

3.4 Power Calculations

For the purposes of this thesis the analyses of data from TEST-BP, SERVED Memory, and the BPV observational study are post-hoc exploratory analyses of outcomes not specified at the conception of the trials. Therefore, although TEST-BP was powered for its primary outcome as described in section 3.1.1, power calculations for the analyses in this thesis were not performed. For CAARBS the primary objectives were the assessment of feasibility, including rates of recruitment, measurement of changes in BPV over three months follow-up, compliance with trial interventions, and safety of trial interventions. However, the trial was designed with the potential to detect a difference between the treatment arms as a pre-specified secondary outcome. If a sample of 150 patients (64 per group allowing for a 15% drop-out rate) was achieved this would have an 80% power at the 5% significance level of detecting an 8mmHg

difference in systolic BPV, assuming a mean systolic BPV SD of 14.97mmHg in the CCB arm and 16.95mmHg in the ACEI/ARB arm [201].

3.5 Data Collection

3.5.1 Clinical Information

Clinical data were collected through direct questioning to the participant and from review of their medical notes. Data collected included demographic information (age, gender, height and weight, smoking and alcohol history), past medical history, drug history, and relevant family history, details of the qualifying cerebrovascular event (the diagnosis and results of neuroimaging), and the results of routine investigations (including blood tests, electrocardiogram (ECG), carotid ultrasound, and further neuroimaging where applicable). For participants in the BPV observational study and CAARBS all routine ward or clinic BP measurements were recorded at baseline.

3.5.2 Enhanced Clinic Blood Pressure

Enhanced CBPM was undertaken in all of the studies, as part of eligibility screening in TEST-BP, and at baseline and follow-up visits in the other trials. I define enhanced CBPM as a set of three clinic/ward-based BP measures taken on the same occasion using a semi-automated oscillometric BP monitor (Omron 705IT, Omron Healthcare UK Ltd., Milton Keynes, UK) that can be used to provide an average BP reading and within-visit BPV data. The Omron 705IT monitor is approved by the British Hypertension Society (BHS) and has been validated against BHS and AAMI criteria [228]. Monitors were regularly checked for accuracy using a greenlight reference monitor. Measurements were taken using an appropriately sized cuff with the patient seated, after a period of five minutes rest, with at least a one minute gap between readings in accordance with guideline recommendations [91, 229]. In the BPV observational study and CAARBS, two sets of enhanced CBPM measurements were recorded at each visit, with a gap of at least 10 minutes between sets.

3.5.3 Ambulatory Blood Pressure Monitoring

Ambulatory monitoring in these studies was undertaken using a Spacelabs 90207 monitor (Spacelabs Healthcare Ltd. (UK), Hertford, UK) which has been validated against BHS and AAMI criteria [230]. Monitoring was done over 24 hours in all studies except CAARBS, where only daytime ABPM was performed. Daytime was defined as between 0700-2200 hours with night-time conversely defined as 2200-0700 hours. Arm circumference was measured prior to device fitting to ensure the use of an appropriately sized cuff. In keeping with guideline recommendations [91], monitors were programmed to measure BP at 20 minute intervals during the daytime and hourly overnight in order to provide a minimum number of 14 daytime measurements and seven night-time measurements.

3.5.4 Home Blood Pressure Measurement

In studies collecting HBPM data (TEST-BP) participants received face-to-face, written, and audiovisual instruction on how to measure their own BP from a member of the research team. The protocol for self-monitoring was in concordance with guideline recommendations [91], with participants being instructed to take two measurements, with a gap of two minutes between them, in the morning and the evening for seven consecutive days. The target was for 75% of readings (i.e. ≥21 readings) to be completed for a set of HBPM to be considered valid. Participants were instructed to take measurements in the non-dominant arm, in a seated position, after a period of five minutes rest. They were also instructed to take measurements prior to antihypertensive medications or meals. In TEST-BP participants randomised to self-monitoring only used an Omron 705IT monitor, whereas participants randomised to self-monitoring with self-management were provided with a different monitor (A&D UA-767PBT, A&D Instruments Ltd., Abingdon, UK) with the facility to telemonitor readings directly to the trial team. The UA-767PBT monitor is also BHS approved and has been validated against BHS and AAMI criteria [231]. Readings from the first day of recording were discarded prior to analysis.

3.5.5 Beat-to-beat Blood Pressure Measurement

Non-invasive beat-to-beat BP recordings of 10 minutes duration were taken using the middle finger of the unaffected hand and an appropriately sized cuff in accordance with manufacturer guidance. The recording length was chosen to try to ensure that a minimum of five minutes valid data was available after inspection and the removal of artefacts. Participants were positioned supine with their arm supported at the level of the heart for the duration of the recording, with ECG leads attached to quantify heart rate by monitoring the R-R interval. A Task Force® Monitor (APC Cardiovascular Ltd, Southport, UK) was used in TEST-BP and SERVED Memory to obtain a single 10 minute recording. These participants also had a brachial oscillometric BP cuff of appropriate size fitted to the opposite arm to provide systemic BP calibration readings throughout the recording. In the BPV observational study and CAARBS recordings were made using the Finapres® MIDI device (Finapres Medical Systems, Enschede, The Netherlands), with two recordings per visit obtained in the former study and three in the latter. The servo adjust mechanism of the Finapres® MIDI was disabled during the recording period to prevent artefacts in the data, but was re-applied prior to each 10 minute recording for calibration. Recordings from the Finapres® MIDI were manually calibrated to systemic BP at the point of data inspection using a CBPM taken immediately prior to the recording. As previously described in section 2.4.2, both of these devices have been validated for the measurement of very short-term changes in BP and the assessment of BPV [95-97].

Both devices measure arterial BP in the finger using the “volume-clamp” method described by Penaz [232]. The finger cuff is inflated until the built-in plethysmograph detects maximal finger arterial pulsation. Finger volume is then calculated and changes in the cuff pressure on a beat-to-beat basis monitored (which equate to changes in arterial pressure). The analogue output from the devices was recorded onto a dedicated computer with an analogue-to-digital signal converter and appropriate software. Task Force® Monitor outputs were recorded using the standard bespoke software. Finapres® MIDI outputs were recorded using specially designed software (Professor Ronney Panerai, Medical Physics, University of Leicester) which was also used for the initial data processing as described in section 3.6.

3.5.6 Tools for Stroke Subtype and Severity

Data on stroke severity were collected using two common scales. The NIHSS is a graded neurological examination designed for use in clinical trials as a rapid method for assessing the extent of stroke impairment. The examination tests a range of potential deficits due to stroke including, but not limited to, motor weakness, visual field defects, language, and ataxia. The scale has since been simplified and the modified version has been widely adopted in clinical practice as a reproducible tool that correlates with functional outcomes [233]. The mRS is probably the most frequently used scale for judging outcomes in stroke research. It is a simple validated scale that assesses whether the patient is functionally independent with activities of daily living or requires some level of assistance due to residual stroke symptoms, with reference to their pre-stroke functional ability [234].

As already described in section 2.1.3 and **Table 1**, another commonly used classification of stroke subtypes is by the pathophysiological TOAST classification [32]. This tool was used in the BPV observational study and CAARBS at baseline data collection. However, a limitation of the TOAST classification is that it cannot be applied until thorough investigations have been completed. An alternative is the OCSP classification (**Table 16**), which was employed in all of the trials described. The OCSP is a clinical classification which divides patients according to the vascular territory involved in the stroke (anterior or posterior circulation) and, for anterior circulation strokes, the extent of the territory involved, based on the pattern of clinical findings [235]. The different OCSP categories correlate with outcomes in terms of the risk of short and long-term mortality and the likelihood of functional recovery.

3.6 Data processing

I processed data from TEST-BP, SERVED Memory, and CAARBS, whereas the research fellow in Leicester (Karen Appiah) processed data from the BPV observational study. Raw BP data from clinic, ABPM, HBPM, and beat-to-beat BP measurements using the Task Force® Monitor were exported directly to Excel where the data were inspected for completeness, outlying values, and artefacts. Raw beat-to-beat BP data recorded

Table 16: The Oxford Community Stroke Project (OCSP) Classification [235].

Subtype	**Criteria**
Total anterior circulation stroke (TACS)	All of: • Motor and/or sensory deficit of at least two of the face/arm/leg • Homonymous visual field defect • Higher cerebral dysfunction (e.g. aphasia, dyscalculia, visuospatial disorder)
Partial anterior circulation stroke (PACS)	One of: • Two out of three components of the TACS subtype • Higher cerebral dysfunction alone • Motor-sensory deficit that is more restricted than the LACS subtype (e.g. confined to one limb)
Lacunar stroke (LACS)	One of the following lacunar syndromes which correlate with occlusion of a single deep penetrating artery at strategic locations: • Pure motor stroke • Pure sensory stroke • Motor-sensory stroke • Ataxic hemiparesis • Dysarthria with clumsy hand
Posterior circulation stroke (POCS)	Any of: • Ipsilateral cranial nerve palsy and contralateral motor and/or sensory deficit • Bilateral motor and/or sensory deficit • Disorder of conjugate eye movement • Cerebellar dysfunction with ipsilateral long tract sign • Isolated hemianopia or cortical blindness

using the Finapres® MIDI were initially processed using specially designed software (Professor Ronney Panerai, Medical Physics, University of Leicester). This software allowed for the visualisation of the arterial waveform and heart trace, and was used to assess the quality of the recording and remove artefacts before the data was exported to Excel for further processing using the same method as for Task Force® Monitor recordings.

The average values and variability of SBP and DBP for each valid recording were calculated using formulae embedded in the Excel worksheet. For the SBP and DBP of each recording the mean, SD, CV, ARV, maximum BP, minimum BP, and MMD were calculated as described in section 2.5.2 and **Table 11**, though for enhanced CBPM this was limited to the mean, SD, and CV due to the small number of measurements. For clinic BP data, variability was derived from all available readings from each visit. For ABPM data, BPV was derived for the whole 24 hour recording and also separately for daytime and night-time periods of the recording where available. For HBPM data, BPV was derived from all readings from days 2-7. For beat-to-beat recordings, the BPV formulae were applied to full recordings and also separately to each 10 minute interval where multiple recordings were made.

4 Blood Pressure Differences Between Home Monitoring and Daytime Ambulatory Values and their Reproducibility in Hypertensive Stroke and TIA Patients

4.1 Declaration

The study presented in this chapter has been published elsewhere as a jointly authored paper [236]. I devised the study and jointly designed the statistical analysis plan along with Dr Allan Clark, carrying out all statistical analyses myself. I authored the paper and the co-authors reviewed it prior to submission for publication. The co-authors were Professor Myint and Professor Potter (co-investigators for TEST-BP which provided the data for the study), and Dr Allan Clark (statistician for TEST-BP). Although the paper has been amended for this thesis some parts, particularly the results section, remain substantively similar to the published version.

4.2 Introduction

In terms of both primary and secondary stroke prevention hypertension is one of, if not the most important modifiable risk factor [8, 43]. However, rates of achieving target BP post-stroke are suboptimal [237]. The diagnosis of high BP and monitoring response to antihypertensive treatment relies on having access to reliable methods that provide accurate and reproducible BP measurements. The traditional standardised method has been CBPM using a manual sphygmomanometer, yet this method may be undermined by factors such as poor technique, unconscious observer bias, terminal digit preference, and BPV [89, 90]. Whilst taking multiple CBPM values at successive visits may counter some of these limitations, CBPM alone is unlikely to provide an accurate BP in all patients (e.g. those with WCH or MH) [93]. Therefore, the use of out-of-office BP monitoring, using either ABPM or HBPM, is recommended to improve the accuracy of hypertension diagnosis and support management [54, 91, 92, 238]. ABPM is held to be the “gold standard” technique by some [91, 156], but use of HBPM has become more widespread following the emergence of evidence that its use

can improve BP control [239]. However, uncertainties remain about the effectiveness of HBPM in patients with cerebrovascular disease [240].

Using the same diagnostic and monitoring threshold values for CBPM and out-of-office BP measurements is considered inappropriate. The guideline threshold for the upper limit of normal BP from daytime ABPM is <135/85mmHg [91, 92], based on comparisons demonstrating that for a CBPM of 140/90mmHg the equivalent daytime ABPM readings are on average 4/3mmHg lower [110]. HBPM is ascribed the same threshold value as daytime ABPM, but some studies suggest this is incorrect [241, 242]. It is acknowledged that there is less evidence comparing HBPM with CBPM than is the case for ABPM [156], but also there are limited direct comparisons of HBPM with ABPM as the reference standard. Studies that have tried to address this gap have reported inconsistent findings, have not assessed the consistency of any differences between ABPM and HBPM, and have not enrolled high-risk patients (e.g. those with cerebrovascular disease) [106, 113-116, 121, 243]. Given the rising interest in BPV, particularly in relation to higher risk cardiovascular patient groups, there is a need to better establish the equivalence of BP measurement techniques as this could help with the standardisation of assessments for variability.

4.3 Hypothesis

This study aimed to investigate, using trial participants with a recent cerebrovascular event, whether differences exist between BP values obtained with daytime ABPM and HBPM. The hypothesis being tested was that the two measurement methods would not be equivalent in this patient group. If differences between daytime ABPM and HBPM were found, then the study also aimed to assess the reproducibility of these differences and explore related factors.

4.4 Methods

Data for this analysis comes from the TEST-BP trial, the methodology for which has been published elsewhere and is described in section 3.1.1 [223]. The methodology

specific to this analysis is summarised here. Participants in TEST-BP were adults with a recent stroke or TIA who also required antihypertensive treatment as part of their stroke secondary prevention management. Those randomised to one of the two home monitoring intervention groups who provided complete BP data (defined as baseline enhanced CBPM taken as the mean of three readings, ≥14 daytime ABPM readings at both baseline and six month follow-up, and ≥21 readings from HBPM performed at six weeks and five months post-randomisation) were considered eligible for this secondary analysis. HBPM data from the second recording period (three months after randomisation) were not used in this analysis. BP data was collected as described in sections 3.5.2 to 3.5.4. Participants had their medication history checked by the study nurse at each visit along with assessment of treatment compliance using a self-report questionnaire (Hill-Bone compliance scale). Anyone whose antihypertensive medications were altered between BP recordings that were planned for comparison in this analysis were excluded. Participants with ICH were also excluded.

Outcomes for this analysis were the comparison of mean SBP and DBP from the baseline daytime ABPM readings with the first (six week) HBPM readings, the follow-up ABPM readings with the last (five month) HBPM readings, and the CBPM readings with both the baseline daytime ABPM and first HBPM readings.

4.5 Statistical Analysis

SPSS version 23.0 was used for data analysis. Excluded participants were compared to those included using either a two-sample Student's t-test for normally distributed continuous variables, a Mann-Whitney U test for non-normally distributed continuous variables, or a chi-squared test for categorical variables. For each measurement method mean SBP and DBP were calculated along with SD. Comparison of the mean difference in SBP and DBP between measurement methods as described above was based on paired Student's t-tests. As the two intervention groups used different home monitors (as described in section 3.5.4), BP differences for each group were initially analysed separately, and subsequently pooled once it was apparent that the results of individually tested outcomes were comparable. Sensitivity and specificity of the diagnostic accuracy of HBPM was assessed against daytime ABPM as the reference

standard using the kappa statistic. A diagnostic threshold for hypertension of ≥135/85mmHg was taken for both methods [54, 91, 92]. The limits of agreement in measuring SBP and DBP, according to Bland and Altman's method, were derived for contemporaneous ABPM and HBPM recordings as defined previously [244]. To investigate variables that might predict individual variance in SBP or DBP difference from ABPM and HBPM exploratory univariate analyses were undertaken. These were initially descriptive, using scatter plots for continuous variables and box and whisker plots for categorical variables. Where descriptive analyses suggested possible relationships they were further explored with formal testing, using Pearson's correlation for continuous variables and independent samples t tests for categorical variables. The potential predictor variables tested were age, gender, body mass index (BMI), baseline clinic BP, being on antihypertensive treatment, history of diabetes, diagnosis (TIA or stroke), baseline mRS, baseline cognition (assessed using MoCA score), and the number of measurements from daytime ABPM and HBPM.

4.6 Results

Ninety-nine participants were randomised to one of the two trial intervention arms and were therefore eligible for inclusion in this analysis. Nineteen of them were excluded, 11 because their antihypertensive therapy was altered in between BP monitoring periods that were compared, and eight because they returned an insufficient number of HBPM measurements from one or both of the recordings. This left 80 participants for analysis. Demographics of those included and are presented in **Table 17**. There were no significant differences between the groups.

Mean CBPM SBP and DBP values were the highest, followed by HBPM values and then daytime ABPM values (**Table 18**). The difference in mean BP values from HBPM and daytime ABPM were consistent across both comparisons (**Figure 5**), were similar for both trial groups, and were unrelated to the HBPM device that was used (**Table 19**). Medication adherence judged by self-assessment was good at baseline and follow-up (median Hill-Bone score 9.0 [IQR 1.0] for both periods).

Table 17: Demographic data. Data presented are mean (SD) or frequency (%). Alcohol use and mRS are presented as median (IQR).

		Included	Excluded
N		80	19
Age (years)		74.1 (10.3)	75.4 (8.8)
Gender	**Male**	53 (66.3%)	12 (63.2%)
BMI (kg/m^2)		28.6 (5.3)	26.8 (2.1)
Smoking status	**Never**	36 (45.0%)	6 (31.6%)
	Ex-smoker	40 (50.0%)	13 (68.4%)
	Current smoker	4 (5.0%)	0 (0.0%)
Alcohol (units/week)		4.0 (14.0)	4.0 (12.0)
Diagnosis	**Stroke**	27 (33.8%)	5 (26.3%)
OCSP classification	**LACS**	9 (33.3%)	4 (80.0%)
	PACS	9 (33.3%)	1 (20.0%)
	TACS	1 (3.7%)	0 (0.0%)
	POCS	8 (29.6%)	0 (0.0%)
Baseline mRS (stroke only)		1.0 (1.0)	1.0 (1.0)
Past medical history	**TIA**	51 (63.7%)	15 (78.9%)
	Stroke	33 (41.3%)	7 (36.8%)
	IHD	20 (25.0%)	4 (21.1%)
	Diabetes	17 (21.3%)	5 (26.3%)
	Hypertension	58 (72.5%)	14 (73.7%)
On antihypertensive therapy		75 (93.8%)	17 (89.5%)
Antihypertensive use by class	**ACEI**	52 (65.0%)	10 (52.6%)
	ARB	11 (13.8%)	4 (21.1%)
	Beta blockers	15 (18.8%)	6 (31.6%)
	CCB	33 (41.3%)	9 (47.4%)
	Thiazide-like diuretics	14 (17.5%)	4 (21.1%)

SD denotes standard deviation; mRS, modified Rankin score; IQR, interquartile range; BMI, body mass index; OCSP, Oxford Community Stroke Project; LACS, lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke; TIA, transient ischaemic attack; IHD, ischaemic heart disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 18: Mean (SD) group systolic and diastolic blood pressure from each measurement method.

Measurement method	Number of measurements	Mean SBP (mmHg)	Mean DBP (mmHg)
Baseline CBPM	3 (0)	150.8 (20.2)	85.1 (11.8)
Baseline daytime ABPM	38.1 (9.1)	133.5 (13.7)	76.4 (8.5)
HBPM at six weeks	27.3 (1.4)	140.1 (15.8)	78.5 (8.7)
HBPM at five months	26.8 (3.1)	134.7 (13.7)	76.2 (9.7)
Daytime ABPM at six months	37.2 (8.4)	127.6 (12.2)	74.2 (9.2)

SD denotes standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; CBPM, clinic blood pressure measurement; ABPM, ambulatory blood pressure measurement; HBPM, home blood pressure measurement.

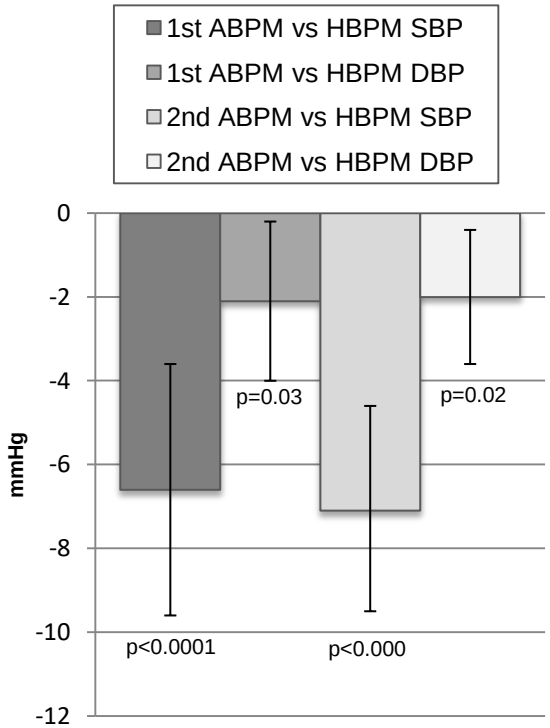

Figure 5: Mean differences in blood pressure for head-to-head comparisons of out-of-office measurement methods. Error bars are 95% confidence intervals. P values represent paired Student's t-tests comparing the difference between measurement methods. ABPM denotes ambulatory blood pressure measurement; HBPM, home blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 19: Mean differences in systolic and diastolic blood pressure between home and daytime ambulatory blood pressure measurements at different time-points according to intervention group and type of home monitor used. Data presented are mean (SD) or mean (95% CI). P values represent independent samples t-tests to investigate the mean difference in blood pressure between the two groups.

	Home monitoring only (N=42)	**Home monitoring with guided self-management (N=38)**	**Mean difference between groups**	**P value**
Baseline daytime ABPM vs. first HBPM SBP (mmHg)	-7.6 (14.4)	-5.5 (12.6)	-2.1 (-8.1 to 4.0)	0.49
Baseline daytime ABPM vs. first HBPM DBP (mmHg)	-1.5 (8.9)	-2.8 (8.1)	1.3 (-2.5 to 5.1)	0.50
Follow-up daytime ABPM vs. last HBPM SBP (mmHg)	-8.1 (11.2)	-5.9 (10.9)	-2.2 (-7.1 to 2.7)	0.38
Follow-up daytime ABPM vs. last HBPM DBP (mmHg)	-1.1 (7.0)	-2.9 (7.4)	1.8 (-1.4 to 5.0)	0.27

SD denotes standard deviation; 95% CI, 95% confidence interval; ABPM, ambulatory blood pressure measurement; HBPM, home blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure.

The limits of agreement for ABPM vs. HBPM for the first comparison of SBP were -33.0 to 19.9mmHg and for the second comparison were -28.7 to 14.5mmHg (**Figure 6**). For DBP the limits of agreement were -18.8 to 14.5mmHg and -16.1 to 12.2mmHg respectively. For the whole cohort the differences in mean SBP and DBP were consistent across both comparisons, however, this was not the case for individual participants. For the difference in SBP between daytime ABPM and HBPM the mean change over time was 11.0 ± 8.3mmHg (range 0.65 to 43.3mmHg), and the mean change for DBP was 6.5 ± 5.1mmHg (range 0.21 to 19.8mmHg) (**Figure 7**). Exploratory analyses for variables that might predict the differences between daytime ABPM and HBPM values did not reveal any clear significant relationships. Descriptive testing suggested possible relationships with being on antihypertensive treatment and baseline clinic SBP (**Figures 8-9**), but further testing of the latter showed only a weak correlation (r=-0.25, p=0.02) that was not consistent across both comparisons. Further testing of the former was not possible due to the small number of participants (N=5) who were not taking antihypertensive medications.

Taking a diagnostic threshold value for hypertension of ≥135/85mmHg for both methods and using daytime ABPM as the reference standard, HBPM had a diagnostic sensitivity of 76.1% and specificity of 55.9% (k=0.36, p=0.004) when comparing the first set of readings. Using the second set of readings provided consistent data, with HBPM having a diagnostic sensitivity of 70.8% and specificity of 55.4% (k=0.22, p=0.03). At baseline, 46/80 (57.5%, 95% CI 46.3-67.9%) participants were classified as having uncontrolled hypertension according to daytime ABPM readings and at follow-up the rate was 24/80 (30.0%, 95% CI 20.0-40.3%). Using HBPM readings, 50/80 (62.5%, 95% CI 52.5-72.7%) were classified as uncontrolled hypertension on the first recording and 42/80 (52.5%, 95% CI 41.7-63.6%) on the second recording. Classification of hypertension status was the same according to both methods in 54/80 (67.5%, 95% CI 57.8-77.8%) participants at the first recording period (35 uncontrolled hypertension and 19 controlled hypertension) and 48/80 (60.0%, 95% CI 49.4-71.6%) at the second recording period (17 uncontrolled hypertension and 31 controlled hypertension).

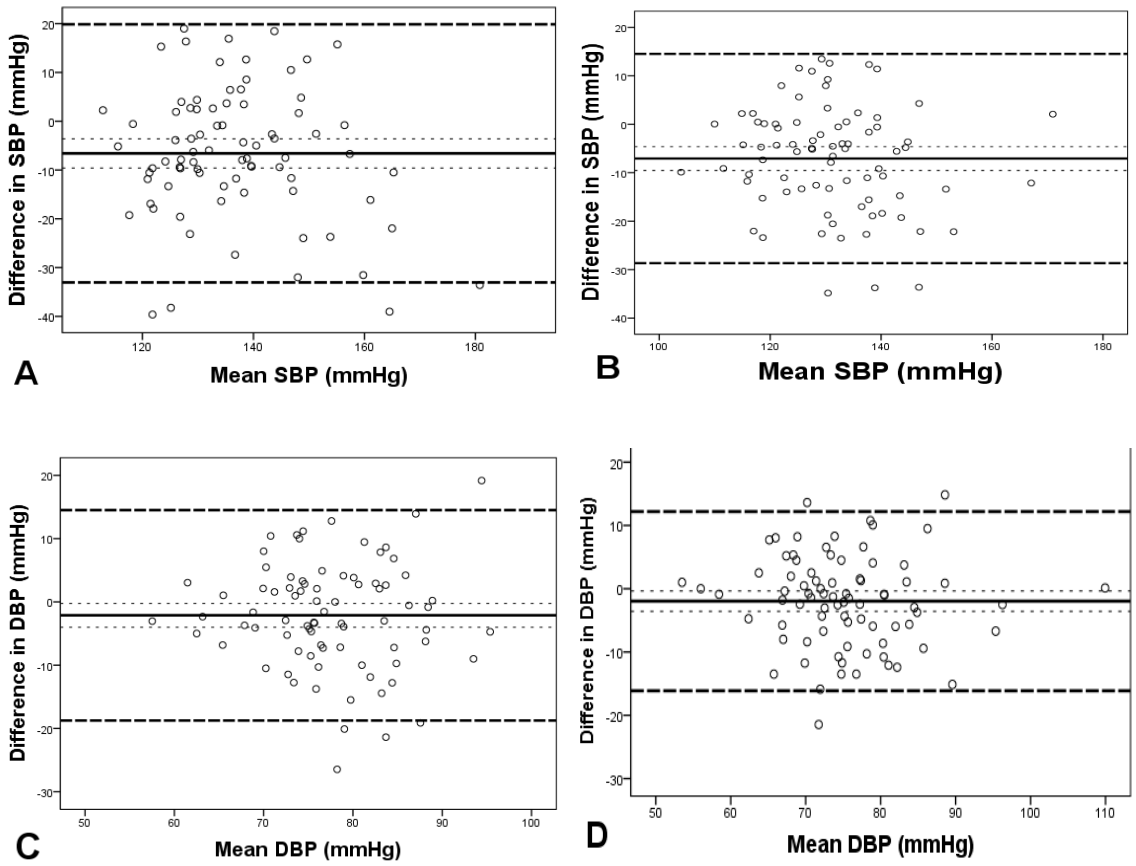

Figure 6: Bland-Altman plots to show the limits of agreement for within-individual blood pressure recorded by ambulatory blood pressure measurement (ABPM) and home blood pressure measurement (HBPM). Thick lines show the mean difference, dotted lines the 95% confidence interval for the mean difference, and dashed lines the limits of agreement (± 2 SD). **A** shows systolic blood pressure (SBP) comparing baseline ABPM and the first HBPM. **B** shows SBP comparing outcome ABPM and the last HBPM. **C** shows diastolic blood pressure (DBP) comparing baseline ABPM and the first HBPM. **D** shows DBP comparing outcome ABPM and the last HBPM. SD denotes standard deviation.

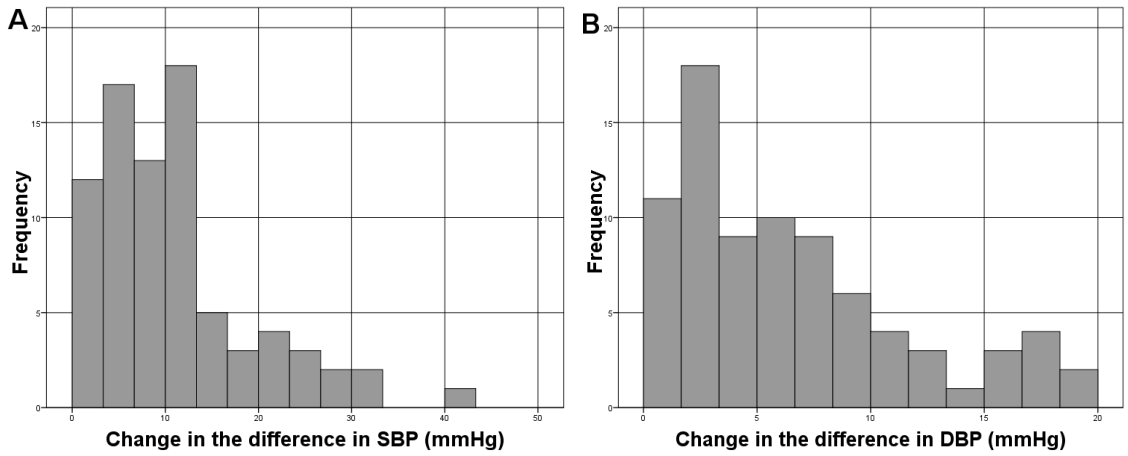

Figure 7: Histograms to show the change in the blood pressure difference recorded by daytime ambulatory and home blood pressure measurement from the first to the second comparison for individuals. **A** shows the change in systolic blood pressure (SBP). **B** shows the change in diastolic blood pressure (DBP).

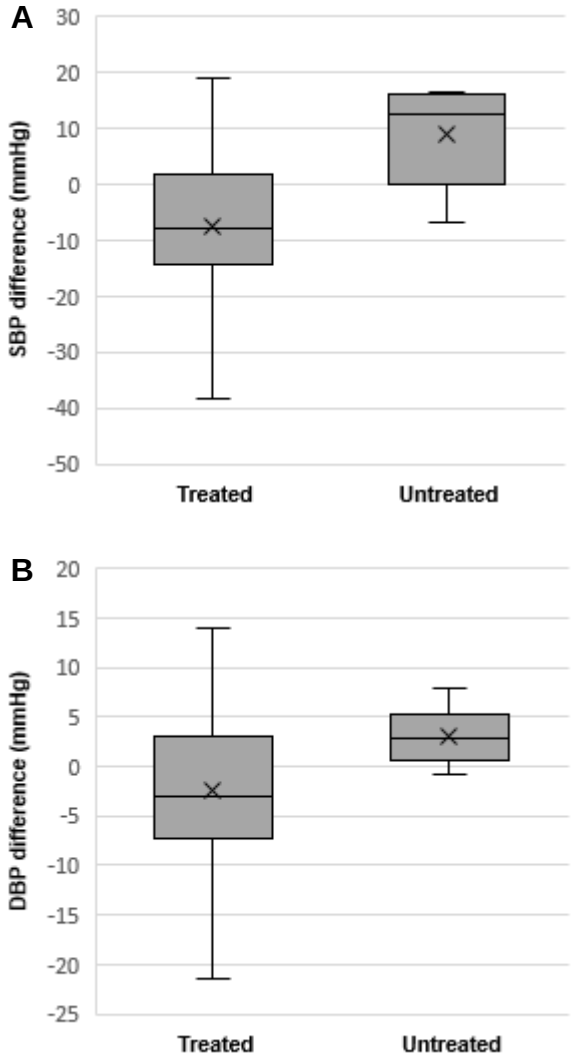

Figure 8: Box and whisker plots showing the difference in blood pressure between baseline daytime ambulatory blood pressure measurement and the first home blood pressure measurement according to whether individuals were taking antihypertensive treatment. **A** is the difference in systolic blood pressure (SBP). **B** is the difference in diastolic blood pressure (DBP).

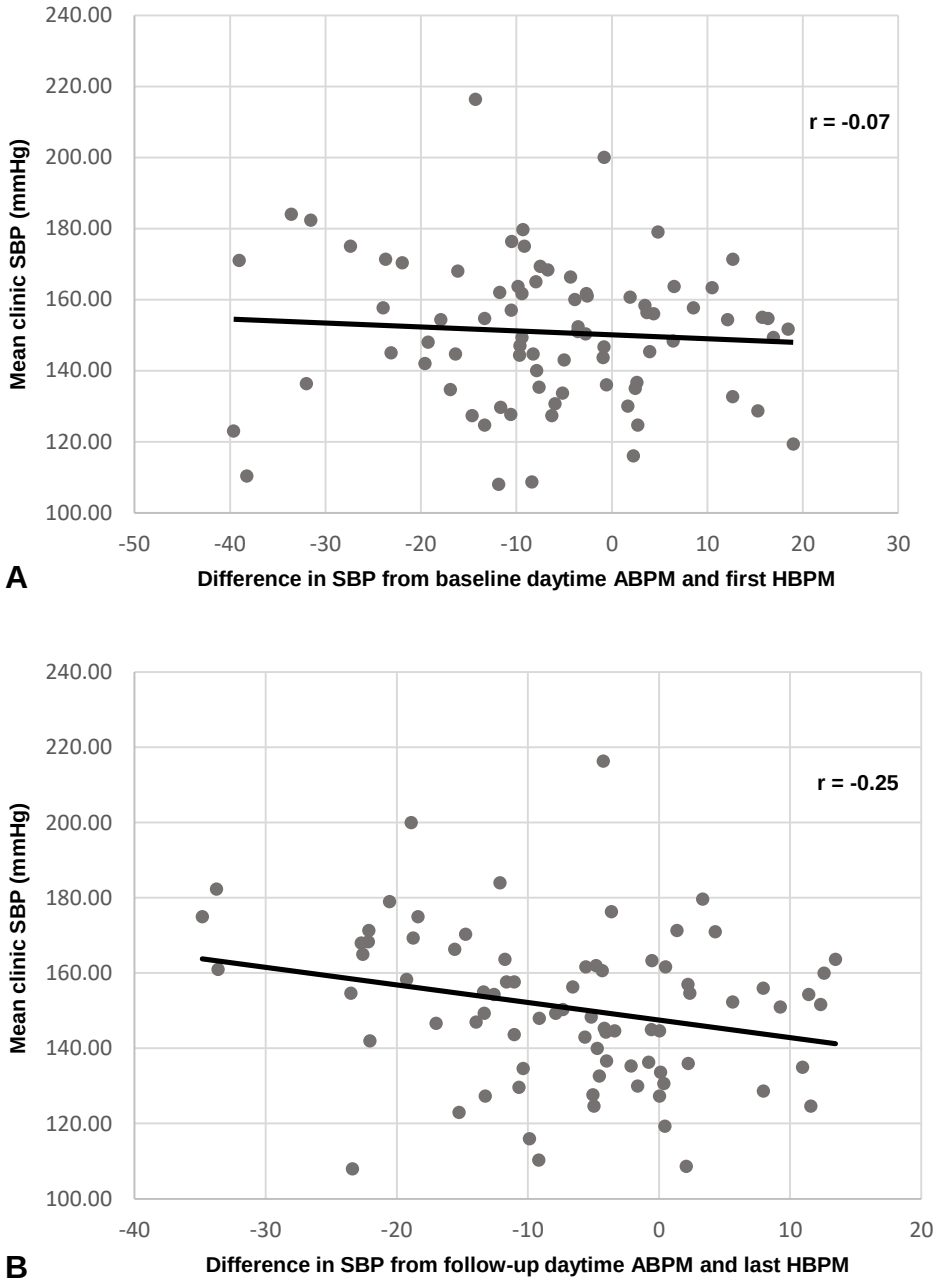

Figure 9: Scatter plots showing mean clinic systolic blood pressure (SBP) at baseline plotted against the difference in SBP from daytime ambulatory blood pressure measurement (ABPM) and home blood pressure measurement (HBPM). Fit lines and r values represent Pearson's correlation between the two values. **A** is the SBP difference from the first comparison. **B** is the SBP difference from the second comparison.

4.7 Discussion

These data show that in a population with a recent cerebrovascular event there are significant differences in BP measurements obtained from daytime ABPM compared to HBPM, with the former approximately 7/2mmHg lower than the latter on average. This difference was consistent across two recording periods several months apart. Although the average difference between the measurement methods was reproducible, the limits of agreement were wide and for individuals the difference between the methods was not consistent over time. This suggests that BP values obtained using daytime ABPM cannot be used to infer values from HBPM, and vice versa, meaning that the methods may not be interchangeable. Additionally, the difference recorded was large enough that it could be clinically important, considering a reduction in SBP in the order of 10mmHg might reduce the risk of stroke by as much as 30% [9, 43]. The difference might also influence patient management, potentially causing discordant treatment decisions depending on which method is used to confirm diagnosis or monitor treatment response. In this group, using the same threshold value for both methods (≥135/85mmHg) resulted in a mismatch in classification of hypertension status in 26/80 (32.5%) participants at baseline and 32/80 (40.0%) at follow-up, which is not an insignificant proportion. Unfortunately, in the exploratory analysis no predictive factors for the observed measurement differences were demonstrated, with the possible relationship with clinic SBP likely to be a chance finding.

CBPM has been used as the reference standard to assess both ABPM and HBPM [110, 245], but fewer studies have directly compared both out-of-office methods. Of those that have, not all have used an HBPM protocol consistent with current guidelines. Several studies have reported findings consistent with this analysis. A randomised controlled trial investigating the benefit of HBPM in hypertensive adults recruited from primary care reported a difference of -3.1/+0.7mmHg between daytime ABPM and HBPM at follow-up, though this was not formally investigated [246]. Similarly, differences between daytime ABPM and HBPM ranging from -5 to -7mmHg for SBP and -1 to -4mmHg for DBP have been reported in three cross-sectional studies that recruited either treated or untreated hypertensive adults [106, 116, 121]. Comparable limits of agreement have also been reported elsewhere [247]. Conversely, equivalence

between daytime ABPM and HBPM has been reported in one study on untreated hypertensive adults [115]. Importantly, none of these studies performed repeated BP measures to investigate the reproducibility of any differences.

The age of included participants could at least in part account for differences in the literature, and may partly explain the results of this analysis, as there is evidence that the difference between the two methods may alter across age groups [113, 114]. It is reported that daytime ABPM values are higher than HBPM values in children, but with increasing age the two values converge and may cross over at around 60 years. That age was not a predictive factor for the difference between the two methods in this cohort might be due to the narrow age range of included participants. Nevertheless, as many people experience their first cerebrovascular event at older ages the difference remains relevant. Alternatively, being on antihypertensive treatment (which is more likely with increasing age) may relate to the difference between the two methods [106, 248]. This could be because morning HBPM measurements are routinely taken prior to medications, thereby capturing BP at the trough of antihypertensive activity. These 'trough values' might be less influential to mean values from daytime ABPM than HBPM due to the increased number of measurements acquired per day. Similarly, increased BPV in an individual might also account for differences between measurement methods with varying numbers of readings. Greater BPV could potentially increase mean values from HBPM relative to daytime ABPM due to there being fewer measurements to contribute to the average, resulting in the differences seen here. Importantly, the recent cerebrovascular event is unlikely to have confounded BP readings from participants in this study as it has been demonstrated that patients with previous stroke are able to accurately measure their own BP [249].

In terms of diagnostic accuracy at a threshold value of ≥135/85mmHg, a sensitivity of 86% and specificity 62% has been reported for HBPM assessed against daytime ABPM as reference, which is in keeping with the findings of this analysis [243]. Whether these values are sufficiently high is at least in part a matter of judgement. However, one other study has suggested, as suggested here, that the difference may have important clinical consequences at an individual patient level by showing that despite both daytime ABPM and HBPM diagnosing the same proportion of a cohort with MH, it was

not the same people that were diagnosed by both methods. In fact, almost half of those diagnosed with MH by daytime ABPM were not according to HBPM [250]. The question of the equivalence and diagnostic accuracy of out-of-office BP measurement methods may also be relevant when considering the measurement of BPV. Firstly, there is evidence that BPV increases linearly with mean BP [130, 251]. Therefore, if different methods are not interchangeable with respect to measuring BP it may also be the case that they differ in their measurement of BPV, perhaps simply because recorded mean BP may be higher, or perhaps because different aspects of an individual's BP profile are captured. Secondly, although threshold values for variability are yet to be established, if threshold values for absolute BP differ between measurement methods it might also be expected that BPV thresholds will not be equivalent. It will therefore be important to assess whether BPV values from different measurement methods are in agreement, and, if not, what level of BPV is of relevance for each method.

These data, and the wider literature, support the assertion that daytime ABPM and HBPM are not interchangeable methods of BP measurement, despite the recommendation in hypertension guidelines that the same threshold values should be used for both methods [91, 229]. It therefore follows that, in an individual, the diagnosis of raised BP and the follow-up of response to antihypertensive treatment should not be based on a mix of out-of-office measurements using these different methods. Choosing which method to utilise may come down to questions of cost, ease of use and interpretation, and patient preference, all of which may favour HBPM over ABPM. However, if accuracy of measurement is the primary concern then it is likely that ABPM will be the method of choice. Firstly, the threshold values for raised BP as they apply to ABPM have been more clearly established than for HBPM. Secondly, ABPM is less prone to measurement and reporting bias because the patient takes no role in acquiring readings. Thirdly, a greater number of BP readings are obtained when using ABPM, with the further addition of nighttime readings when recording is performed over 24 hours. For these reasons, and also because it is likely that improved accuracy will be important for the measurement of BPV, it is my opinion that at present ABPM should be favoured over HBPM where both modalities are available.

A strength of this study is that it was possible to compare values from daytime ABPM and HBPM at two different times in the same population, thereby providing data about the consistency of the difference between the two methods and allowing consideration of the reproducibility of this difference. It was also the first study, to the best of my knowledge, to compare and assess the limits of agreement between daytime ABPM and HBPM in a population with cerebrovascular disease. However, the study is not without its limitations. Firstly, whilst I argue that selecting a high-risk population is a strength of the study, it does also limit the generalisability of the findings. Secondly, this is a post-hoc analysis with a relatively small sample size and so should be interpreted with caution, as it was not powered to assess the stated outcomes. Thirdly, the findings could be influenced by methodological factors, such as the short time lag between measurements that were compared, the use of two different home BP monitors, or patients being on antihypertensive treatment. With regard to the former this is not a unique feature of this study, with other studies comparing measurements taken up to 4-6 weeks apart [114, 116, 121], and I have tried to mitigate the impact of the latter two potential issues through the statistical analysis approach and participant selection.

4.8 Summary

- Significant differences exist between BP values from daytime ABPM and HBPM, despite guidelines recommending the same threshold values for both methods.
- Differences were not consistent between individuals suggesting that daytime ABPM and HBPM are not interchangeable.
- The difference might be clinically important given its magnitude and the potential to result in over or under-treatment of patients depending on which measurement method is used.
- The difference also has implications for the measurement of BPV as, if different measurement methods are not equivalent in their assessment of absolute BP, it might reasonably be expected that they will also be at variance in their assessment of BPV.

- It is my opinion that ABPM should be favoured over HBPM as this method is likely to provide the most accurate estimation of a patient's BP and its variability.

5 A Comparison of Beat-to-beat Blood Pressure Variability with Variability Derived from other Blood Pressure Measurement Methods in Patients with Cerebrovascular Disease

5.1 Introduction

BPV, as opposed to mean BP level, has been proposed as a potential explanatory factor for gaps in the established theory of BP as a cardiovascular risk factor [126]. Evidence is accumulating to suggest that BPV is a cardiovascular risk factor independent of mean BP [128, 152, 153]. Increased BPV may also be associated with adverse outcomes after acute ischaemic stroke [98], its relevance being related to the reliance of CBF on systemic BP in the face of disordered cerebral autoregulation post stroke [13]. In the previous chapter it was demonstrated that there are discrepancies between commonly used out-of-office BP measurement methods in quantifying mean BP in patients with a recent ischaemic cerebrovascular event. This may have implications for the measurement of BPV, as variability from different measurement methods may also be discordant in this patient group. At present there is a lack of consistency in how BPV is defined in the literature, with no consensus on the optimal approach to measurement and calculation, and a lack of evidence as to whether treatment that reduces BPV is of value [90, 155, 156].

One factor in this lack of consistency is that BPV can be measured over different timescales depending on the BP measurement method used. Potential timescales range from the very short-term (over seconds to minutes) using beat-to-beat BP monitoring, through the short-term (minutes to hours) and medium-term (hours to days) using ABPM and HBPM respectively, up to the long-term (months to years) usually derived from repeated CBPM over time. All timescales of BPV have been shown to predict cardiovascular risk [128, 131, 200, 252-254], but studies suggest that their prognostic relevance may not be equal [90, 131, 155]. Furthermore, the few studies that have made direct comparisons of different timescales of variability indicate that they are not closely correlated. Comparisons reported to date include within-visit or visit-to-visit clinic BPV over eight weeks with 24 hour or daytime ABPM and HBPM

[160], daytime ABPM with HBPM and visit-to-visit clinic BPV over four weeks [118], and beat-to-beat BPV with 24 hour ABPM and HBPM [134].

Beat-to-beat BPV is increased in acute ischaemic stroke [100]. Furthermore, the evidence that BPV is associated with stroke outcome relates to short-term BPV measured over minutes or hours [15]. Beat-to-beat BPV may therefore be of particular importance in this patient group. However, beat-to-beat BP measurement is not routinely used in clinical practice, with guideline recommended methods, such as CBPM, ABPM and HBPM, being more commonplace [91, 92]. Consequently, only one study comparing timescales of BPV has included beat-to-beat measurements [134]. This study enrolled untreated hypertensive adults without any cerebrovascular disease and did not assess whether beat-to-beat BPV has any relationship with other shorter-term BPV measurements (i.e. within-visit clinic BPV, or within-hour BPV calculated from ABPM measurements). Investigation of this would be useful to determine if these alternative measurements could be used as a surrogate for beat-to-beat BPV measurement.

5.2 Hypothesis

Using data from the TEST-BP trial, the aim of this analysis was to compare beat-to-beat BPV with variability from other measurement methods with the intention of assessing comparisons not previously reported, and making these comparisons in a cohort of patients with cerebrovascular disease. The hypothesis being tested is that BPV values calculated over different timescales will not have significant inter-relationships and will not provide interchangeable data.

5.3 Methods

Data for this analysis comes from the TEST-BP trial, which was a trial of BP self-monitoring and guided self-management in patients with a recent stroke or TIA. The general methodology for TEST-BP is described in section 3.1.1 and has been published elsewhere [223]. The methodology specific to this secondary analysis is described here.

Eligible participants were subjects from TEST-BP who had a complete set of baseline BP data, including enhanced CBPM with three readings, daytime ABPM with ≥14 readings, and beat-to-beat measurement with a recording duration of ≥ 5minutes after data cleaning, all of which were recorded at the same visit. An additional subgroup of participants who undertook HBPM six weeks after the baseline visit was also included. Participants with BP data that was incomplete according to these criteria or who were diagnosed with ICH were excluded. Participants were excluded from the subgroup if they provided <21 HBPM readings or if their antihypertensive medications were altered between the baseline visit and the HBPM recording period at six weeks.

BP measurements from the baseline visit have been used in this analysis, along with the first set of HBPM measurements taken at six weeks for the subgroup. BP measurements for each method were taken as described in sections 3.5.2 to 3.5.5. Mean and variability values for SBP and DBP from each BP measurement method were calculated as described in section 3.6. In addition to variability over the whole daytime period, within-hour BPV was calculated from ABPM recordings. For each hourly period with at least two valid measurements the mean, SD, CV, ARV and MMD of these measurements were calculated, with the arithmetic means of these calculated values representing within-hour mean and BPV values.

Outcomes for this analysis were the comparison of beat-to-beat BPV indices with the same index from other contemporaneous measurement methods, including CBPM, daytime ABPM, and HBPM, and the assessment of their limits of agreement.

5.4 Statistical Analysis

Data were analysed using SPSS version 25.0. Scatter plots were constructed to visually assess the relationship between each BPV index from beat-to-beat measurements with the same BPV index from other measurement methods. BPV data were not normally distributed; therefore formal testing of correlations between BPV indices from different measurement sets was undertaken using Spearman's rho. Conversely, mean BP measurements were normally distributed and so were formally compared using Pearson's correlations. Correlations were considered weak if r or r_s=0.10-0.29,

moderate if r or r_s=0.30-0.49, and strong if r or r_s=>0.50 [255]. Further exploration of the relationships between beat-to-beat BPV and variability from other measurement methods was conducted where there was a suggestion of a positive relationship. This was done using Bland and Altman's method for assessing the limits of agreement between tests [244]. The mean value for both methods was plotted against the difference between them, with reference lines added to the plot to show the mean difference and two standard deviations either side of the mean. Outliers were excluded to ensure that the differences between methods were normally distributed ($p>0.05$ using the Kolmogorov-Smirnov test correlated against a histogram of the data with distribution curve). Due to weak or moderate correlations between the mean values and the differences, the latter were plotted as ratio data rather than absolute values. As this was an exploratory analysis no adjustments for multiple testing were made, with $p<0.05$ considered statistically significant.

5.5 Results

One hundred and thirty three participants from the trial had complete baseline BP data, with a subgroup of 82 providing valid HBPM data in addition to the baseline measurements. Demographic data for the full cohort and the HBPM subgroup is presented in **Table 20**.

Mean SBP and DBP, and median values for BPV indices from each measurement method for the whole cohort and the HBPM subgroup are displayed in **Tables 21-22**. BPV values from within-hour ABPM appeared to be more closely matched to beat-to-beat BPV than other methods. The exception to this was ARV, where values from within-hour ABPM were more closely matched to daytime ABPM, with ARV from beat-to-beat measurements different to all other methods.

Mean SBP and DBP from each method was moderately or strongly correlated with the corresponding mean value from beat-to-beat BP (r=0.33-0.62, $p<0.01$ for all correlations). However, correlations between BPV indices were either weak or non-significant, with the exception of ARV of DBP from daytime ABPM and HBPM with beat-to-beat measurement which showed moderate correlations (r_s=0.32 and 0.34

Table 20: Demographic data. Data presented are mean (SD) for normally distributed continuous variables, median (IQR)* for non-normally distributed continuous variables, and frequency (%) for categorical variables.

		All	HBPM subgroup
N		133	82
Age (years)		73.7 (9.9)	74.9 (9.6)
Gender	**Male**	86 (64.7%)	55 (67.1%)
BMI (kg/m^2)		28.7 (5.0)	28.5 (4.8)
Smoking status	**Never smoked**	53 (39.8%)	33 (40.2%)
	Ex smoker	74 (55.6%)	46 (56.1%)
	Current smoker	6 (4.5%)	3 (3.7%)
Alcohol (units/wk)*		4.0 (16.0)	5.0 (16.0)
Diagnosis	**Stroke**	41 (30.8%)	26 (24.4%)
NIHSS (stroke patients only)*		3.0 (2.5)	2.0 (2.0)
OCSP classification	**LACS**	17 (41.5%)	11 (42.3%)
	PACS	16 (39.0%)	8 (30.8%)
	TACS	1 (2.4%)	1 (3.8%)
	POCS	7 (17.1%)	6 (23.1%)
Past medical history	**TIA**	93 (69.9%)	56 (68.3%)
	Stroke	52 (39.1%)	33 (40.2%)
	IHD	28 (21.1%)	20 (24.4%)
	Diabetes	35 (26.3%)	20 (24.4%)
	Hypertension	98 (73.7%)	63 (76.8%)
On antihypertensive therapy		124 (93.2%)	76 (92.7%)
No. of antihypertensives		1.7 (0.9)	1.7 (1.0)
Antihypertensive	**ACEI**	78 (58.6%)	50 (61.0%)

use by class	**ARB**	22 (16.5%)	14 (17.1%)
	Beta blockers	34 (25.6%)	18 (22.0%)
	CCB	54 (40.6%)	31 (37.8%)
	Thiazide-like diuretics	23 (17.6%)	15 (18.3%)

SD denotes standard deviation; IQR, interquartile range; HBPM, home blood pressure measurement; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxford Community Stroke Project; LACS, lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke; TIA, transient ischaemic attack; IHD, ischaemic heart disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 21: Average baseline blood pressure and blood pressure variability parameters from each measurement method in the full cohort. Mean systolic and diastolic blood pressure are presented as mean (SD). Systolic and diastolic variability values are presented as median (IQR).

	Enhanced CBPM	Beat-to-beat BP	Daytime ABPM	Within-hour ABPM
Mean SBP (mmHg)	152.1 (19.3)	131.9 (16.3)	135.1 (14.0)	134.9 (14.0)
Mean DBP (mmHg)	83.7 (12.0)	81.0 (12.7)	76.1 (8.9)	76.0 (9.0)
SD SBP (mmHg)	5.4 (3.7)	5.4 (2.9)	13.2 (5.1)	6.3 (2.2)
SD DBP (mmHg)	2.9 (3.3)	4.2 (2.3)	8.9 (3.1)	4.4 (1.4)
CV SBP (%)	3.7 (2.4)	4.1 (2.1)	9.7 (3.5)	4.6 (1.4)
CV DBP (%)	3.5 (3.4)	5.2 (2.6)	11.6 (4.7)	5.8 (2.1)
ARV SBP (mmHg)	-	1.5 (1.0)	9.4 (3.0)	10.1 (3.1)
ARV DBP (mmHg)	-	1.1 (0.8)	7.1 (2.3)	7.0 (2.6)
MMD SBP (mmHg)	-	32.5 (21.6)	58.0 (24.0)	33.8 (20.3)
MMD DBP (mmHg)	-	26.8 (16.9)	46.0 (13.5)	23.8 (12.7)

CBPM denotes clinic blood pressure measurement; BP, blood pressure; ABPM, ambulatory blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation; ARV, average real variability; MMD, maximum-minimum difference.

Table 22: Average baseline blood pressure and blood pressure variability parameters from each measurement method in the home blood pressure measurement subgroup. Mean systolic and diastolic blood pressure are presented as mean (SD). Systolic and diastolic variability values are presented as median (IQR).

	Enhanced CBPM	Beat-to-beat BP	Daytime ABPM	Within-hour ABPM	HBPM
Mean SBP (mmHg)	151.2 (19.6)	132.9 (17.0)	135.0 (13.6)	134.9 (13.3)	141.7 (16.6)
Mean DBP (mmHg)	84.4 (11.6)	81.6 (12.5)	76.4 (8.3)	76.3 (8.4)	77.8 (8.4)
SD SBP (mmHg)	5.4 (4.1)	5.4 (2.7)	13.2 (5.4)	6.3 (2.3)	11.2 (4.4)
SD DBP (mmHg)	3.1 (3.3)	4.0 (2.4)	9.1 (3.1)	4.3 (1.3)	6.2 (2.8)
CV SBP (%)	3.8 (2.4)	4.2 (2.2)	9.6 (3.3)	4.7 (1.5)	8.0 (3.0)
CV DBP (%)	3.8 (3.2)	5.0 (2.9)	11.5 (4.5)	5.7 (1.8)	8.3 (3.0)
ARV SBP (mmHg)	-	1.5 (1.0)	9.2 (3.2)	9.9 (3.6)	11.2 (5.2)
ARV DBP (mmHg)	-	1.0 (0.9)	7.1 (2.3)	7.0 (2.5)	6.0 (3.1)
MMD SBP (mmHg)	-	33.0 (23.3)	58.5 (23.8)	32.7 (21.8)	47.0 (19.3)
MMD DBP (mmHg)	-	26.5 (19.1)	44.5 (14.3)	23.9 (12.1)	25.0 (12.0)

CBPM denotes clinic blood pressure measurement; BP, blood pressure; ABPM, ambulatory blood pressure measurement; HBPM, home blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation; ARV, average real variability; MMD, maximum-minimum difference.

respectively, p<0.01 for both correlations) (**Tables 23-24**). Correlations between beat-to-beat BPV and within-hour ABPM variability parameters were not stronger than correlations with variability from other methods. The Bland-Altman analyses of the relationship between beat-to-beat and within-hour ABPM systolic BPV (**Figure 10**) showed a large bias for ARV of SBP (mean difference -142.82% (95% confidence interval -146.53% to -139.11%), but not for SD (mean difference -11.60% (95% confidence interval -19.04% to -4.16%), CV (mean difference -9.08% (95% confidence interval -16.29% to -1.87%), or MMD (mean difference -0.73% (95% confidence interval -9.67% to 8.20%). However, the limits of agreement were wide ranging for all measures of systolic BPV (SD = -96.61% to 73.41%, CV = -91.50% to 73.34%, ARV = -184.39% to -101.25%, MMD = -102.83% to 101.37%). The analyses comparing beat-to-beat with daytime ABPM systolic BPV (**Figure 11**) and beat-to-beat with HBPM systolic BPV (**Figure 12**) showed a moderate to large bias and wide ranging limits of agreement for all BPV indices. Findings for DBP were similar to those for SBP (**Figures 13-15**). Further comparison of beat-to-beat BPV and within-visit clinic BPV was deemed not appropriate.

5.6 Discussion

These data show that there is no evidence of significant relationships between BPV from beat-to-beat BP measurements and within-visit variability from enhanced CBPM. They also show that, despite apparent similarities between the average values obtained with beat-to-beat and within-hour ABPM BPV measurements, which are not present between beat-to-beat and other methods of assessing BPV, these two methods of measuring BPV are not closely correlated. Furthermore, the limits of agreement between the two methods are wide ranging, suggesting that they are not interchangeable methods of measuring BPV. When assessing beat-to-beat with daytime ABPM and beat-to-beat with HBPM the correlations were also weakly significant at best, with even more wide ranging limits of agreement and marked bias in the mean differences between these methods.

Table 23: Correlations for systolic blood pressure and variability between beat-to-beat and other blood pressure measurement methods. Correlations are based on the full cohort, except those with home blood pressure measurements which are based on the subgroup only. Correlations are Pearson's r for mean values and Spearman's rho for BPV values. *p<0.05 **p<0.01.

Comparator	Mean	SD	CV	ARV	MMD
Enhanced CBPM	0.50**	0.04	-0.01	-	-
Daytime ABPM	0.35**	0.26**	0.23**	0.23**	0.17
Within-hour ABPM	0.33**	0.20*	0.20*	0.25**	0.11
HBPM	0.50**	0.20	0.17	0.27*	0.20

SD denotes standard deviation; CV, coefficient of variation; ARV, average real variability; MMD, maximum-minimum difference; CBPM, clinic blood pressure measurement; ABPM, ambulatory blood pressure measurement; HBPM, home blood pressure measurement.

Table 24: Correlations for diastolic blood pressure and variability between beat-to-beat and other blood pressure measurement methods. Correlations are based on the full cohort, except those with home blood pressure measurements which are based on the subgroup only. Correlations are Pearson's r for mean values and Spearman's rho for BPV values. *p<0.05 **p<0.01.

Comparator	Mean	SD	CV	ARV	MMD
Enhanced CBPM	0.62**	0.06	0.02	-	-
Daytime ABPM	0.57**	0.27**	0.28**	0.32**	0.18*
Within-hour ABPM	0.55**	0.17	0.21*	0.29**	0.13
HBPM	0.55**	0.28*	0.28*	0.34**	0.29**

SD denotes standard deviation; CV, coefficient of variation; ARV, average real variability; MMD, maximum-minimum difference; CBPM, clinic blood pressure measurement; ABPM, ambulatory blood pressure measurement; HBPM, home blood pressure measurement.

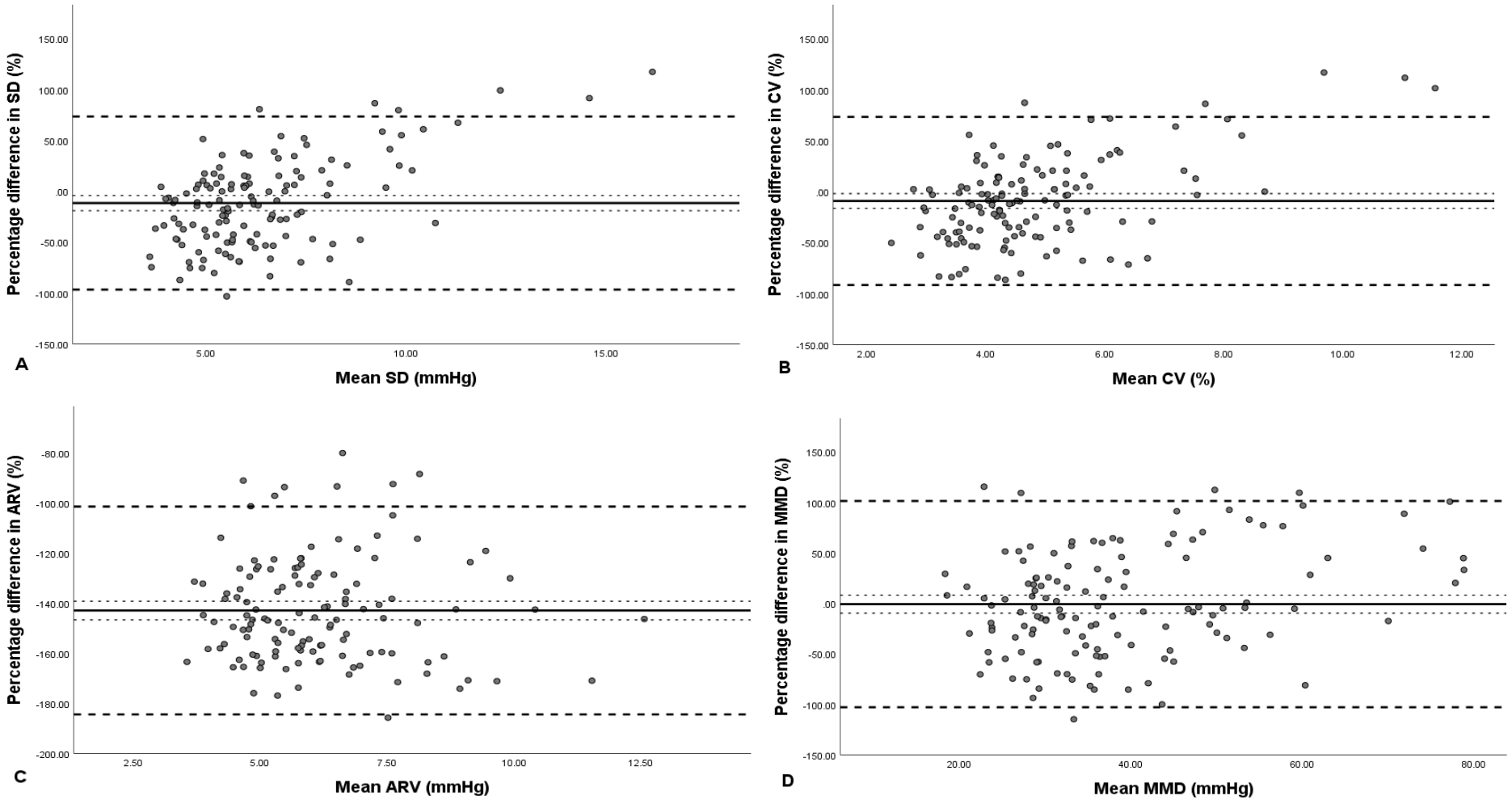

Figure 10: Bland-Altman plots to show the limits of agreement for short-term within-individual systolic blood pressure variability (BPV) from beat-to-beat blood pressure measurement and within-hour ambulatory blood pressure measurement. Thick lines show the mean difference, dotted lines the 95% confidence interval for the mean difference, and dashed lines the limits of agreement (± 2 SD). **A** shows BPV assessed as standard deviation (SD). **B** shows BPV assessed as coefficient of variation (CV). **C** shows BPV assessed as average real variability (ARV). **D** shows BPV assessed as maximum-minimum difference (MMD).

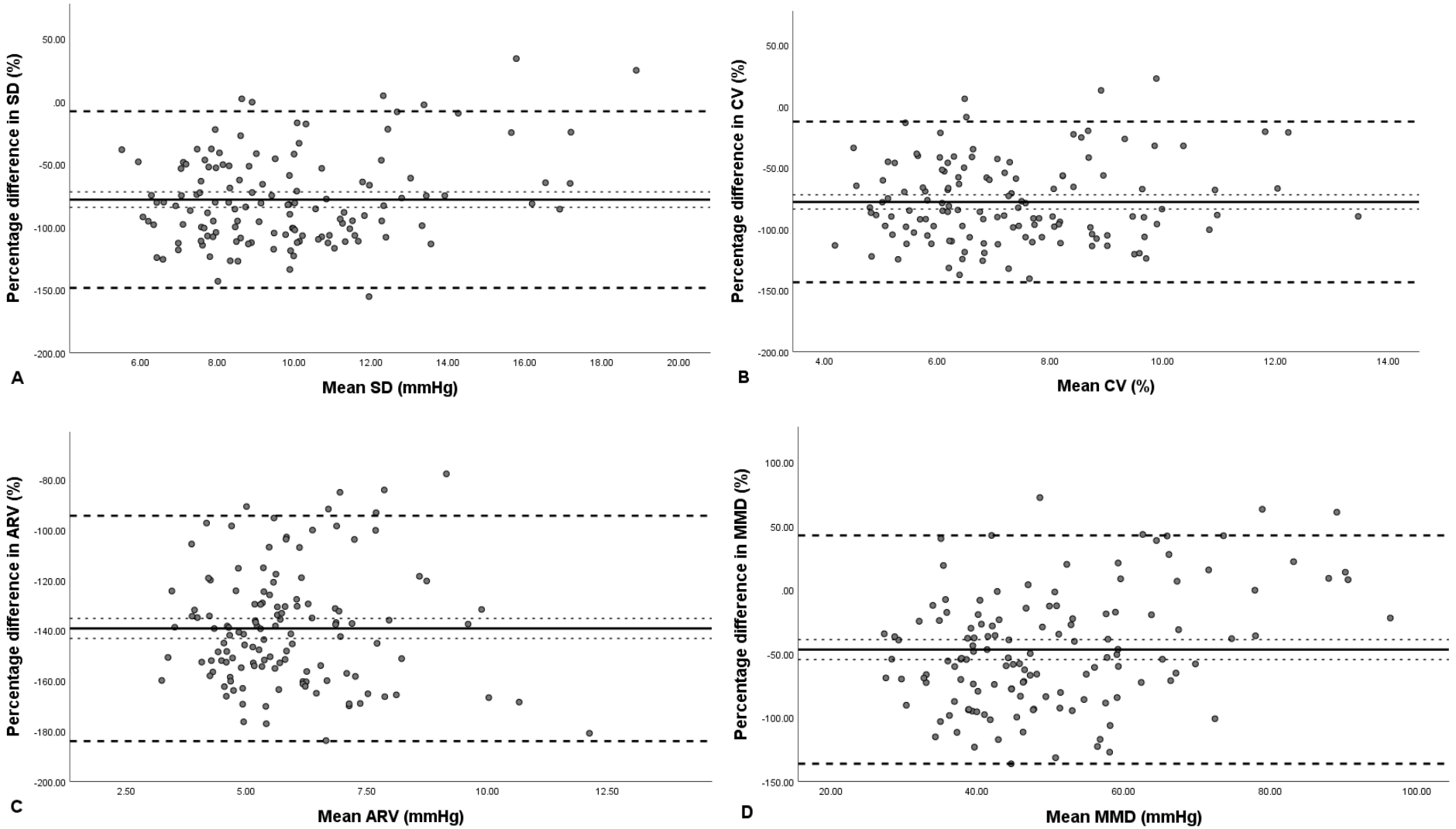

Figure 11: Bland-Altman plots to show the limits of agreement for short-term within-individual systolic blood pressure variability (BPV) from beat-to-beat blood pressure measurement and daytime ambulatory blood pressure measurement. Thick lines show the mean difference, dotted lines the 95% confidence interval for the mean difference, and dashed lines the limits of agreement (± 2 SD). **A** shows BPV assessed as standard deviation (SD). **B** shows BPV assessed as coefficient of variation (CV). **C** shows BPV assessed as average real variability (ARV). **D** shows BPV assessed as maximum-minimum difference (MMD).

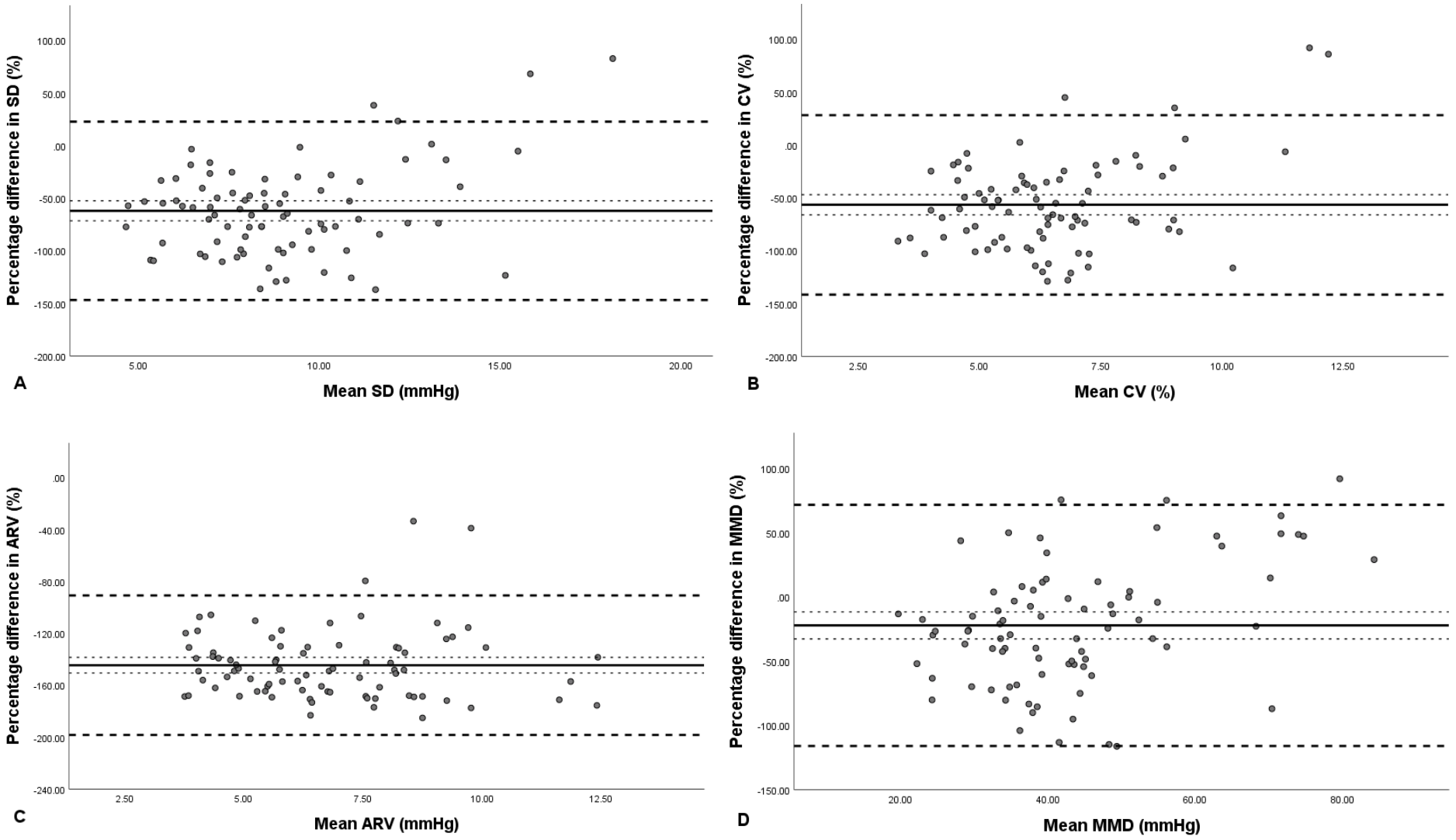

Figure 12: Bland-Altman plots to show the limits of agreement for short-term within-individual systolic blood pressure variability (BPV) from beat-to-beat blood pressure measurement and home blood pressure measurement. Thick lines show the mean difference, dotted lines the 95% confidence interval for the mean difference, and dashed lines the limits of agreement (± 2 SD). **A** shows BPV assessed as standard deviation (SD). **B** shows BPV assessed as coefficient of variation (CV). **C** shows BPV assessed as average real variability (ARV). **D** shows BPV assessed as maximum-minimum difference (MMD).

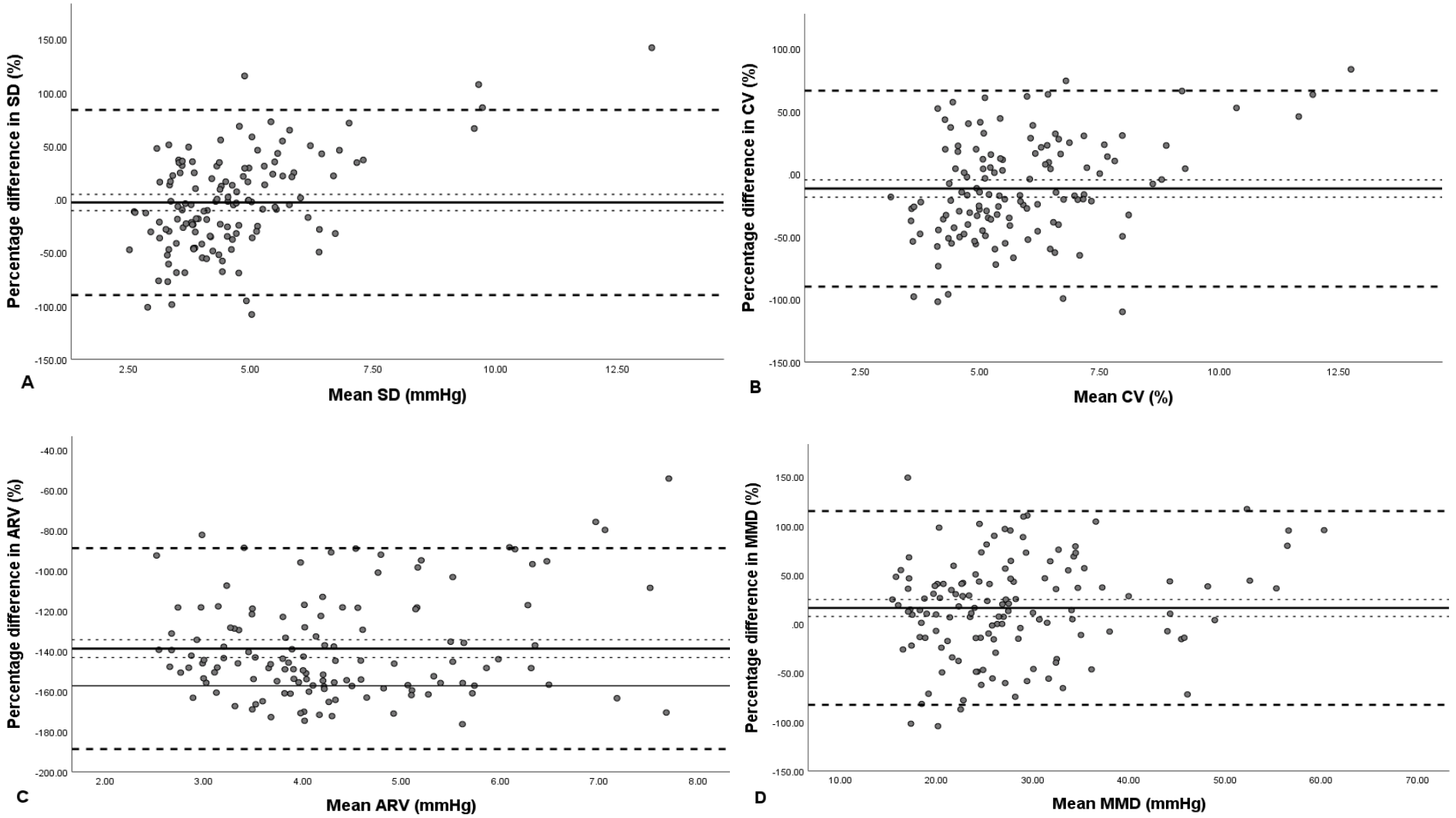

Figure 13: Bland-Altman plots to show the limits of agreement for short-term within-individual diastolic blood pressure variability (BPV) from beat-to-beat blood pressure measurement and within-hour ambulatory blood pressure measurement. Thick lines show the mean difference, dotted lines the 95% confidence interval for the mean difference, and dashed lines the limits of agreement (± 2 SD). **A** shows BPV assessed as standard deviation (SD). **B** shows BPV assessed as coefficient of variation (CV). **C** shows BPV assessed as average real variability (ARV). **D** shows BPV assessed as maximum-minimum difference (MMD).

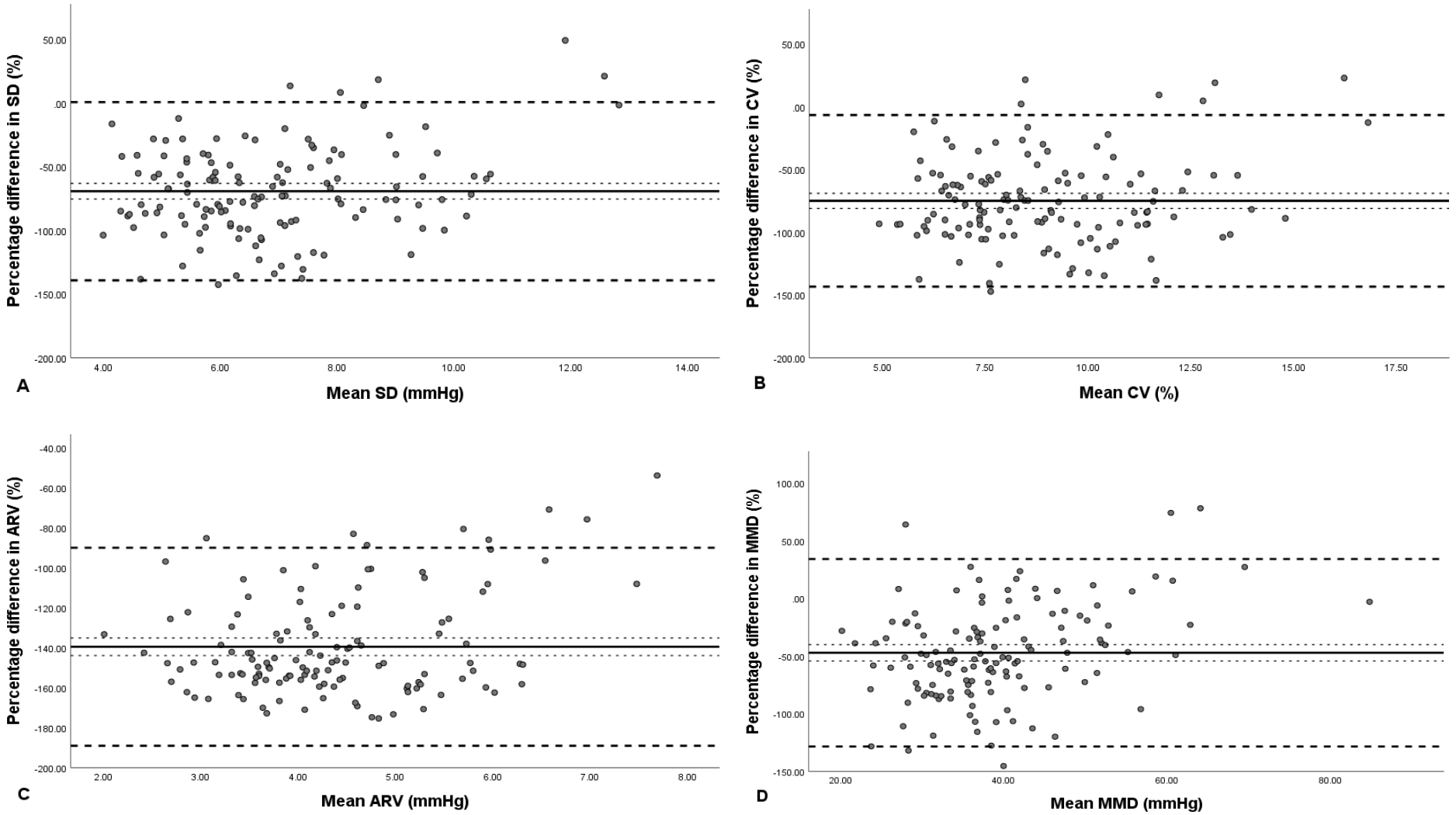

Figure 14: Bland-Altman plots to show the limits of agreement for short-term within-individual diastolic blood pressure variability (BPV) from beat-to-beat blood pressure measurement and daytime ambulatory blood pressure measurement. Thick lines show the mean difference, dotted lines the 95% confidence interval for the mean difference, and dashed lines the limits of agreement (± 2 SD). **A** shows BPV assessed as standard deviation (SD). **B** shows BPV assessed as coefficient of variation (CV). **C** shows BPV assessed as average real variability (ARV). **D** shows BPV assessed as maximum-minimum difference (MMD).

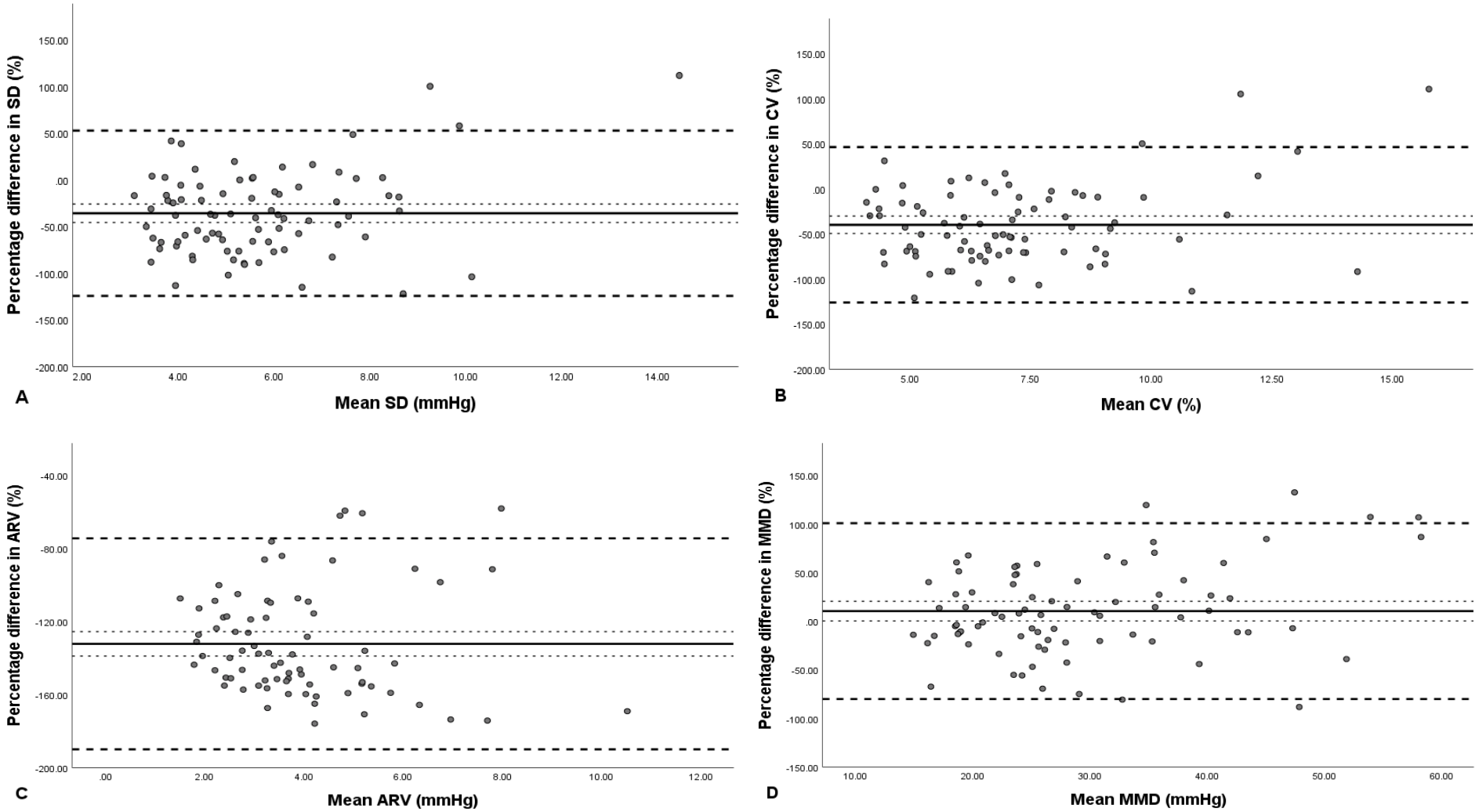

Figure 15: Bland-Altman plots to show the limits of agreement for short-term within-individual diastolic blood pressure variability (BPV) from beat-to-beat blood pressure measurement and home blood pressure measurement. Thick lines show the mean difference, dotted lines the 95% confidence interval for the mean difference, and dashed lines the limits of agreement (± 2 SD). **A** shows BPV assessed as standard deviation (SD). **B** shows BPV assessed as coefficient of variation (CV). **C** shows BPV assessed as average real variability (ARV). **D** shows BPV assessed as maximum-minimum difference (MMD).

No previous studies have investigated the relationships between beat-to-beat BPV and very short-term or short-term BPV derived from within-visit enhanced CBPM or a within-hour analysis of daytime ABPM. However, a few other studies have presented detailed comparisons of variability from other BP measurement methods, with findings that are in keeping with this analysis. In a cohort of adults with stable hypertension (N=108, 15% with established coronary heart disease or cerebrovascular disease) clinic BP from eight weekly visits, 24 hour ABPM, and HBPM over three days were carried out, with BPV calculated as SD, CV, and ARV from each set of measurements [160]. From the HBPM data variability was assessed over the whole measurement period and over a series of shorter periods (daily variability and variability within each day's morning and evening measurements only). Correlations between all measures of BPV were found to be either weak or non-significant. Similarly, in a larger cohort incorporating healthy adults and adults with stable hypertension but no established cardiovascular or cerebrovascular disease (N=461) BPV calculated as SD, CV, ARV, MMD, and VIM from clinic BP over four weekly visits, daytime ABPM, and HBPM over four days were all either weakly correlated or not correlated [118]. Two additional studies have presented correlations with beat-to-beat BPV. In a cohort of untreated hypertensive adults without established cardiovascular or cerebrovascular disease (N=256) Wei et al. demonstrated weak or non-significant correlations in ARV, MMD, and VIM from beat-to-beat BP, 24 hour ABPM, and HBPM over seven days [134]. Similarly, in a cohort of adults with a recent stroke or TIA (N=472) Webb et al. showed only weak correlations in CV from beat-to-beat BP, daytime ABPM, and HBPM [200].

As suggested by the results of the previous chapter these results may be related to discrepancies in BP values obtained from the different measurement methods. However, it may also be the case that different timescales of BPV have different underlying physiological or pathophysiological mechanisms. Whilst the underlying mechanisms of BPV have not been fully established, there is evidence that very short-term BPV is associated with reduced cardiac BRS in both the acute and chronic phases after ischaemic stroke [13, 67, 68, 256]. Furthermore, previous work using this cohort has demonstrated that reduced BRS and heart rate variability (HRV) were predictors for increased beat-to-beat BPV following a cerebrovascular event [257]. Conversely,

medium and long-term BPV are associated with markers of arterial stiffness [167, 170, 174], yet beat-to-beat variability has an uncertain relationship with these factors [134, 258]. Whilst the parameter chosen to calculate BPV may not matter (different parameters derived from the same set of measurements are strongly correlated regardless of the BP measurement method used [118, 157, 259]), it seems the timescale over which it is measured may be important. This is reflected by the inequalities in prognostic relevance to cardiovascular events that the different timescales of BPV provide [128, 131, 200, 252-254]. Ultimately, BPV may not be a singular concept and work to establish which measures are most relevant to different patient groups is required.

Strengths of this study include that it provides a comprehensive comparison of beat-to-beat BPV with variability from other BP measurement methods, using a variety of commonly reported BPV indices, some of which have not previously been reported. Furthermore, to the best of my knowledge, it is the first study to compare beat-to-beat BPV with an analysis of very short-term variability from ABPM (i.e. within-hour variability). In using the Bland-Altman method to compare different timescales of BPV, I have been able to provide a level of insight into their relationships that has not been present in previous studies. However, several important limitations to the study deserve mention. Firstly, as TEST-BP was an interventional trial with the aim of improving BP control after stroke the gap between the first HBPM used in this analysis and the other baseline BP measurements may limit comparisons with that measurement method as BP levels could have altered in the interim, thereby affecting variability. However, by excluding participants whose antihypertensive treatment was altered between the two measurement periods the design of the analysis should have mitigated the impact of this limitation. Secondly, with the majority of participants being on antihypertensive therapy, but being prescribed agents from diverse classes it is possible that the results were influenced by treatment. However, as the Bland-Altman analyses compared within-individual BPV measurements, and change in BPV over time was not an outcome measure, I would argue that antihypertensive treatment is unlikely to have had an impact. Furthermore, in the study by Abellan-Huerta et al. participants were also on antihypertensive therapy [160]. Thirdly, the findings may not be generalizable to patients without cerebrovascular disease.

However, they are consistent with other studies that have included both patients with and without previous stroke, and if beat-to-beat BPV is particularly relevant to patients with cerebrovascular disease as previously suggested then this may actually be a positive aspect of the study.

5.7 Summary

- There appears to be little relationship between BPV derived from beat-to-beat BP recordings and any other BP measurement method.
- The initial data suggested that there might be a relationship between beat-to-beat variability and within-hour variability, but further analysis using Bland and Altman's technique demonstrated very wide limits of agreement, indicating any relationship was insufficient for the latter to be a surrogate for the former.
- It seems plausible that shorter and longer-term BPV are not a singular phenomenon.
- The inclusion of beat-to-beat assessment of BPV in future research is recommended, along with further work to clarify which timescales of BPV are most relevant to cardiovascular risk and outcomes after stroke.

6 Associations Between Blood Pressure Variability and Stroke Severity or Subtype in Patients with a Recent Ischaemic Stroke

6.1 Declaration

I would like to acknowledge the contribution of Karen Appiah, research fellow in Leicester, to this chapter. Her work in processing the data from the BPV observational study helped to make this work possible.

6.2 Introduction

In the preceding experimental chapters the focus of this thesis has been on the measurement of BPV following an ischaemic cerebrovascular event. I will now turn my attention to investigating the potential of BPV as a therapeutic target in this patient group. In acute ischaemic stroke, the area of under-perfused penumbral tissue surrounding the core infarct is vulnerable to changes in CBF, with reduced blood flow potentially leading to infarct expansion and increased blood flow resulting in haemorrhagic change or cerebral oedema [35]. Due to disruption of cerebral autoregulatory mechanisms post stroke, CBF becomes more dependent upon systemic BP [13, 183]. Consequently, variability in systemic BP could influence CBF and overall infarct volume. BPV is increased in acute ischaemic stroke [100], and similar patterns may be seen in chronic stroke patients [256]. Furthermore, evidence is accumulating that increased BPV is associated with early clinical deterioration [188, 189], secondary haemorrhagic transformation [187], and poor long-term functional outcomes in ischaemic stroke patients [197-199]. Consequently, interest has arisen in whether BPV may be a therapeutic target in patients with stroke and, if so, which patients might benefit from these treatments.

In addition to abnormal BPV, autonomic dysfunction has been demonstrated in acute ischaemic stroke. HRV and cardiac BRS are two measureable indicators of autonomic function, both of which are reduced post-stroke [179, 181, 182]. As with BPV, these changes may persist into the chronic phase [256]. Although it remains a topic of

debate, there is some evidence that autonomic functions may be lateralised within the central nervous system, with sympathetic activity being focused in the right cerebral hemisphere and parasympathetic activity focused in the left [63, 179]. Therefore, the degree of HRV and cardiac BRS reduction may differ depending on which cerebral hemisphere is involved. Given the role of cardiac baroreceptors in the regulation of systemic BP, the cerebral hemisphere affected by stroke may also influence the degree of BPV, though this is yet to be established.

Should BPV prove to be a viable therapeutic target it would be useful to know whether all patients with ischaemic stroke would benefit equally from such treatment, or whether it would be prudent to focus on treating certain groups of patients? To that end, it would be of relevance to know if there are differences in BPV amongst subgroups of ischaemic stroke patients, but presently this has not been investigated. It could be expected that patients with more severe ischaemic stroke might also exhibit greater BPV due to the larger extent of damage to cerebral tissue, and the potential for a larger penumbra that might necessitate greater adjustments in systemic BP to maintain adequate CBF. Furthermore, we might anticipate that there will be differences in the degree of BPV between patients with left hemisphere and right hemisphere lesions due to associated imbalances in autonomic BP regulation.

6.3 Hypothesis

The aim of this study was to investigate potential relationships between BPV and stroke severity (according to commonly applied clinical tools) and affected cerebral hemisphere. Data from three cohorts including subjects with a recent ischaemic stroke have been pooled to test two hypotheses. Firstly, that differences will exist in BPV values across participants with a range of stroke severity, with the expectation that BPV values will be greater in those with a higher NIHSS score or more disabling stroke according to the OCSP classification. Secondly, that BPV values will not be the same in participants with unilateral left hemisphere or right hemisphere infarcts.

6.4 Methods

Combined data from participants recruited to TEST-BP, SERVED Memory, and the BPV observational trial was used to generate the database for this study. The general methodologies for these trials are described in sections 3.1.1 to 3.1.3, with TEST-BP and SERVED Memory having also been published elsewhere [222, 223]. The methodology specific to this analysis is described here. Eligible subjects were participants in any of the above trials with a diagnosis of ischaemic stroke who had complete baseline BP data, incorporating enhanced CBPM with three measurements and daytime ABPM with ≥14 readings. A subgroup of these participants who also had baseline beat-to-beat BP measurement with a recording duration of ≥5 minutes after data cleaning was also included in the analysis. Participants with BP data that was incomplete according to these criteria or who were diagnosed with TIA or ICH were excluded.

All baseline BP measurements were recorded as outlined in the general methodology chapter; enhanced CBPM as described in section 3.5.2, daytime ABPM as described in section 3.5.3, and beat-to-beat BP as described in section 3.5.5. For each set of BP measurements average and variability values for SBP and DBP were calculated as described in section 3.6. Stroke severity was assessed using the NIHSS score at baseline and the OCSP classification, both of which are described in section 3.5.6. The involved cerebral hemisphere was inferred from any lateralising clinical features of the stroke and any positive findings on cerebral imaging investigations where applicable and was classified as “left” or “right”. If there were no lateralising features or positive findings on neuroimaging then the participant was not categorised as having a unilaterally involved hemisphere and was excluded from the testing of the second hypothesis.

Outcomes for this analysis were the separate assessment of relationships between BPV derived from each of the three measurement methods described above with (i) stroke severity according to baseline NIHSS score, (ii) stroke severity according to OCSP classification, and (iii) stroke subtype according to the affected cerebral hemisphere.

6.5 Statistical Analysis

Data were analysed using SPSS version 25.0. Assessment of median NIHSS score by OCSP classification was based on a Kruskal-Wallis test. All BP and BPV variables were visually assessed for normality by constructing histograms with overlaid distribution curves and formally tested using the Kolmogorov-Smirnov test ($p>0.05$ deemed consistent with normal distribution). Mean SBP and DBP values were normally distributed, but BPV data from all measurement methods were not. Therefore, a logarithmic transformation was applied to these variables prior to any statistical testing. This transformation resulted in normalisation of the variables. The results of any testing on transformed variables have been back-transformed for presentation. Initial exploratory univariate analyses were undertaken to assess the relationship between BPV variables and each measure of stroke severity or subtype. The relationship between BPV and NIHSS was assessed using Pearson's correlations. Correlations were considered weak if r=0.10-0.29, moderate if r=0.30-0.49, and strong if r=>0.50 [255]. The relationship between BPV and OCSP classification was assessed using one-way ANOVA with the BPV parameter as the dependent variable and OCSP classification as the grouping variable. Post-hoc testing was carried out where any between-group differences were identified in the model as a whole. The relationship between BPV and affected hemisphere was assessed using independent samples t tests, with 'affected hemisphere' as the bivariate grouping variable and the BPV parameter as the dependent variable. Where univariate analyses suggested significant relationships further multivariate analyses were conducted using a regression model, with the BPV parameter as the dependent variable, adjusted for differences between the trial cohorts and factors known to influence BPV [130, 251, 260]. Independent variables used in the model in addition to those tested with univariate analysis included time from stroke onset to baseline measurement, age, gender, mean BP (from the relevant BP measurement method), past medical history of hypertension, and past medical history of diabetes.

Table 25: Demographic data. Data presented are mean (SD) for normally distributed continuous variables, median (IQR)* for non-normally distributed continuous variables, and frequency (%) for categorical variables.

		All	Beat-to-beat subgroup
N		181	67
Age (years)		70.6 (11.0)	71.0 (10.3)
Gender	**Male**	134 (74.0%)	49 (73.1%)
BMI (kg/m^2)		28.5 (5.5)	29.5 (6.1)
Smoking	**Never**	71 (39.2%)	31 (46.3%)
	Ex smoker	90 (49.7%)	34 (50.7%)
	Current smoker	19 (10.5%)	2 (3.0%)
Alcohol (units/wk)*		4.0 (12.0)	4.0 (16.0)
NIHSS*		3.0 (4.0)	3.0 (2.0)
OCSP classification	**LACS**	60 (33.7%)	24 (35.8%)
	PACS	78 (43.8%)	29 (43.3%)
	TACS	6 (3.4%)	1 (1.5%)
	POCS	34 (19.1%)	13 (19.4%)
Affected hemisphere	**Left**	80 (55.2%)	44 (66.7%)
Past medical history	**TIA**	19 (10.7%)	13 (19.4%)
	Stroke	78 (43.6%)	53 (79.1%)
	IHD	23 (12.8%)	9 (13.4%)
	Diabetes	34 (19.0%)	19 (28.4%)
	Hypertension	105 (58.7%)	44 (65.7%)
No. on antihypertensive treatment		118 (65.2%)	55 (82.1%)
No. of antihypertensives*		1.0 (2.0)	1.0 (1.0)
Antihypertensive use by class	**ACEI**	60 (33.1%)	33 (49.3%)
	ARB	25 (13.8%)	11 (16.4%)

	Beta blockers	24 (13.3%)	14 (20.9%0
	CCB	57 (31.5%)	29 (43.3%)
	Thiazide-like diuretics	15 (8.3%)	9 (13.4%)

SD denotes standard deviation; IQR, interquartile range; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxford Community Stroke Project; LACS, lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke; TIA, transient ischaemic attack; IHD, ischaemic heart disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 26: Average baseline blood pressure and variability parameters. Clinic and ambulatory blood pressure data are for the full cohort. Beat-to-beat data are for the subgroup only. Mean systolic and diastolic blood pressure are presented as mean (SD). Systolic and diastolic variability values are presented as median (IQR).

	Enhanced CBPM	**Daytime ABPM**	**Beat-to-beat BP**
Mean SBP (mmHg)	151.4 (21.6)	138.1 (16.8)	135.1 (18.8)
Mean DBP (mmHg)	83.7 (12.6)	78.9 (10.8)	81.7 (15.0)
SD SBP (mmHg)	5.8 (4.1)	12.4 (5.6)	6.5 (4.5)
SD DBP (mmHg)	3.4 (3.0)	8.7 (3.3)	4.7 (3.2)
CV SBP (%)	4.0 (2.5)	9.1 (3.8)	5.1 (3.4)
CV DBP (%)	4.2 (3.8)	11.2 (5.0)	6.0 (4.5)
ARV SBP (mmHg)	-	8.9 (2.8)	2.1 (2.1)
ARV DBP (mmHg)	-	6.8 (2.8)	1.5 (1.3)

CBPM denotes clinic blood pressure measurement; ABPM, ambulatory blood pressure measurement; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation; ARV, average real variability.

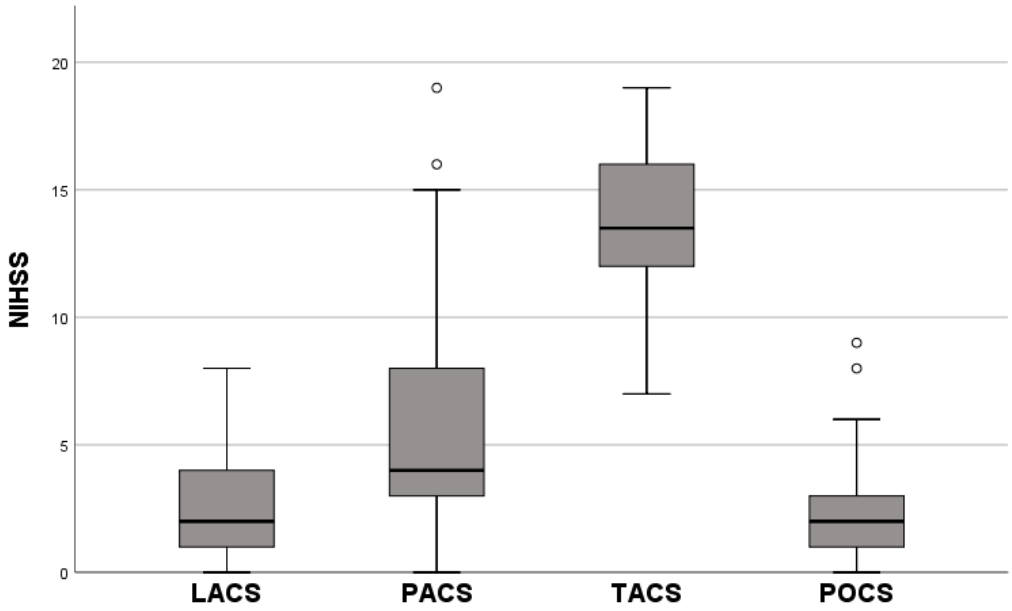

Figure 16: Box and whisker plot showing distribution of National Institutes of Health Stroke Scale (NIHSS) scores across different Oxford Community Stroke Project classification groups. LACS denotes lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke.

Table 27: Correlations between baseline National Institutes of Health Stroke Scale score and mean blood pressure and variability indices from clinic, daytime ambulatory, and beat-to-beat measurements. Values presented are Pearson's r. *p<0.01.

	Enhanced CBPM	Daytime ABPM	Beat-to-beat BP
Mean SBP	-0.02	0.10	0.02
SD SBP	0.10	-0.24*	0.06
CV SBP	0.11	-0.28*	0.05
ARV SBP	-	0.09	0.15
Mean DBP	-0.08	0.05	-0.04
SD DBP	0.12	-0.20*	0.01
CV DBP	0.14	-0.21*	0.02
ARV DBP	-	0.06	0.03

CBPM denotes clinic blood pressure measurement; ABPM, ambulatory blood pressure measurement; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation; ARV, average real variability.

Table 28: Summary of results from multivariate testing for the relationship between National Institutes of Health Stroke Scale (NIHSS) score and blood pressure variability from daytime ambulatory blood pressure measurement. Independent variables entered in the model were time from symptom onset to measurement, age, gender, mean blood pressure, past medical history of hypertension, past medical history of diabetes, and NIHSS.

Dependent variable	**R^2**	**F (df)**	**P value**	**Standardised beta coefficient for NIHSS**	**P value**
SD SBP	0.135	3.27 (8, 168)	0.002	-0.26	0.001
CV SBP	0.139	3.39 (8, 168)	0.001	-0.26	<0.0001
SD DBP	0.058	1.30 (8, 168)	0.25	-	-
CV DBP	0.117	2.77 (8, 168)	0.007	-0.19	0.01

SD denotes standard deviation; SBP, systolic blood pressure; CV, coefficient of variation; DBP, diastolic blood pressure.

6.6 Results

Demographic data for the full cohort and the subgroup is presented in **Table 25**. Average BP and BPV values for each measurement method are displayed in **Table 26**. Mean BP values from CBPM were greater than both daytime ABPM and beat-to-beat measurements, with BPV values also differing depending between measurement methods. Median NIHSS score was not the same across OCSP classification groups ($p<0.0001$), with LACS<PACS<TACS and POCS similar to LACS (**Figure 16**). There were no significant correlations between baseline NIHSS score and mean SBP or DBP from any BP measurement method. Correlations between baseline NIHSS score and BPV parameters were all non-significant apart from weak negative correlations with SD and CV of SBP and DBP from daytime ABPM (**Table 27**). In linear regression models with these BPV parameters from daytime ABPM as the dependent variables, NIHSS remained a significant independent variable in all models except for SD of DBP (**Table 28**). None of the other independent variables in the model were statistically significant.

There were no significant between-group differences for mean SBP or DBP on one-way ANOVA testing with OCSP classification as the grouping variable for any of the BP measurement methods. Mean BPV parameters by OCSP grouping for each BP measurement method are presented in **Figures 17-19**. For clinic and beat-to-beat BPV there were no significant between-group differences. For daytime ABPM the one-way ANOVA testing suggested significant between-group differences for SD and CV of SBP ($p=0.002$ and $p=0.001$ respectively), and SD and CV of DBP ($p=0.01$ and $p=0.03$ respectively). However, following post-hoc testing only significant between-group differences for SD and CV of SBP remained, with variability higher in patients with LACS compared to PACS and TACS, and lower variability in patients with TACS than POCS (**Table 29**). These significant between-group differences remained on multivariate testing, with the exception of difference in SD of SBP between participants with LACS or TACS (**Table 30**). There were no significant differences in mean BP or any BPV parameter between participants with left hemisphere stroke compared to right hemisphere stroke, with the exception of mean SBP from beat-to-beat BP measurements (**Tables 31-33**).

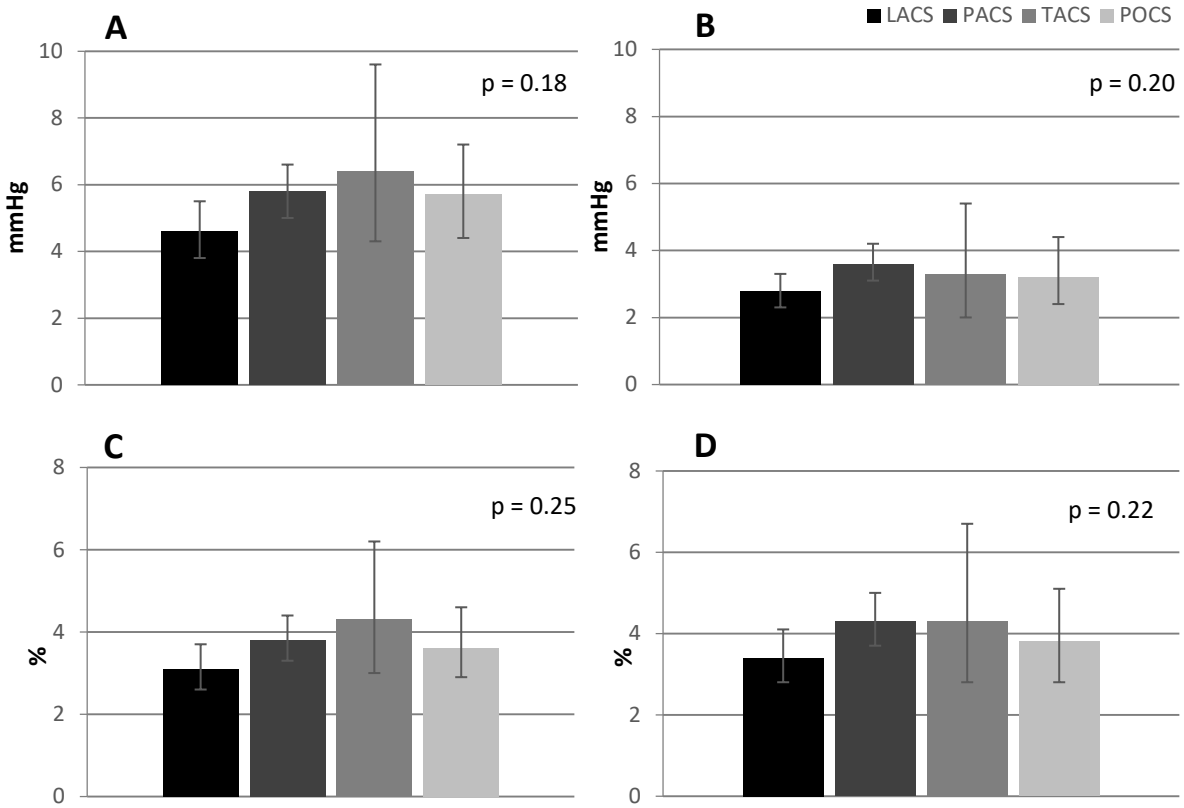

Figure 17: Histograms showing mean blood pressure variability from enhanced clinic blood pressure measurement by Oxford Community Stroke Project classification of ischaemic stroke. Error bars are 95% confidence intervals. P values are from a one-way ANOVA to assess for between-group differences across the whole group. **A** shows standard deviation (SD) of systolic blood pressure (SBP). **B** shows SD of diastolic blood pressure (DBP). **C** shows coefficient of variation (CV) of SBP. **D** shows CV of DBP. LACS denotes lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke.

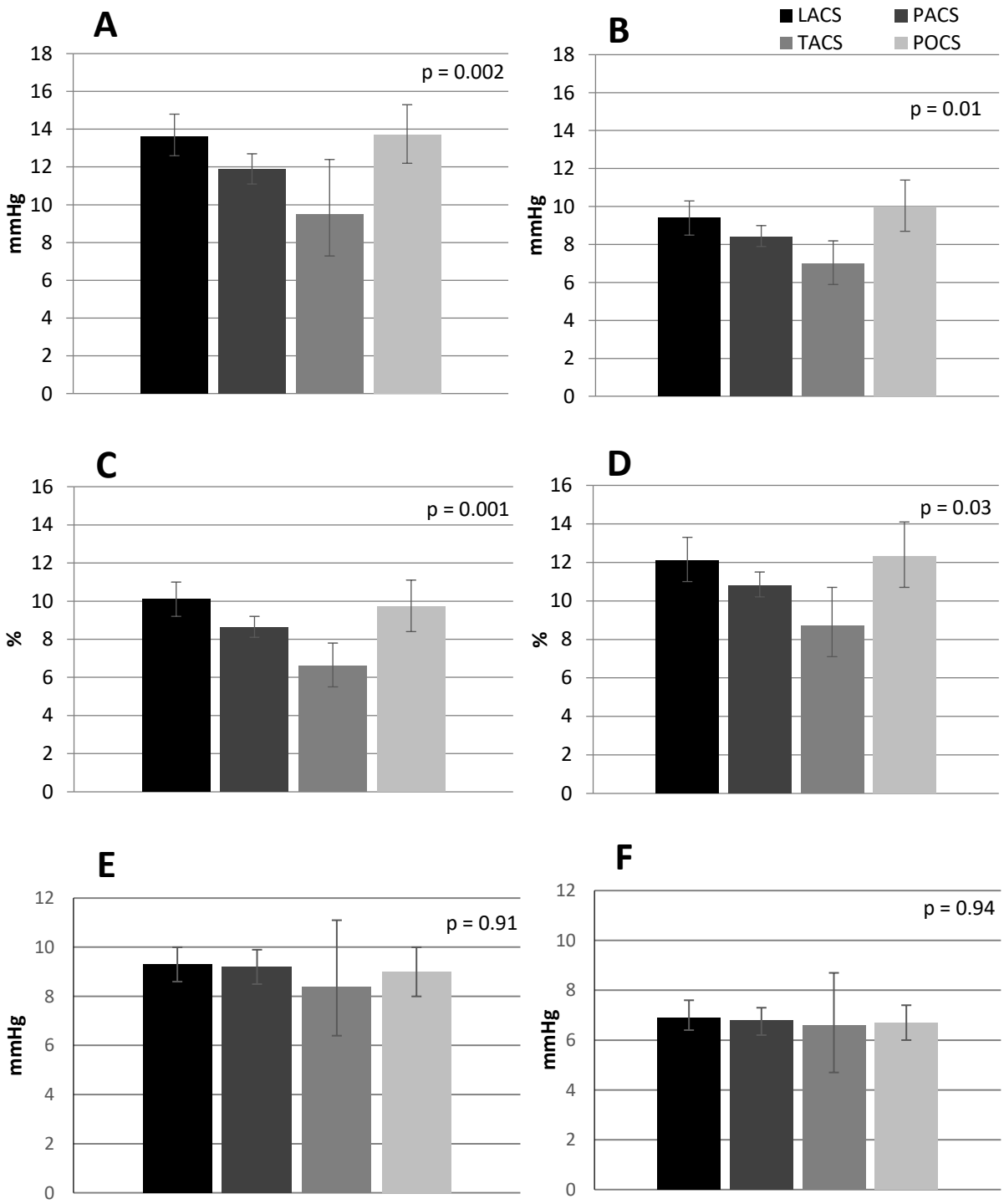

Figure 18: Histograms showing mean blood pressure variability from daytime ambulatory blood pressure measurements by Oxford Community Stroke Project classification of ischaemic stroke. Error bars are 95% confidence intervals. P values are from a one-way ANOVA to assess for between-group differences across the whole group. **A** shows standard deviation (SD) of systolic blood pressure (SBP). **B** shows SD of diastolic blood pressure (DBP). **C** shows coefficient of variation (CV) of SBP. **D** shows CV of DBP. **E** shows average real variability (ARV) of SBP. **F** shows ARV of DBP. LACS denotes lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke.

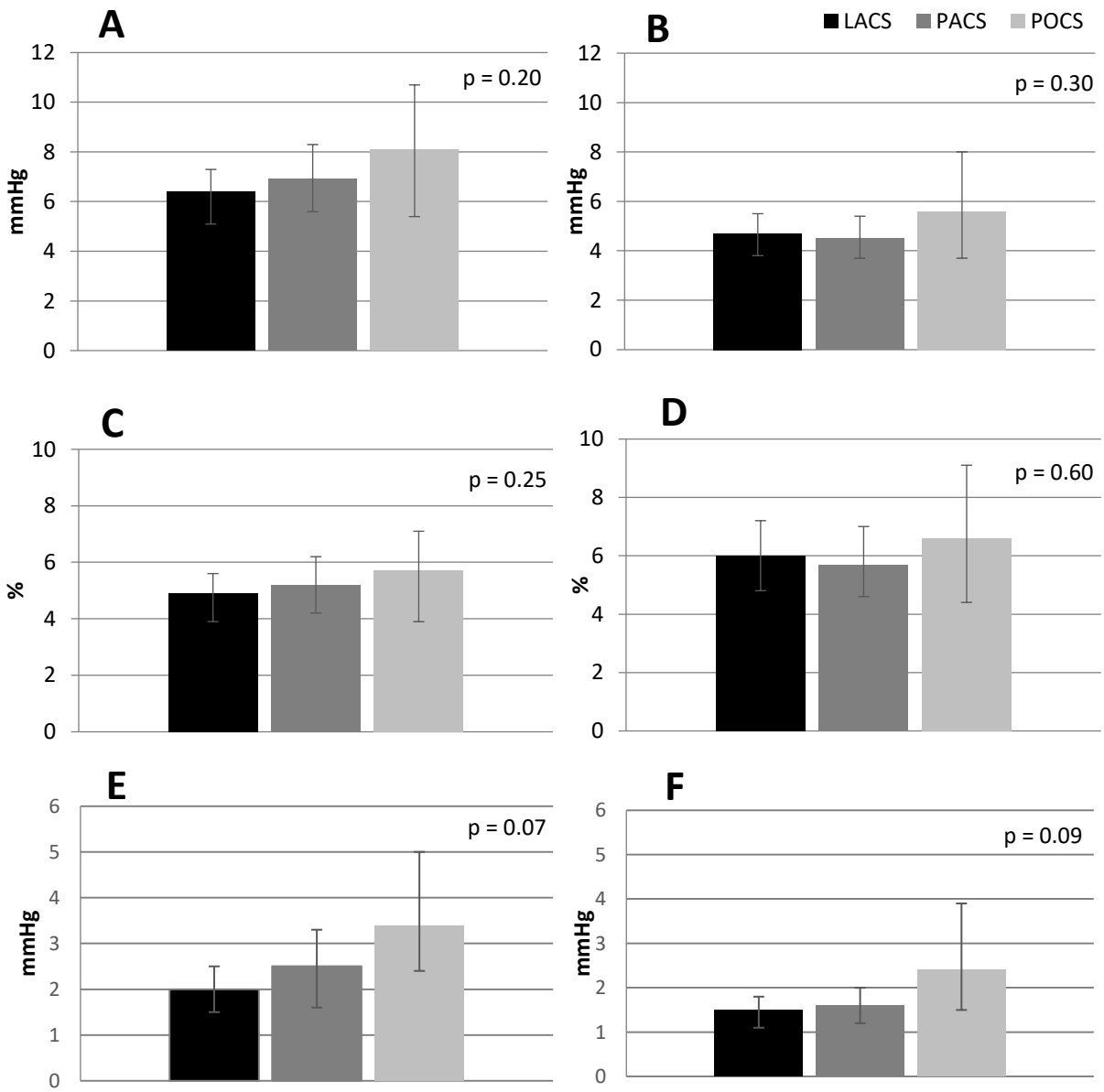

Figure 19: Histograms showing mean blood pressure variability from beat-to-beat blood pressure measurements by Oxford Community Stroke Project classification of ischaemic stroke. Error bars are 95% confidence intervals. P values are from a one-way ANOVA to assess for between-group differences across the whole group. **A** shows standard deviation (SD) of systolic blood pressure (SBP). **B** shows SD of diastolic blood pressure (DBP). **C** shows coefficient of variation (CV) of SBP. **D** shows CV of DBP. **E** shows average real variability (ARV) of SBP. **F** shows ARV of DBP. LACS denotes lacunar stroke; PACS, partial anterior circulation stroke; POCS, posterior circulation stroke.

Table 29: Post-hoc testing from the one-way ANOVA for between-group differences in systolic blood pressure variability from daytime ambulatory blood pressure measurements according to Oxford Community Stroke Project grouping. Differences are expressed as ratios (95% CI).

	Difference in SD SBP	P value	Difference in CV SBP	P value
LACS vs. PACS	1.15 (1.01 to 1.32)	0.04	1.17 (1.03 to 1.34)	0.01
LACS vs. TACS	1.44 (1.03 to 2.01)	0.03	1.53 (1.10 to 2.13)	0.01
LACS vs. POCS	0.99 (0.85 to 1.18)	1.00	1.04 (0.88 to 1.22)	0.95
PACS vs. TACS	1.25 (0.90 to 1.74)	0.31	1.30 (0.94 to 1.81)	0.16
PACS vs. POCS	0.87 (0.74 to 1.02)	0.10	0.88 (0.75 to 1.04)	0.19
TACS vs. POCS	0.69 (0.49 to 0.98)	0.04	0.68 (0.48 to 0.96)	0.02

95% CI denotes 95% confidence interval; SD, standard deviation; SBP, systolic blood pressure; CV, coefficient of variation; LACS, lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke.

Table 30: Summary of results from multivariate testing for the relationship between Oxford Community Stroke Project (OCSP) classification and blood pressure variability from daytime ambulatory blood pressure measurements. Independent variables entered in the model were time from symptom onset to measurement, age, gender, mean blood pressure, past medical history of hypertension, past medical history of diabetes, and OCSP classification.

Dependent variable	**Independent variable**	**R^2**	**F (df)**	**P value**	**Standardised beta coefficient for OCSP classification**	**P value**
SD SBP	LACS vs. PACS	0.17	3.19 (8, 128)	0.003	0.25	0.003
	LACS vs. TACS	0.18	1.56 (8, 56)	0.16	-	-
	TACS vs. POCS	0.39	2.33 (8, 29)	0.05	-0.40	0.01
CV SBP	LACS vs. PACS	0.12	2.19 (8, 128)	0.03	0.26	0.002
	LACS vs. TACS	0.24	2.25 (8, 56)	0.04	0.38	0.003
	TACS vs. POCS	0.50	3.62 (8, 29)	0.01	-0.36	0.01

*standardised beta coefficient

SD denotes standard deviation; SBP, systolic blood pressure; LACS, lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke; CV, coefficient of variation.

Table 31: Mean blood pressure and variability from enhanced clinic blood pressure measurement and differences between participants with left or right hemisphere infarct. Average values for each hemisphere are mean (SD). Differences for mean blood pressure are absolute differences. Differences for mean variability are ratios (95% CI).

	Left	Right	Difference with 95% CI (left vs. right)	P value
Mean SBP	150.7 (21.6)	150.9 (22.2)	-0.25 (-7.5 to 7.0)	0.95
SD SBP	5.0 (2.1)	5.3 (2.0)	0.94 (0.76 to 1.19)	0.61
CV SBP	3.4 (2.0)	3.6 (2.0)	0.95 (0.76 to 1.18)	0.61
Mean DBP	82.8 (13.4)	84.7 (11.9)	-1.90 (-6.1 to 2.3)	0.37
SD DBP	2.9 (2.2)	3.4 (2.0)	0.87 (0.68 to 1.12)	0.27
CV DBP	3.6 (2.2)	4.0 (2.0)	0.90 (0.71 to 1.14)	0.37

SD denotes standard deviation; 95% CI, 95% confidence interval; SBP, systolic blood pressure; CV, coefficient of variation; DBP, diastolic blood pressure.

Table 32: Mean blood pressure and variability from daytime ambulatory blood pressure measurement and differences between participants with left or right hemisphere infarct. Average values for each hemisphere are mean (SD). Differences for mean blood pressure are absolute differences. Differences for mean variability are ratios (95% CI).

	Left	Right	Difference with 95% CI (left vs. right)	P value
Mean SBP	137.1 (17.3)	136.8 (16.2)	0.36 (-5.2 to 5.9)	0.89
SD SBP	12.3 (1.3)	12.3 (1.4)	1.00 (0.91 to 1.10)	0.98
CV SBP	9.1 (1.3)	9.1 (1.4)	0.99 (0.91 to 1.10)	0.98
ARV SBP	9.1 (1.3)	9.2 (1.3)	0.99 (0.91 to 1.09)	0.87
Mean DBP	78.3 (12.5)	78.3 (9.2)	-0.06 (-3.6 to 3.5)	0.98
SD DBP	8.4 (1.3)	8.7 (1.3)	0.97 (0.89 to 1.05)	0.42
CV DBP	10.9 (1.3)	11.2 (1.3)	0.97 (0.89 to 1.07)	0.53
ARV DBP	6.8 (1.3)	6.7 (1.3)	1.02 (0.92 to 1.13)	0.69

SD denotes standard deviation; 95% CI, 95% confidence interval; SBP, systolic blood pressure; CV, coefficient of variation; ARV, average real variability; DBP, diastolic blood pressure.

Table 33: Mean blood pressure and variability from beat-to-beat blood pressure measurement and differences between participants with left or right hemisphere infarct. Average values for each hemisphere are mean (SD). Differences for mean blood pressure are absolute differences. Differences for mean variability are ratios (95% CI).

	Left	Right	Difference with 95% CI (left vs. right)	P value
Mean SBP	131.6 (18.7)	141.7 (16.7)	-10.16 (-19.6 to -0.7)	0.04
SD SBP	6.4 (1.7)	7.7 (1.7)	0.83 (0.64 to 1.09)	0.18
CV SBP	5.0 (1.7)	5.5 (1.6)	0.90 (0.69 to 1.18)	0.45
ARV SBP	2.2 (1.8)	2.9 (2.3)	0.77 (0.52 to 1.16)	0.21
Mean DBP	78.9 (15.4)	85.9 (13.0)	-6.94 (-14.6 to 0.7)	0.08
SD DBP	4.6 (1.6)	5.1 (1.7)	0.91 (0.70 to 1.16)	0.45
CV DBP	5.9 (1.7)	6.0 (1.7)	1.00 (0.75 to 1.33)	0.98
ARV DBP	1.6 (2.0)	1.6 (2.1)	0.89 (0.62 to 1.28)	0.54

SD denotes standard deviation; 95% CI, 95% confidence interval; SBP, systolic blood pressure; CV, coefficient of variation; ARV, average real variability; DBP, diastolic blood pressure.

6.7 Discussion

These data show that there are significant associations between short-term BPV derived from daytime ABPM and stroke severity defined by NIHSS and OCSP classification. Furthermore, the associations are independent of mean BP. Although the correlations between short-term BPV and NIHSS were relatively weak, the relationship indicated that BPV was increased in participants with lower NIHSS scores. Similarly, BPV was greater in participants with lacunar stroke compared to those with PACS or TACS, which is consistent with the relationship with NIHSS as the data also indicated that these participants had lower NIHSS scores. This would be expected as in an individual with LACS fewer of the domains tested by the NIHSS are clinically affected, as has been reported in other ischaemic stroke cohorts [261]. The findings also suggested that BPV might be increased in POCS compared to partial or total anterior circulation stroke, although a significant difference was only demonstrated with TACS. This could also be consistent with the inverse correlation between BPV and NIHSS as, similar to those with LACS, patients with POCS tend to have lower NIHSS scores as the scale does not capture POCS symptoms as well as those of partial or total anterior circulation stroke [262]. The findings are somewhat surprising as they are at odds with the hypotheses that were tested and the wider literature, which suggests that increased BPV is predictive of poor outcomes following stroke whereas patients with LACS tend to have a good prognosis. Potential explanations for this discrepancy are discussed in the following paragraph, yet it remains that the findings are potentially of relevance. This is because if BPV is proven to be a valid therapeutic target after stroke to improve outcomes and/or prevent recurrent stroke, they suggest that any such treatments may be most beneficial in patients with apparently less severe forms of ischaemic stroke. The data showed no significant associations between short-term or very short-term BPV and the cerebral hemisphere affected by ischaemic stroke, however this grouping may have been overly simplistic. It may be necessary to analyse relationships with ischaemic stroke affecting specific cerebral areas (e.g. the insular cortex) within each hemisphere, but this was not possible in this analysis.

That the findings of this analysis were not in keeping with the proposed hypotheses regarding the relationship between BPV and stroke severity could be related to the population studied. Firstly, this group consisted of mostly of patients with mild to moderate stroke symptoms (median NIHSS 3.0 [IQR 4.0]) and contained a limited number of patients with TACS classification (N=6). Furthermore, those patients with TACS were at the milder end of the spectrum for this classification as none of the trials that provided data for this analysis allowed inclusion of participants via proxy consent. Consequently, the study population may not be fully representative of the general stroke population in terms of stroke severity and stroke type, and may not have provided an accurate assessment of the degree of BPV in those with more severe ischaemic stroke. Secondly, the classification of severity was based on clinical presentation as opposed to radiological findings. Although an experienced stroke physician confirmed the clinical diagnoses, it is possible that some patients categorised as LACS may have had larger infarcts if it had been possible to confirm all diagnoses with MRI or other cerebral imaging. Thirdly, the proportion of participants who were recruited after a recurrent cerebrovascular event was higher than might be expected in the general stroke population (43.6% with a previous stroke, rising to above 50% if previous TIA is also included). If raised BPV can persist into the chronic phase post-stroke [256], then this could have influenced the findings. Finally, although the findings did reach statistical significance there remains the possibility that they are due to chance. This potential explanation should be considered given that there are very limited reports in the literature for comparison. Having said that, the only other study to report on BPV in relation to OCSP classification is consistent with the findings of this analysis. In a small study of cerebral autoregulation in patients with acute ischaemic stroke (N=56, recruited within 72 hours of onset) Eames et al. showed that SD of SBP derived from beat-to-beat BP monitoring was greater in patients with LACS as opposed to PACS, TACS, and POCS [13]. To the best of my knowledge there have been no studies of BPV differences by OCSP classification using variability derived from BP measurement methods other than beat-to-beat measurement. However, one study has reported that increases in short-term BPV from repeated CBPM were greatest in patients with ischaemic stroke due to small vessel occlusion according to the TOAST classification [189]. Conversely, there is conflicting data regarding the relationship between BPV and NIHSS. A review of 2566 subjects with a first-episode ischaemic

stroke, recruited within 24 hours of onset, found that diastolic BPV from days 1-3 post-event increased by quartile of baseline NIHSS, yet there was a non-significant trend for systolic BPV to reduce by quartile in the same cohort [199]. Other studies of BPV in the acute phase of ischaemic stroke have reported no significant relationship between BPV and baseline NIHSS [186, 198, 263]. However, none of these studies has used ABPM to derive BPV, which could account for the different findings of this analysis.

Another slightly surprising aspect of the data from this analysis that may necessitate further caution in the interpretation of the findings relates to the mean BP and variability levels as measured by the different methods (**Table 26**). Firstly, that mean BP as recorded by CBPM was higher than that from daytime ABPM is not surprising. Nonetheless, the difference found was greater than is suggested by the literature [110]. This may be partly explained by the presence of some degree of white coat effect within the study population; however as other members of the research team collected some measurements I cannot guarantee that there was not some variation in practice (e.g. leaving insufficient time between clinic readings, or using a cuff of incorrect size) that may have introduced measurement bias. Secondly, as opposed to the findings in this study, it might be expected that beat-to-beat BP measured at the finger would be higher than CBPM measured at the brachial artery due to increasing arterial stiffness with distance from the aorta. However, the age of the study population may partly explain this finding as arterial stiffness alters with ageing and so the effect of BP amplification due to arterial stiffness throughout the arterial tree will also alter. Alternatively, the influence on peripherally measured BP of the reflected pressure wave may not be so great when the BP is measured at the most distal point (i.e. the finger), leading to a lower reading at this point than in the brachial artery. A final consideration is also the accuracy of beat-to-beat BP measurement devices. Although they have been shown to be accurate for tracking changes in BP, they may not be sufficiently accurate to measure mean BP due to the SD of measurements [95]. Indeed, limits of agreement up to ±17mmHg for SBP have been reported in direct comparison of the Finapres® with brachial CBPM [264]. Thirdly, any differences in BPV values between the different methods are likely due to a combination of the number of readings obtained and the time between measurements (particularly where BPV is derived using ARV).

No other studies have previously looked at the relationship between BPV and the cerebral hemisphere affected by ischaemic stroke. However, autonomic dysfunction post-stroke has been investigated. Evidence for the lateralisation of functions is mixed, with some studies demonstrating altered HRV and BRS in right-sided lesions, but others the opposite [179, 181, 182]. As suggested above, differentiating left vs. right alone may be an oversimplification. Damage to the insular cortex in particular has been implicated in post-stroke autonomic dysfunction [265], therefore it may be the affected region(s) within the hemisphere rather than the hemisphere itself which is of importance. This level of detail was not available for this cohort and so it was not possible to classify participants beyond the level of the involved hemisphere. Had it been possible to do so, it may have resulted in larger between-group differences in BPV. Despite this, it is worth highlighting that the differences in beat-to-beat BPV between left and right hemisphere lesions, although not reaching statistical significance, were larger than differences in BPV derived from other measurement methods. This may add weight to the idea that there is a stronger relationship between very short-term BPV and autonomic function/dysfunction than variability over longer timescales, and might further suggest that beat-to-beat BP measurement is the most appropriate method for investigating BPV in relation to autonomic function post-stroke.

If, as suggested by this study, there is a genuine relationship between increased BPV and LACS, then no inference regarding causality can be made on the basis of the cross-sectional analysis conducted here. However, there may be plausible reasons to suggest that increased BPV is more likely to cause LACS than other stroke subtypes, or vice versa. It is a subject of debate as to whether lacunar stroke is distinct from other stroke subtypes as a pathophysiological entity [266]. Comparison of risk factor profiles in ischaemic stroke subtypes indicates that LACS are less likely to be associated with previous IHD, a determined cardio-embolic source, or carotid stenosis [267]. It has also been proposed that atherothrombotic or embolic vessel occlusion may not be the only mechanism to cause LACS, rather endothelial damage and breakdown of the blood-brain barrier may be a distinct causal mechanism [268]. Alternatively, cerebral tissue supplied by chronically damaged small vessels may be vulnerable to injury due to

vessel spasm and subsequent reductions in CBF in the context of disordered cerebral autoregulation [266]. Increased BPV could theoretically play a part in these alternative pathological processes, either causing small vessel endothelial damage by generating pulsatile haemodynamic stresses [269, 270], or by reducing CBF below critical levels sufficient to cause ischaemia in the context of this chronic small vessel damage. Conversely, it may be hypothesised that LACS could cause increased BPV by virtue of the involvement of subcortical structures. For example, damage to the thalamus has been implicated, with one study demonstrating autonomic dysfunction manifesting as reduced HRV following stroke affecting this region [271]. This analysis may not support this latter idea however, as if autonomic function is more involved in the regulation of very short-term BPV it might be expected that subjects with LACS would demonstrate increased beat-to-beat, as opposed to ambulatory BPV.

The major positive aspect of this study is its novelty, it being the first, to my knowledge, to assess the relationship between OCSP classification of ischaemic stroke and BPV assessed as within-visit BPV from enhanced CBPM and BPV from daytime ABPM. It is also the first assessment of the association between BPV and affected stroke cerebral hemisphere. In addition, the study has also shed further light on the relationship between beat-to-beat BPV and stroke classification, which has previously only been sparsely reported. Several important limitations to the study also deserve mention, some of which have been discussed in detail above. Firstly, as a post-hoc exploratory analysis of trial data it was not powered to investigate the stated outcomes. Secondly, as a cross-sectional analysis no conclusions can be drawn about any potential causal relationship between increased BPV and stroke severity. Thirdly, there were some unexpected differences in BP values obtained using the different measurement methods and measurement bias cannot be excluded as a potential cause for these differences. Fourthly, there were some differences between the three trial cohorts that were pooled for this analysis, most notably the time from the qualifying stroke to the baseline assessment. In particular, although it was adjusted for in the multivariate analyses and not shown to be a significant predictive factor, this aspect could have confounded the relationship between BPV and NIHSS score, possibly reducing the effect seen as some participants (in TEST-BP and SERVED Memory) were recruited several weeks after their qualifying event. Fifthly, approximately two thirds

of participants were on antihypertensive treatment, including some who were on beta blockers. If there are class effects of antihypertensive medications on BPV as discussed in section 2.8, then this may have influenced the findings. However, those on different treatment regimens were evenly distributed across groups that were compared (e.g. different OCSP classification), and the study did not assess change in BPV over time, thereby minimising the potential impact of medications. Finally, it was only possible to analyse beat-to-beat BPV in a subgroup of patients, as this data was unavailable for participants in the BPV observational study. This limited the sample size and could increase the possibility of type two error in relation to the analysis of very short-term variability in this study.

6.8 Summary

- BPV is associated with severity of ischaemic stroke, with greater increases in variability associated with lacunar stroke as opposed to partial or total anterior circulation stroke.
- This suggests that any interventions designed to reduce BPV following ischaemic stroke may be most beneficial for patients with lacunar stroke.
- Furthermore, this relationship may support the concept that lacunar stroke, as a pathophysiological entity, is not identical to other stroke subtypes.
- Although this study did not demonstrate a relationship between BPV and the affected cerebral hemisphere, this may be due to methodological limitations of the analysis.
- These findings were at odds with the hypotheses being tested and so further work to corroborate them and investigate differences in BPV relating to subtypes of stroke, would be valuable, particularly as and when a consensus on measuring BPV in patients with stroke is achieved. This could help inform research into treatments aimed at reducing BPV post stroke.

7 The Influence of Antihypertensive Medication Class on Baseline Blood Pressure Variability in Patients with a Recent Stroke or TIA

7.1 Declaration

I would like to acknowledge the contribution of Karen Appiah, research fellow in Leicester, to this chapter. Her work in processing the data from the BPV observational study helped to make this work possible.

7.2 Introduction

BPV is increased in patients with acute ischaemic stroke [100], and this increase may persist into the chronic phase post stroke [256]. Furthermore, raised BPV may not be benign, being associated with adverse outcomes following ischaemic stroke [197-199], risk of recurrent stroke [200], and cardiovascular risk in general [128]. These assertions, coupled with the findings of the previous chapter which suggested BPV may be related to stroke severity, have raised interest in identifying treatments that have the potential to reduce BPV in addition to mean BP levels. Whether all established antihypertensive treatment classes might fulfill both goals to the same extent has been questioned, as a retrospective review of antihypertensive drug trials suggests this may not be the case [133]. In particular, beta blockers appear to be less effective at reducing the risk of stroke events compared to other antihypertensive classes. One potential explanation for this observation is that different antihypertensive drug classes do not all equally alter BPV, an explanation that is supported by data demonstrating that beta blockers may actually increase BPV [201, 203, 211]. Conversely, CCB and, to a lesser extent, thiazide-like diuretics seem to reduce BPV, with ACEI and ARB possibly neutral or increasing BPV. These potentially different class effects on BPV, if proven, might relate to differing class effects on vascular smooth muscle, with the classes that exert vasodilatory effects being those that also reduce BPV.

Hypertension guidelines recommend using an ACEI or ARB as the first-line treatment for patients under 55 years of age, and using a CCB or thiazide-like diuretic in patients over 55 years of age or of Afro-Caribbean ethnicity for primary prevention [91]. Recommendations for secondary prevention are the same in UK stroke guidelines [18], but American stroke guidelines suggest that thiazide-like diuretics (alone or in combination with ACEI) may be the most appropriate first-line therapy regardless of patient age [57]. In patients at high-risk of, or with established cardiovascular disease ACEI and ARB have become established treatments due to their inhibitory effects on atherosclerotic processes, and data suggest they may also have protective effects against stroke in addition to BP reduction [59]. However, data from major stroke secondary prevention trials question their value, suggesting that thiazide-like diuretics may be more effective [51, 52]. Limited evidence from systematic reviews and meta-analyses supports this, indicating that treatment with thiazide-like diuretics as opposed to other antihypertensive classes may convey the lowest risk of recurrent stroke [8, 272]. The mechanism for this is unclear, but may be related to vasodilation rather than natriuretic activity, as that is the likely mechanism for long-term BP reduction with this medication class [219, 273].

Whether any particular antihypertensive medication class should be preferred for secondary prevention post stroke, or whether it is simply BP lowering per se which is the important factor remains a subject of debate. The growing evidence relating to antihypertensive class effects on BPV is likely to fuel that debate. Furthermore, it seems to cast further doubt on whether drugs that inhibit the renin-angiotensin system are the most appropriate choice in this patient group. Crucially, with respect to the relevance of BPV to this debate there have been no dedicated prospective trials investigating the impact of antihypertensive medication class on BPV, and most retrospective analyses have focused on long-term visit-to-visit BPV rather than shorter timeframes of variability.

7.3 Hypothesis

This study aimed to add to the evidence base by exploring potential class effects of antihypertensive medications on shorter-term BPV in patients with established

cerebrovascular disease. Using data pooled from three trials that recruited patients with a recent ischaemic stroke or TIA, including some from a dedicated cohort study designed to investigate BPV post-stroke, it investigated if there are differences in short-term and very short-term baseline BPV in patients taking an ACEI or ARB based antihypertensive regimen as opposed to a CCB based regimen (either alone or in combination) with both groups compared separately to a control group. The hypothesis being tested is that BPV will be greater compared to control in those taking an ACEI or ARB than in those taking a CCB, irrespective of the BP measurement method used to derive BPV.

7.4 Methods

Combined data from participants recruited to TEST-BP, SERVED Memory, and the BPV observational trials were used to generate the database for this study. The general methodologies for these trials are described in sections 3.1.1-3.1.3, with TEST-BP and SERVED Memory having also been published elsewhere [222, 223]. The methodology specific to this analysis is described here. Eligible patients were participants in any of the above trials with a diagnosis of ischaemic stroke or TIA who were on at least one medication for hypertension at the time of baseline assessment. Participants also needed to have complete enhanced CBPM and daytime ABPM with ≥14 readings from the baseline assessment. A subgroup of these participants who also had baseline beat-to-beat BP measurement with a recording duration of ≥5 minutes after data cleaning was also included in the analysis. Participants who were not on antihypertensive treatment, who were diagnosed with ICH, or whose BP data were incomplete were excluded.

All baseline BP measurements were recorded as outlined in the general methodology chapter; enhanced CBPM as described in section 3.5.2, daytime ABPM as described in section 3.5.3, and beat-to-beat BP as described in section 3.5.5. For each set of BP measurements average and variability values for SBP and DBP were calculated as described in section 3.6. Medication history, including drug name (but not dose) was assessed by the study nurses at the baseline visit and corroborated using the medical notes. Participants taking an ACEI, an ACEI or ARB, or a dihydropyridine CCB were

grouped for comparison with a control group (consisting of participants taking any antihypertensive medication from classes other than the class being tested) as they are the most commonly prescribed classes of antihypertensive in UK clinical practice. These groups were also selected for consistency with the methodology of the feasibility trial presented in the subsequent experimental chapter. Participants taking an ARB were grouped with those taking an ACEI due to the similarities in mechanism of action and because the number of participants taking that medication class was too small to test independently. Treatment compliance at baseline was assessed in TEST-BP using the Hill-Bone compliance questionnaire and in SERVED Memory using the eight-item Morisky Medication Adherence Scale, but was not assessed in the BPV observational trial.

Outcomes for this analysis were the assessment of differences in systolic and diastolic BPV from enhanced CBPM, daytime ABPM, and beat-to-beat measurements in participants taking antihypertensive monotherapy or combination therapy. Groups tested were (i) ACEI vs. control; (ii) ACEI or ARB vs. control; (iii) CCB vs. control.

7.5 Statistical Analysis

Data were analysed using SPSS version 25.0. All BP and BPV variables were visually assessed for normality by constructing histograms with overlaid distribution curves and formally tested using the Kolmogorov-Smirnov test ($p>0.05$ deemed consistent with normal distribution). Mean SBP and DBP values were normally distributed, but BPV data from all measurement methods were not. Therefore a logarithmic transformation was applied to these variables prior to any statistical testing. This transformation resulted in normalisation of the variables. The results of any testing on transformed variables have been back-transformed for presentation. Initial exploratory univariate analyses were undertaken to assess any differences in BPV between those participants taking the medication of interest compared to a control group as described above. Testing was first restricted to participants taking antihypertensive monotherapy and then expanded to participants on combination therapy. Univariate testing was based on independent samples t tests, using whether the participant was taking the medication class of interest as a bivariate grouping variable and the BPV

parameter as the dependent variable. Where univariate testing suggested significant between-group differences ($p<0.05$ taken as the level for statistical significance) then further multivariate testing using a regression model was carried out, with the BPV parameter as the dependent variable, adjusted for differences between the trial cohorts and factors known to influence BPV [130, 251, 260]. Independent variables used in the model in addition to those tested with univariate analysis included time from stroke onset to baseline measurement, age, gender, mean BP, past medical history of hypertension, and past medical history of diabetes.

7.6 Results

Data from 238 participants were pooled for this analysis, with 142 participants making up the subgroup with valid beat-to-beat BP measurements as this data was not available for participants in the BPV observational trial. Demographic data for the full cohort and the subgroup is presented in **Table 34**. The majority of patients were taking an ACEI either alone or in combination, followed by CCB as the second most commonly prescribed antihypertensive medication class (**Table 35**). Fewer participants were taking an ARB than an ACEI, but this proportion was still greater than the proportion of participants taking a beta blocker or thiazide-like diuretic. Alpha blockers were the least commonly prescribed antihypertensive medication class.

Results including participants taking a combination of antihypertensive medications were the same as results for testing restricted to those on antihypertensive monotherapy. The former are presented as this approach incorporated a larger sample size. There were no differences in mean SBP or mean DBP values between any of the designated testing groups compared to control, regardless of the method used to measure BP (**Table 36**).

Table 34: Demographic data. Data presented are mean (SD) for normally distributed continuous variables, median (IQR)* for non-normally distributed continuous variables, and frequency (%) for categorical variables.

		All	Beat-to-beat subgroup
N		238	142
Age (years)		73.3 (9.7)	73.6 (9.8)
Gender	**Male**	159 (66.8%)	97 (68.3%)
BMI (kg/m^2)		28.5 (5.1)	28.9 (5.1)
Smoking	**Never smoked**	99 (41.6%)	60 (42.3%)
	Ex smoker	118 (49.6%)	76 (53.5%)
	Current smoker	21 (8.8%)	6 (4.2%)
Alcohol (units/wk)*		4.0 (14.0)	4.0 (16.0)
Diagnosis	**TIA**	123 (51.7%)	88 (62.0%)
	Stroke	115 (48.3%)	54 (38.0%)
OCSP classification (stroke only)	**LACS**	36 (31.9%)	20 (37.0%)
	PACS	51 (45.1%)	24 (44.4%)
	TACS	4 (3.5%)	1 (1.9%)
	POCS	22 (19.5%)	9 (16.7%)
NIHSS (stroke only)*		3.0 (3.0)	2.5 (3.0)
Past medical history	**TIA**	103 (43.6%)	87 (61.3%)
	Stroke	85 (35.7%)	60 (42.3%)
	IHD	47 (19.7%)	31 (21.8%)
	Diabetes	52 (21.8%)	36 (25.4%)
	Hypertension	185 (77.7%)	112 (78.9%)
No. of antihypertensives*		1.0 (1.0)	2.0 (1.0)

SD denotes standard deviation; IQR, interquartile range; BMI, body mass index; OCSP, Oxford Community Stroke Project; LACS, lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke; TIA, transient ischaemic attack; IHD, ischaemic heart disease.

Table 35: Proportions of participants taking each class of antihypertensive medication (as monotherapy or in combination).

	All		Subgroup	
	Monotherapy	**Combination**	**Monotherapy**	**Combination**
ACEI	60 (47.6%)	130 (54.6%)	34 (53.1%)	85 (59.9%)
ARB	17 (13.5%)	46 (19.3%)	7 (10.9%)	25 (17.6%)
Alpha blocker	3 (2.4%)	20 (8.4%)	0 (0.0%)	10 (7.0%)
Beta blocker	12 (9.5%)	54 (22.7%)	8 (12.5%)	42 (29.6%)
CCB	31 (24.6%)	101 (42.4%)	15 (23.4%)	62 (43.7%)
Thiazide-like diuretic	3 (2.4%)	35 (14.7%)	0 (0.0%)	24 (16.9%)

ACEI denotes angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 36: Differences in mean enhanced clinic, daytime ambulatory, and beat-to-beat systolic and diastolic blood pressure between the defined testing groups and control. Data presented are mean (SD) or difference (95% CI). P>0.05 for all differences.

	Antihypertensive medication regimen grouping					
	ACEI	**Control**	**ACEI or ARB**	**Control**	**CCB**	**Control**
Enhanced CBPM SBP (mmHg)	151.0 (20.5)	152.6 (21.2)	152.0 (21.7)	151.1 (18.5)	151.8 (18.7)	151.7 (22.3)
Difference	1.6 (-3.8 to 6.9)		-0.9 (-7.0 to 5.2)		-0.2 (-5.6 to 5.2)	
Enhanced CBPM DBP (mmHg)	83.9 (12.3)	83.5 (12.0)	83.4 (12.3)	84.5 (11.7)	82.9 (11.4)	84.2 (12.6)
Difference	-0.4 (-3.5 to 2.7)		1.1 (-2.5 to 4.6)		1.3 (-1.9 to 4.4)	
Daytime ABPM SBP (mmHg)	135.1 (15.6)	136.1 (16.6)	135.4 (15.6)	135.9 (17.1)	136.8 (14.8)	134.7 (16.8)
Difference	1.0 (-3.1 to 5.1)		0.5 (-4.2 to 5.2)		-2.1 (-6.3 to 2.0)	
Daytime ABPM DBP (mmHg)	77.3 (9.7)	77.0 (10.4)	76.8 (10.0)	78.1 (10.1)	76.3 (8.4)	77.8 (11.0)
Difference	-0.4 (-2.9 to 2.2)		1.3 (-1.6 to 4.2)		1.5 (-1.0 to 4.0)	
Beat-to-beat SBP (mmHg)	134.0 (18.3)	131.0 (16.0)	133.6 (17.7)	130.2 (16.5)	130.7 (17.1)	134.5 (17.6)
Difference	-3.0 (-8.9 to 2.9)		-3.4 (-10.4 to 3.5)		3.8 (-2.0 to 9.7)	
Beat-to-beat DBP (mmHg)	82.1 (13.2)	79.8 (13.7)	81.4 (13.7)	80.3 (12.5)	80.0 (13.2)	82.1 (13.5)
Difference	-2.4 (-6.9 to 2.2)		-1.2 (-6.5 to 4.2)		2.1 (-2.4 to 6.6)	

SD denotes standard deviation; 95% CI, 95% confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CBPM, clinic blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure measurement.

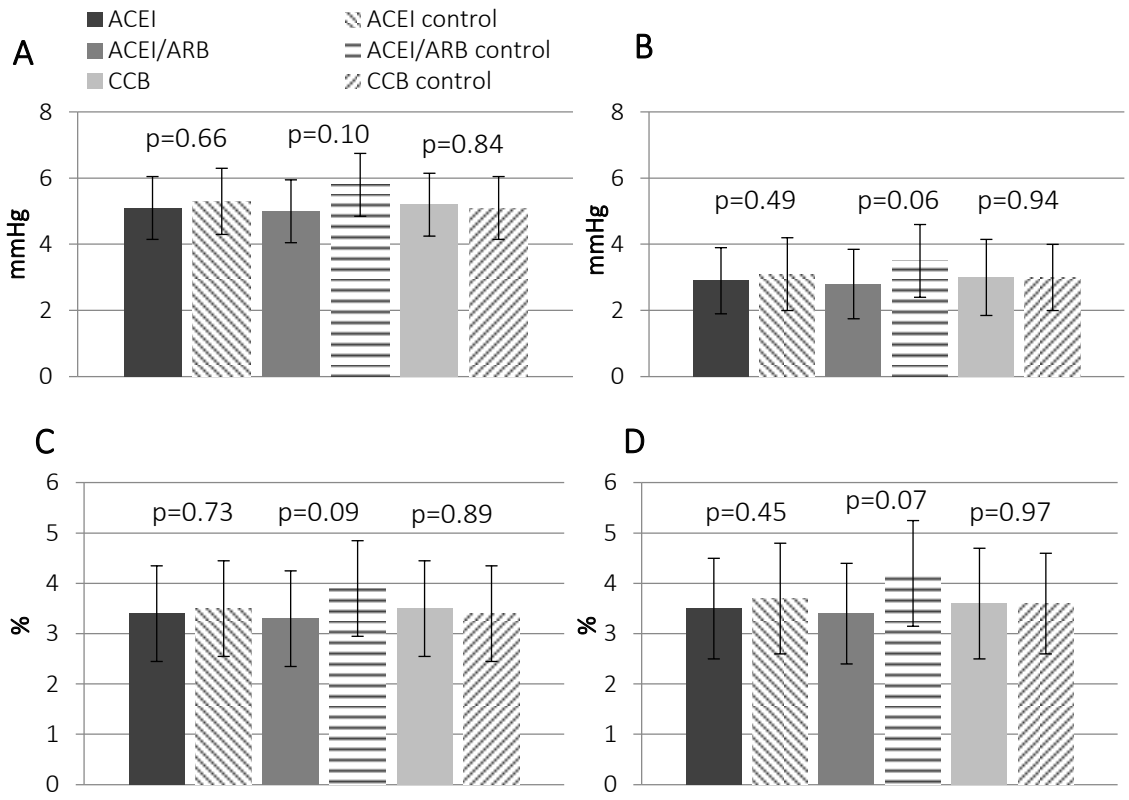

Figure 20: Histograms showing mean blood pressure variability from enhanced clinic blood pressure measurement in participants on medications from different antihypertensive classes compared to control. Error bars are standard deviation (SD). P values are based on independent samples t tests for the difference between each active group and control. **A** shows SD of systolic blood pressure (SBP). **B** shows SD of diastolic blood pressure (DBP). **C** shows coefficient of variation (CV) of SBP. **D** shows CV of DBP. ACEI denotes angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

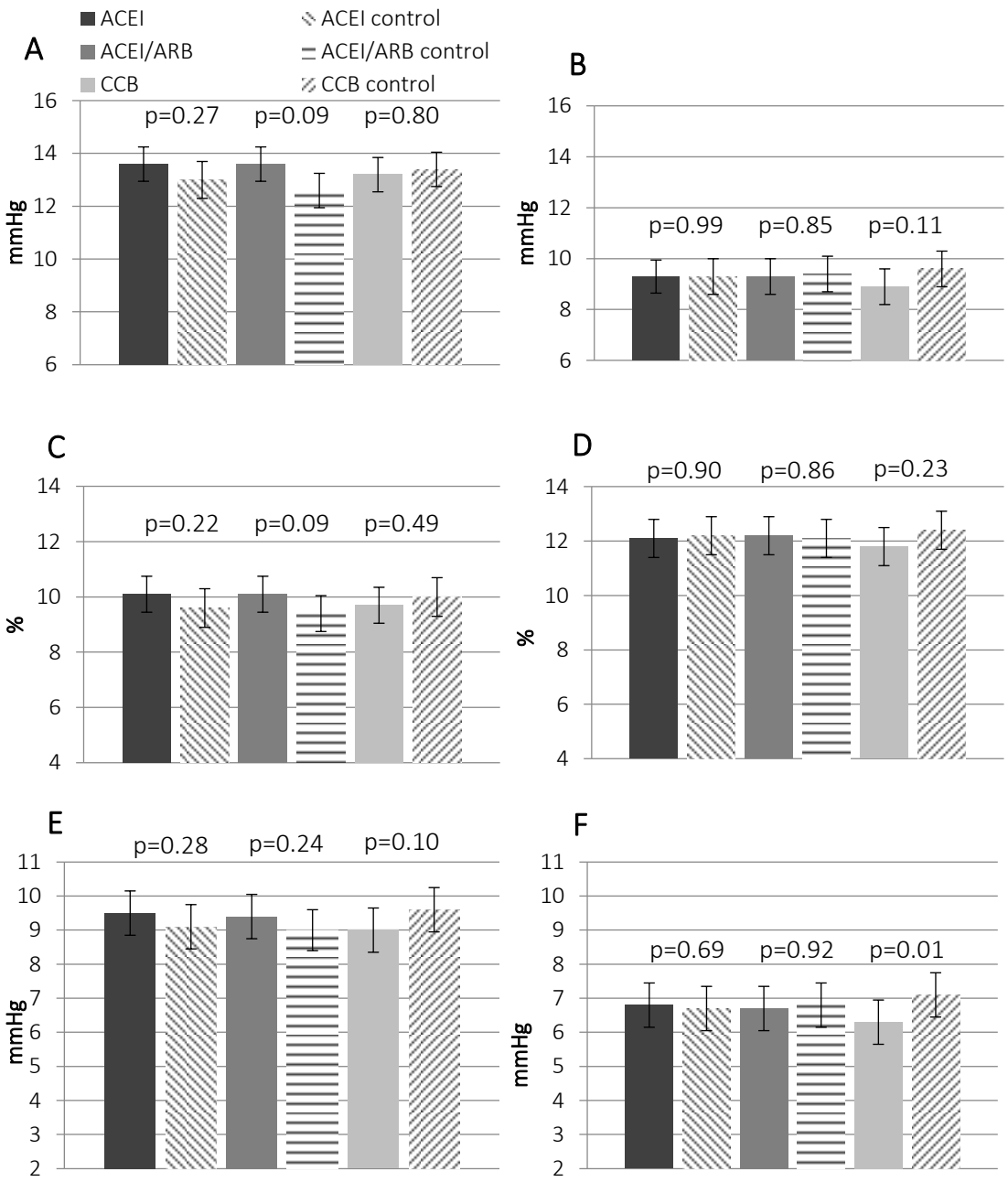

Figure 21: Histograms showing mean blood pressure variability from daytime ambulatory blood pressure measurement in participants on medications from different antihypertensive classes compared to control. Error bars are standard deviation (SD). P values are based on independent samples t tests for the difference between each active group and control. **A** shows SD of systolic blood pressure (SBP). **B** shows SD of diastolic blood pressure (DBP). **C** shows coefficient of variation (CV) of SBP. **D** shows CV of DBP. **E** shows average real variability (ARV) of SBP. **F** shows ARV of DBP. ACEI denotes angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

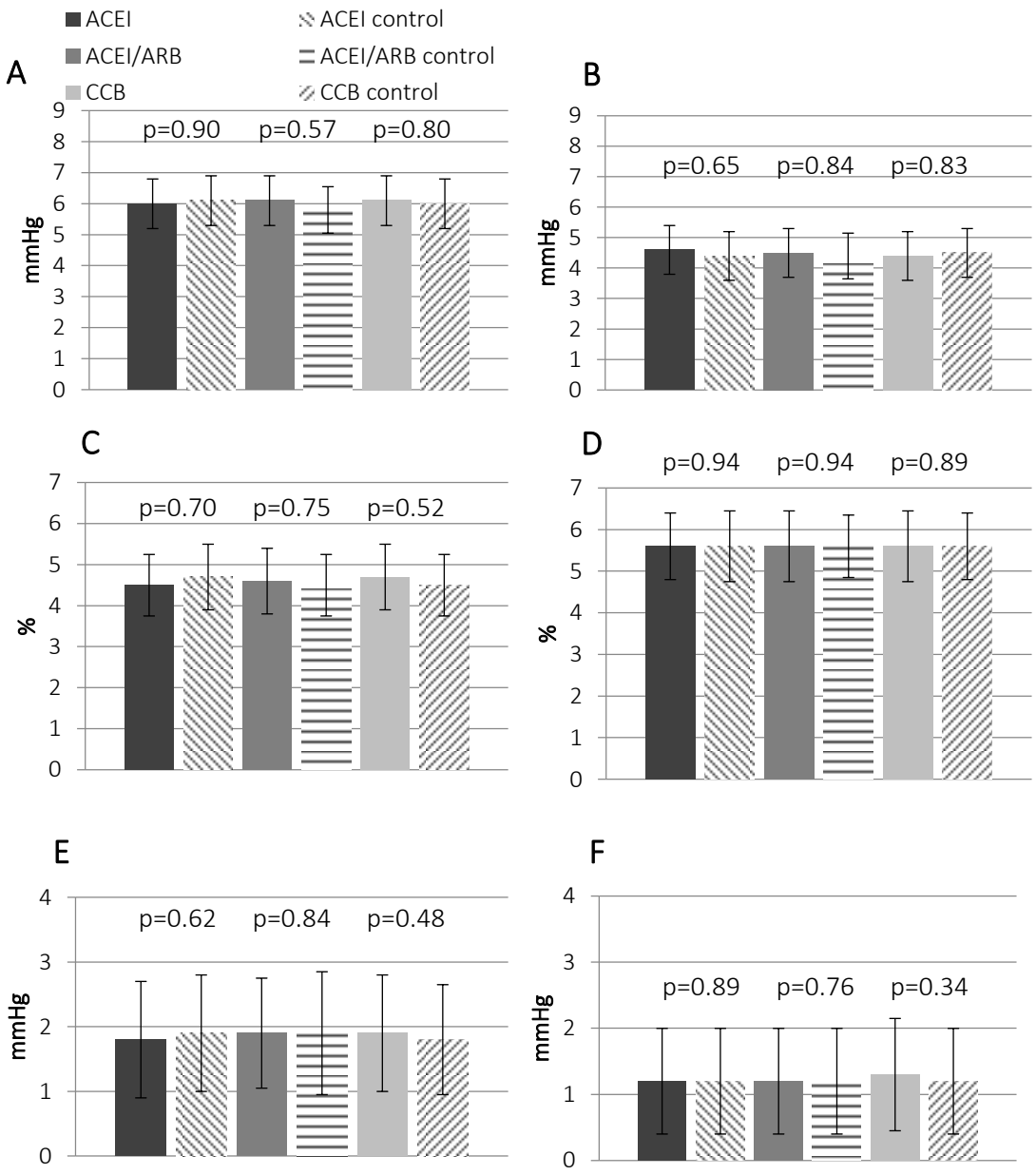

Figure 22: Histograms showing mean blood pressure variability from beat-to-beat blood pressure in participants on medications from different antihypertensive classes compared to control. Error bars are standard deviation (SD). P values are based on independent samples t tests for the difference between each active group and control. **A** shows SD of systolic blood pressure (SBP). **B** shows SD of diastolic blood pressure (DBP). **C** shows coefficient of variation (CV) of SBP. **D** shows CV of DBP. **E** shows average real variability (ARV) of SBP. **F** shows ARV of DBP. ACEI denotes angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

With regard to BPV measures, there were no significant differences between any of the designated testing groups and control, with the exception of daytime ABPM ARV of DBP for CCB vs. control (mean difference ratio 1.12 [95% CI 1.03 to 1.21], p=0.01), with this difference not remaining after multivariate testing (**Figures 20-22**). Although not statistically significant, the findings for daytime ABPM variability indicated a pattern of increased BPV compared to control for ACEI and ACEI or ARB, and decreased BPV for CCB compared to control.

7.7 Discussion

This cross-sectional analysis did not demonstrate significant differences in mean BP or BPV in patients with a recent ischaemic cerebrovascular event who were taking antihypertensive medication regimens based on different drug classes, regardless of the method used to measure BP. However, there was a possible opposing trend in systolic BPV from daytime ABPM for renin-angiotensin inhibitors and CCB compared to control, with variability possibly increased in the former and decreased in the latter. Whilst this may be a chance finding, it might also be that it is a genuine difference and that the study is hindered by an insufficient sample size. Post hoc power calculations indicate that the required sample size to detect a difference in SD of SBP with 80% power at the 5% significance level would be N=522, assuming a SD of 10.5 ± 4.9mmHg for CCB and 12.2 ± 5.8mmHg for ACEI [202]. Assuming the same effect size, the power of this sample to detect a genuine difference was between 0.57 and 0.68 depending on the comparison. The negative findings may also relate to another aspect of the study methodology. Rather than with cross-sectional analysis, differences in BPV attributable to antihypertensive medications might be better investigated with changes in variability over time. Thirdly, it is possible that medication dose as well as class is relevant to levels of BPV, with one study showing that change in variability from 24 hour ABPM was reduced in patients taking high doses of ACEI or CCB, but not low doses (high dose defined as 20mg of enalapril or lercanidipine, low dose defined as 10mg) [274]. Due to the available data it was not possible to account for dose in this study. The results also suggested that the trends in BPV in different groups, if genuine, might not be the same for variability from CBPM and daytime ABPM. This difference

may be explained by differences in mean BP seen from CBPM and daytime ABPM measurements. Mean values in the latter were consistent with controlled hypertension, whereas they were raised in the former. This suggests a possible white coat effect in this cohort, which could have confounded the results.

No other study results of the effect of antihypertensive medication class on BPV are directly comparable with those presented here. Either they have derived BPV over a different timeframe, or they have not included patients with cerebrovascular disease. However, although the trends in BPV from daytime ABPM seen in this study were not statistically significant, they are in keeping with those reported elsewhere. In a larger cross-sectional analysis of short-term BPV in patients with treated hypertension (N=2780, 10% with previous stroke), the SD of SBP from daytime ABPM was lower in participants taking a CCB (mean difference -0.22 ± 0.12mmHg) and higher in those taking an ACEI (mean difference 0.20 ± 0.15mmHg) or ARB (mean difference 0.40 ± 0.18mmHg) compared to control (defined the same as in this study) [211]. SD of DBP was also reduced in the CCB group, but was unchanged in the ACEI and ARB groups. In the only other study to recruit patients with a recent cerebrovascular event (N=288), Webb et al. demonstrated a 4% reduction in systolic residual CV from HBPM 1-2 weeks after starting or increasing the dose of a CCB, but only a 1% reduction with a new or increased dose of ACEI/ARB [213]. Similarly, post hoc analysis of the X-CELLENT trial (N=496 with hypertension but no previous cerebrovascular or coronary heart disease) showed that the SD of SBP from daytime ABPM was significantly reduced after three months of treatment with CCB compared to placebo (-1.1mmHg [95% CI -1.9 to -0.3]), but not with ARB (-0.6mmHg [95%CI -1.4 to 0.3]) [210]. Finally, similar results are reported for long-term BPV, with a post hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial indicating that systolic SD of visit-to-visit variability over 28 months of follow-up was lower in those treated with amlodipine compared to lisinopril (10.5mmHg [95% CI 10.3 to 10.7] vs. 12.2mmHg [95% CI 12.0 to 12.4]) [202]. Conversely, Asayama et al. reported no difference in the change in systolic VIM from HBPM between antihypertensive medication regimens after 2-4 weeks of monotherapy (N=2484 with no previous cardiovascular disease) [212]. However, the HBPM protocol used in the trial was not consistent with guideline

recommendations, requesting only a single BP measurement in the morning and evening for five consecutive days, which could have influenced the variability data.

The mechanisms through which CCB (and thiazide-like diuretics) might reduce BPV have not been proven, but it is suggested that the effect may be mediated by vascular smooth muscle relaxation and vasodilation; ACEI and ARB having relatively little effect on vascular tone compared to CCB and thiazide-like diuretics [133, 211, 218, 219, 273]. In an RCT comparing treatment with a CCB or thiazide-like diuretic in addition to an ARB (N=207), Matsui et al. showed a greater reduction in the SD of SBP from HBPM after six weeks treatment in the CCB group [220]. Furthermore, they demonstrated that the reduction in BPV in the CCB group was independently associated with a concurrent reduction in c-fPWV. An alternative mechanism for the reduction in BPV may be modulation of the autonomic nervous system, specifically via increased cardiac BRS. A small study of the effect of lacidipine on 24 hour BPV in adults with hypertension and diabetes (N=10) found that BPV was reduced with four weeks of treatment compared to placebo, and was also associated with improved BRS [275]. This finding was replicated in the larger X-CELLENT trial, where the reduction in BPV observed in the CCB group was at least partly related to a reduction in HRV, indirectly suggesting a concomitantly increased BRS [210]. Interestingly, beta blockers have also been shown to increase cardiac BRS [276], yet they do not seem to effect BPV in the same way as CCB. Perhaps the effect on BRS seen with CCB, but not beta blockers, is due to increased activity of stretch receptors located in the aortic arch as a result of reduced arterial stiffness, and this combination of reduced arterial stiffness and increased BRS is important for the reduction of BPV.

Strengths of this study include that it assessed BPV from a variety of BP measurement methods and is the only study, to the best of my knowledge, to investigate any differential effects of antihypertensive medication classes on beat-to-beat BPV. However, it also has limitations that require mention. As already discussed, the sample size may have been insufficient to detect statistically significant differences and it was not possible to stratify the analysis according to medication dose in addition to class. As it was only possible to investigate beat-to-beat variability in a subgroup these results in particular may be undermined by the small sample size. Furthermore,

although compliance was assessed in two of the trials providing data, it was not assessed in the BPV observational study. Similarly, it cannot be excluded that participants may have recently commenced antihypertensive therapy or had a recent dose adjustment prior to enrolment in any of the trials. Consequently, any effect on baseline BPV may be underestimated. Finally, participants on combinations of antihypertensive therapy were included in both the investigative and control groups; therefore any effect on BPV may not be entirely attributable to the medication class in question. However, other studies have shown that any medication class effects on BPV persist when the relevant medications are used in combination and so this approach is justifiable [217, 220, 277].

7.8 Summary

- This study did not show significant differences in baseline BPV compared to control for participants taking an ACEI/ARB or CCB based antihypertensive medication regimen.
- However, the study probably lacked sufficient statistical power to demonstrate a difference and may have been limited by the use of a cross-sectional analysis.
- The trends seen for variability from daytime ABPM were comparable with those reported elsewhere.
- Prospective, randomised trials to assess the impact of different antihypertensive medications on BPV post stroke would be valuable.

8 A Calcium channel or Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker Regime to reduced Blood pressure variability in acute ischaemic Stroke (CAARBS): A Feasibility Trial

8.1 Introduction

In the preceding chapter, although the analysis did not demonstrate any significant differences in baseline BPV between patients taking an ACEI/ARB or a CCB compared to control, the argument remains that there is a need for prospective trials investigating the possibility of treating BPV post stroke. Following an acute ischaemic stroke BP levels are frequently above the accepted threshold value for hypertension of 140/90mmHg [91, 92], even when there is no prior history of hypertension [10, 11]. The causes of this, often transient, increase are probably multifactorial, but one possibility is that it is a protective physiological response to maintain CBF to the ischaemic penumbra in the face of dysfunctional cerebral autoregulatory mechanisms [13, 63]. This explanation is supported by data demonstrating a spontaneous BP decrease in many patients, usually between 4-14 days after stroke onset [11, 63]. However, data from major stroke trials also indicates that raised BP in the acute period is associated with a poor prognosis [69]. In fact, the relationship between BP in the acute phase and both short and long-term mortality and morbidity from ischaemic stroke from observational studies is probably 'U' shaped, with the optimal BP level in the region of 150mmHg systolic [70]. Despite this, trials investigating the treatment of raised BP in acute ischaemic stroke have not shown any benefit to BP reduction [11], even if treatment is administered within 1-2 hours of symptom onset [278], with one trial reporting that it is possibly harmful [77]. Consequently, the management of raised BP in acute stroke remains uncertain, with guidelines suggesting that it is unlikely to be beneficial to start or continue treatment in the first few days after symptom onset unless there are adverse features related to accelerated hypertension or the patient has had thrombolytic therapy [18, 19, 57].

That trials of BP lowering in acute ischaemic stroke have shown no benefit may be because it is BPV rather than absolute BP level which is the important factor [126]. BP fluctuations may damage the vulnerable ischaemic penumbra, with drops in BP causing

hypoperfusion and infarct expansion, and spikes in BP causing increased oedema and haemorrhagic transformation. This may at least partly explain why the relationship between BP and stroke outcome appears to be 'U' shaped, and a growing body of evidence that BPV is a cardiovascular risk factor independent of mean BP also supports the theory [14, 128, 152, 153]. Furthermore, research has demonstrated that BPV is also increased in acute ischaemic stroke [100], is associated with adverse outcomes [98, 197-199], and is associated with the risk of recurrent stroke [200]. Whether BPV is a potential target for therapeutic intervention has not yet been tested. There are reports that some classes of routinely used antihypertensive medications can reduce BPV in addition to mean BP [133, 202, 209], but the evidence presented is either from observational cohorts or retrospective post-hoc analyses of trial data, and so cannot be said to be conclusive. Interestingly, some of these reports also indicate that not all commonly used antihypertensive medication classes effect BPV equally, despite lowering mean BP to a similar degree. CCB and thiazide-like diuretics are consistently reported to lower BPV, whereas beta blockers increase it, with renin-angiotensin inhibitors variably reported to be neutral or also increase BPV [201, 203, 211]. There is a need for prospective randomised trials to further investigate these reported effects. Furthermore, if lowering BPV is possible and it is the case that certain medication classes are more effective than others, it needs to be established whether lowering BPV following the acute period conveys any benefit in terms of morbidity and mortality after stroke.

8.2 Hypothesis

This study aimed to test the hypothesis that conducting a trial assessing the effect of two commonly used classes of antihypertensive medication on BPV in patients with a recent ischaemic cerebrovascular event in the subacute period was feasible. Specifically, the ability to recruit and retain trial subjects, the feasibility of measuring a change in BPV from baseline to three months post-event, compliance with the trial procedures, and the safety/side-effect profile of the intervention. Exploratory secondary aims were the assessment of functional and cognitive outcomes at three months to estimate potential differences between the intervention arms, which may help with the planning of a future definitive trial.

8.3 Trial Setup and Management

I authored the protocol for the trial in conjunction with the investigators, Professor Tom Robinson, Professor John Potter, and Professor Peter Rothwell between November 2016 and May 2017. Following sponsor review by the University of Leicester, I applied for ethical approval on 25th July 2017 (IRAS ID 216241) and this was granted by the London – Central Research Ethics Committee on 25th September 2017 (REC No. 17/LO/1427) after interview. As this was a clinical trial with investigational medicinal products I also applied for approval from the Medicines and Healthcare products Regulatory Agency, which was granted on 21st September 2017 (EudraCT number 2017-002560-41). Local Research and Development Department approval was provided for each trial site prior to sponsor green light approval to commence the trial. Recruitment for the trial opened on 3rd January 2018 in Leicester, 19th February 2018 in Norwich, and 26th March 2018 in Oxford.

During the recruitment phase several amendments were made to the trial. A substantial amendment to the eligibility criteria was implemented on 11th September 2018 in order to try and improve recruitment. This amendment increased the window of eligibility from <72 hours from symptom onset, to <7 days. Two non-substantial amendments were also made. The first was required to produce specific correspondence letters to the GP for use at the Oxford site to reflect that they were only recruiting participants from the outpatient clinic. This amendment was implemented on 20th March 2018. The second was required in order to extend the trial beyond the original end date and was implemented on 20th November 2018. This was done so that the trial could complete the originally planned duration of 15 months (12 months recruitment with a further 3 months for follow-up) despite unexpected delays in the setup process.

Oversight of the trial was conducted by the Trial Management Group, consisting of myself and Professor's Tom Robinson, John Potter, and Peter Rothwell, meeting at minimum three monthly intervals. A separate Independent Trial Steering Committee was convened consisting of the trial management group, the trial statistician, independent clinicians (Professor Marcus Flather, Professor David Werring, and Dr

Kneale Metcalf), and a representative of the funding body (Kate Holmes). The Trial Steering Committee met at six monthly intervals following the commencement of the trial and provided independent advice to the Trial Management Group. In addition, a Data Safety Monitoring Committee consisting of further independent clinicians and an independent statistician also met at six monthly intervals to advise the Trial Management Group and Trial Steering Committee regarding any arising ethical or safety issues that might require adjustment to, or early termination of, the trial.

8.4 Methods

CAARBS was a multi-centre, open-label, randomised parallel group controlled feasibility trial. The methodology of the trial is described in detail in section 3.1.4 and has also been published in full elsewhere [224]. In brief, eligible patients were aged ≥18 years with a first-episode TIA or mild/moderate ischaemic stroke (NIHSS <10), presenting within 72 hours of symptom onset (subsequently amended to within seven days of symptom onset), and requiring antihypertensive therapy for secondary stroke prevention (defined as repeated CBPM >130/80mmHg). Patients were excluded from the trial if they had a known contraindication to the proposed investigational medicinal products, clinically required treatment with a specific class of antihypertensive, had a pre-event mRS >3, life expectancy <3 months, or AF. Patients presenting to both the inpatient and outpatient stroke services at participating sites (outpatient services only in Oxford) were screened for eligibility by the trial nurse or Clinical Research Fellow. In accordance with local protocols, patient's pre-existing antihypertensive therapy was stopped or suspended by the clinical team at admission and new antihypertensive therapy was not commenced (as part of the trial or otherwise) until at least 48 hours after symptom onset unless clinically indicated. All diagnoses were reviewed by two experienced stroke physicians to confirm eligibility. Eligible patients willing to participate in the trial provided written informed consent prior to being randomised in a 1:1 ratio using a computer generated protocol in blocks of four, to treatment with either a dihydropyridine CCB or an ACEI/ARB. Each trial site had a unique randomisation table and managed the randomisation process locally to simplify the process. Intervention groups were defined according to antihypertensive class, with

the choice of medication from within the randomly allocated class at the discretion of the treating clinician.

At the baseline consultation clinical information was collected as described in section 3.5.1. BP data were collected using enhanced CBPM as described in section 3.5.2, daytime ABPM as described in section 3.5.3, and beat-to-beat BP as described in section 3.5.5. In addition, stroke severity was recorded using the tools described in section 3.5.6 and participants completed a cognitive battery based on the MoCA as a screening test enhanced with the Albert's line test for inattention and the MiND-B for frontal lobe cognitive symptoms. Participants also completed the Geriatric Depression Scale to exclude depression as a potential confounding factor for reduced cognitive assessment scores. An interim follow-up visit was completed after 21 ± 7 days, at which time treatment compliance was assessed with a tablet count and a self-rating scale [279], and enhanced CBPM and beat-to-beat BP measurements were repeated. Participants were asked to report any treatment side effects and those in the ACEI/ARB group had blood taken to check their renal function as a safety measure, as per routine clinical practice. The final follow-up visit was completed after 90 ± 14 days, at which time treatment compliance assessment, all baseline BP measurements, assessment of stroke severity and functional recovery, and the cognitive battery were repeated.

The primary outcome measure for the trial was the assessment of rates of recruitment and retention, including reasons for exclusion. Secondary feasibility outcomes were (i) change in BPV from baseline to follow-up by intervention arm; (ii) rates of treatment compliance and discontinuation by intervention arm; (iii) completion rates of BPV measurements; (iv) serious adverse event rates by intervention arm. In addition, secondary exploratory outcomes were (i) difference in mean BP at day 21 and day 90 by intervention arm; (ii) difference in BPV at day 21 and day 90 by intervention arm; (iii) mRS at day 21 and day 90 by intervention arm; (iv) difference in MoCA score at day 90 by intervention arm.

The primary objective of CAARBS was the assessment of the feasibility of recruitment, retention, compliance, and the safety of the trial. However, a sample size calculation

pre-hoc was performed to estimate the number of participants required to detect a potential difference in BPV between the treatment arms. Assuming a mean systolic BPV SD of 14.97mmHg in the CCB arm and 16.95mmHg in the ACEI/ARB arm [201], a sample of 150 patients (64 per group allowing for a 15% drop-out rate) was estimated to be required to detect an 8mmHg difference in systolic BPV with 80% power at the 5% significance level.

8.5 Statistical analysis

Data were analysed using SPSS (version 25.0). Only descriptive analyses were undertaken, in keeping with the CONSORT recommendations for reporting pilot and feasibility trials [280], as the required sample size for detecting a between-group difference in BPV described above was not achieved. Screening and management logs were assessed to determine the proportion of patients screened that were eligible for the trial, the proportion of eligible patients that were recruited, and the proportion of participants that completed follow-up. Reasons for ineligibility were recorded and assessed. Also, when offered, reasons for eligible patients declining to participate and reasons for participants withdrawing from the trial were recorded and assessed. All exploratory variables were assessed for normality. Normally distributed variables are presented as mean (SD) and non-normally distributed variables are presented as median (IQR). For the descriptive analysis of change in BPV from baseline to follow-up the mean (SD) absolute change for each intervention arm is described.

8.6 Results

Recruitment for the trial commenced on 3rd January 2018 and continued until 31st December 2018, with all follow-up completed three months post-randomisation. A total of 2321 patients were screened across the three sites, 14 (0.6%) of whom were eligible and consented to participate in the trial (**Figure 23**). A breakdown of screening and recruitment by site is shown in **Table 37**. Of those screened, 2264 (98.1%) were ineligible, with 1858 (81.7%) having a single reason for exclusion recorded on the screening log and 463 (18.3%) having multiple reasons recorded. The most common

reasons for patients being deemed ineligible were recurrent stroke/TIA (N=496 [21.4%]), non-stroke diagnosis (N=453 [19.5%]), and concurrent AF (N=431 [18.5%] **Table 38**). Patients presenting outside of the designated timeframe was also a prominent reason for ineligibility when screening against the initial window of <72 hours from symptom onset (N=314 [19.4%]). However, following the substantial amendment to the eligibility criteria described above, late presentation became a less frequent reason for exclusion (N=46 [6.6%]). With a few exceptions, the main reasons for exclusion were similar across all three sites (**Figure 24**). Non-stroke diagnosis was a more frequent reason for exclusion at the Leicester site as medical outliers on the stroke ward were included in screening numbers. Presenting beyond 72 hours from symptom onset was a greater problem in Oxford where screening and recruitment for the trial was exclusively outpatient based. In Norwich a proportion of patients were excluded as their pre-event antihypertensive therapy was not suspended at the point of admission to the stroke services.

In addition to those patients who were excluded, a further 43 (1.9%) met the eligibility criteria but did not want to participate in the trial. Patients who declined to participate in the trial were not obliged to provide a reason for their decision and not all offered an explanation for their choice. However, several patients stated that they felt unable to commit the time to attend trial visits (N=7) or did not wish to travel to the hospital for additional appointments (N=3), despite the offer of reimbursement for travel costs. Two patients also stated that they did not like the idea of being randomly assigned to a medical treatment.

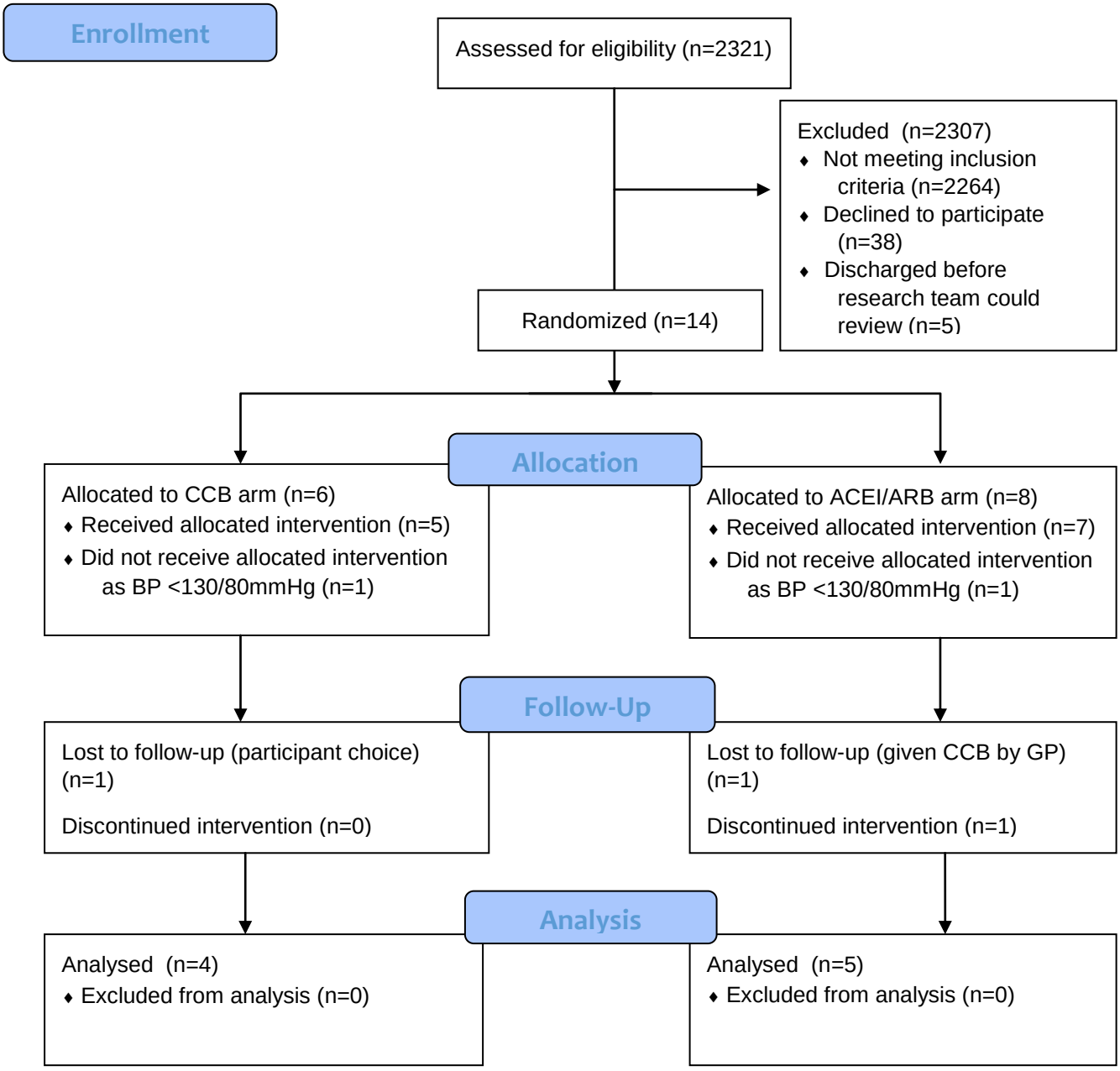

Figure 23: CAARBS CONSORT flow diagram. CCB denotes calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; GP, general practitioner.

Table 37: CAARBS screening and recruitment data by participating site.

		Norwich	Leicester	Oxford
Screened		1249	803	269
Excluded		1241	800	266
Ineligible		1225	774	265
Randomised	**CCB**	4	1	1
	ACEI/ARB	4	2	2
Lost or withdrawn		4	0	1
Completed follow-up		4	3	2

CCB denotes calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

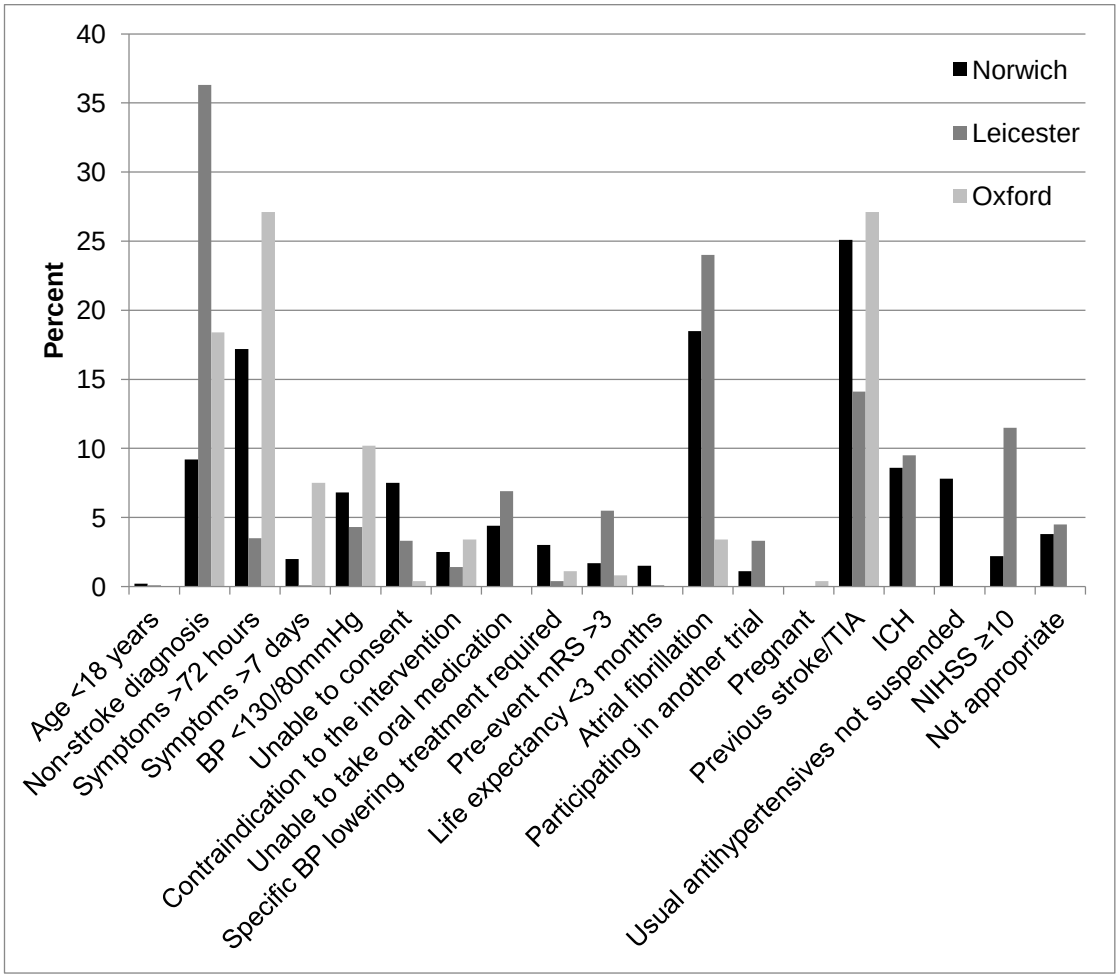

Figure 24: Histogram showing rates of each reason for exclusion of ineligible patients by trial site. BP denotes blood pressure; mRS, modified Rankin scale; TIA, transient ischaemic attack; ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale.

Table 38: Reasons for exclusion of patients screened for the trial who did not meet the eligibility criteria. Data presented are frequency (%).

Reason for exclusion		**Frequency**
Age <18 years		3 (0.1%)
Non-stroke diagnosis		453 (19.5%)
Late presentation	>72 hours from symptom onset	314 (19.4%)*
	>7 days from symptom onset	46 (6.6%)**
BP <130/80mmHg		145 (6.2%)
Unable to consent		120 (5.2%)
Contraindication to the intervention		51 (2.2%)
Unable to take oral medication		110 (4.7%)
Clinical need for urgent antihypertensive therapy or treatment with specific antihypertensive class		43 (1.9%)
Pre-event mRS >3		67 (2.9%)
Life expectancy <3 months		19 (0.8%)
Atrial fibrillation		431 (18.6%)
Participating in another investigational drug trial		40 (1.7%)
Pregnant		1 (0.04%)
Previous stroke/TIA		496 (21.4%)
ICH		183 (7.9%)
Usual antihypertensive therapy not suspended		97 (4.2%)
NIHSS ≥10		119 (5.1%)
Deemed inappropriate to approach for research by clinical team due to co-morbidities		83 (3.6%)

*Out of 1619 patients screened before the eligibility criteria were amended

**Out of 702 patients screened after the eligibility criteria were amended

BP denotes blood pressure; mRS, modified Rankin scale; TIA, transient ischaemic attack; ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale.

Randomised participants were evenly split between the two intervention groups in the context of the small sample size. Baseline characteristics are displayed in **Table 39**. Two participants (both from the Norwich site) were withdrawn as "screening failures" and provided no baseline data as their initial BP was >130/80mmHg, but repeated measurements at the baseline consultation were below this threshold value for secondary prevention treatment. Therefore, it was felt to be unethical for them to continue in the trial. One participant withdrew from the CCB arm of their own choice (they felt unable to commit the time required for follow-up visits), one participant was withdrawn from the ACEI/ARB arm by the trial team as they were commenced on a CCB by another clinical team in addition to their trial medication, and one participant from the ACEI/ARB arm discontinued treatment due to side effects and withdrew from the trial. Apart from this single treatment discontinuation there were no other major side effects and no serious adverse events recorded in either intervention arm.

Completion rates of CBPM and beat-to-beat BP measurements were good across all study visits, with all completed readings judged to be valid (**Table 40**). However, completion rates of daytime ABPM measurements were lower, in part due to a software failure at the Leicester site meaning no ABPM recordings were possible in their participants, and in part due to participants refusing this method (N=2). Furthermore, of the completed daytime ABPM measurements, only 6/13 (46.2%) provided ≥14 readings and were considered valid for analysis. Compliance with trial treatment according to the self-rating questionnaire was good, with 8/9 (88.9%) of participants who completed the trial indicating compliance ≥80%. However, tablet count was unsuccessful at assessing compliance as participants often failed to bring their medication to follow-up visits, being completed in only 5/18 (27.7%) consultations.

Table 39: Baseline characteristics of randomised participants. Data presented are mean (SD) or frequency (%), except alcohol consumption which is median (IQR).

		CCB	ACEI/ARB
N		5	7
Age (years)		74.8 (4.2)	64.9 (9.1)
Gender	**Male**	4 (80.0%)	4 (57.1%)
Ethnicity	**White-British**	4 (80.0%)	6 (85.7%)
BMI (kg/m^2)		28.2 (4.6)	27.1 (5.8)
Smoking	**Never smoked**	2 (40.0%)	2 (28.6%)
	Ex-smoker	3 (60.0%)	2 (28.6%)
	Current smoker	0 (0.0%)	3 (42.8%)
Alcohol (units/wk)		5 (17.5)	14 (26.5)
Diagnosis	**TIA**	3 (60.0%)	3 (42.9%)
	Stroke	2 (40.0%)	4 (57.1%)
Past medical history	**Hypertension**	3 (60.0%)	1 (14.3%)
	Diabetes	1 (20.0%)	0 (0.0%)
	IHD	0 (0.0%)	0 (0.0%)
Mean enhanced CBPM (mmHg)	**SBP**	163.6 (17.3)	152.7 (14.5)
	DBP	81.8 (5.9)	83.1 (6.5)
SD enhanced CBPM (mmHg)	**SBP**	8.4 (5.2)	6.8 (5.3)
	DBP	5.6 (3.0)	6.0 (3.4)
CV enhanced CBPM (%)	**SBP**	4.9 (2.6)	4.5 (3.4)
	DBP	7.0 (3.9)	7.2 (4.0)
Mean beat-to-beat BP (mmHg)	**SBP**	156.6 (5.7)	151.0 (11.9)
	DBP	79.8 (7.1)	82.6 (6.1)
SD beat-to-beat BP (mmHg)	**SBP**	9.9 (3.9)	9.2 (5.5)
	DBP	5.2 (2.2)	5.1 (2.4)
CV beat-to-beat BP (%)	**SBP**	6.3 (2.5)	6.0 (2.6)
	DBP	6.6 (2.6)	6.3 (3.0)

CCB denotes calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; TIA, transient ischaemic attack; IHD, ischaemic heart disease; CBPM, clinic blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation; BP, blood pressure.

Table 40: Completion rates of each blood pressure measurement method.

	Enhanced CBPM	Beat-to-beat BP	Daytime ABPM
Baseline	12/12 (100.0%)	11/12 (91.7%)	7/12 (58.3%)
21 days	9/10 (90.0%)	9/10 (90.0%)	-
90 days	9/9 (90.0%)	8/9 (88.9%)	6/9 (66.6%)

CBPM denotes clinic blood pressure measurement; BP, blood pressure; ABPM, ambulatory blood pressure measurement.

Table 41: Mean blood pressure and variability from enhanced clinic blood pressure measurement at day 21 and day 90 by intervention arm. Data presented are mean (SD) with change from baseline being the absolute difference in the mean values.

		CCB		ACEI/ARB	
		SBP	DBP	SBP	DBP
Mean BP (mmHg)	**21 days**	151.8 (4.1)	74.2 (2.5)	137.1 (13.0)	77.5 (9.9)
	Change from baseline	-11.8	-7.6	-15.6	-5.6
	90 days	128.6 (10.1)	72.6 (4.1)	130.9 (17.9)	75.5 (8.2)
	Change from baseline	-35.0	-9.2	-21.8	-7.6
SD (mmHg)	**21 days**	5.2 (1.5)	3.4 (1.0)	6.2 (2.9)	4.6 (2.7)
	Change from baseline	-3.2	-2.2	-0.6	-1.4
	90 days	5.1 (2.1)	4.3 (2.2)	3.9 (1.7)	3.1 (1.7)
	Change from baseline	-3.3	-1.3	-2.9	-2.9
CV (%)	**21 days**	3.4 (0.9)	4.5 (1.2)	4.6 (2.3)	5.8 (2.8)
	Change from baseline	-1.5	-2.5	0.1	-1.4
	90 days	4.0 (1.7)	5.8 (2.7)	3.1 (1.5)	4.3 (1.6)
	Change from baseline	-0.9	-1.2	-1.4	-2.9

SD denotes standard deviation; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; CV, coefficient of variation.

Table 42: Mean blood pressure and variability from beta-to-beat blood pressure measurement at day 21 and day 90 by intervention arm. Data presented are mean (SD) with change from baseline being the absolute difference in the mean values.

		CCB		ACEI/ARB	
		SBP	**DBP**	**SBP**	**DBP**
Mean BP (mmHg)	**21 days**	142.0 (7.4)	68.1 (1.3)	127.4 (14.8)	71.7 (11.4)
	Change from baseline	-14.6	-11.7	-23.6	-10.9
	90 days	136.4 (3.7)	71.5 (6.2)	137.5 (27.5)	75.8 (8.9)
	Change from baseline	-20.2	-8.3	-13.5	-6.8
SD (mmHg)	**21 days**	9.7 (4.0)	4.9 (2.5)	8.6 (4.6)	4.0 (1.7)
	Change from baseline	-0.2	-0.3	-0.6	-1.1
	90 days	6.2 (3.0)	2.8 (1.4)	8.7 (5.9)	3.9 (2.7)
	Change from baseline	-3.7	-2.4	-0.5	-1.2
CV (%)	**21 days**	6.7 (2.4)	7.2 (3.6)	6.6 (2.6)	5.7 (1.7)
	Change from baseline	0.4	0.6	0.6	-0.6
	90 days	4.5 (2.1)	3.8 (1.8)	6.0 (2.9)	4.9 (2.9)
	Change from baseline	-1.8	-2.1	0.0	-1.4

SD denotes standard deviation; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; CV, coefficient of variation.

Enhanced CBPM and beat-to-beat mean BP and BPV were reduced at 90 days compared to baseline in both trial arms (**Tables 41-42**), and the reductions seen were similar. There were also no apparent differences in functional or cognitive outcome between the intervention arms. In the CCB arm median (IQR) mRS was 0.0 (0.0) at day 21 and 0.0 (1.0) at day 90, and mean (SD) MoCA score was 23.5 (2.7). In the ACEI/ARB arm mRS was 1.0 (0.8) at day 21 and 1.0 (1.0) at day 90, and MoCA score was 23.6 (3.7).

8.7 Discussion

Recruitment for this trial was difficult owing to the high rate of ineligibility of patients who were screened (98.1%), this being an issue across all three trial sites. The trial did not meet its pre-specified recruitment target and consequently it must be concluded that in its current form it would not be feasible to scale up this study design to attempt a definitive RCT. The main reasons for patient ineligibility were having a previous stroke or TIA, having a non-stroke diagnosis, presenting outside of the window of eligibility, and having concurrent AF. Amending the inclusion criteria to extend the window of eligibility markedly reduced the number of patients excluded for this reason, but this did not translate into a major increase in recruitment. However, that the major reasons for exclusion were similar across all sites suggests that a future trial could be successful if the eligibility criteria were modified more comprehensively.

A proportion of patients who are ultimately diagnosed with a stroke mimic must be accepted, but there are other criteria that could be adapted. Firstly, the findings suggest that retaining the extended window of eligibility could be helpful. Not only could it directly increase patient eligibility at the point of presentation to stroke services, it may also allow time for patients who would be too unwell to participate in the first 72 hours post event (e.g. if they are nil by mouth) to recover sufficiently for inclusion. Secondly, although increased BPV may persist into the chronic phase post-stroke [256], there is the potential for large gains if patients with a previous stroke are included. The use of minimisation criteria to ensure equal numbers of first and recurrent stroke patients in each trial arm, or pre-specified analysis plans to offset

their inclusion, such as planned subgroup analysis of patients with first-ever stroke or adjustment for previous stroke in statistical testing, could be employed to ensure the accuracy of results. Thirdly, as it is accepted that most patients require multiple agents in order to achieve BP control [214-216], it may be necessary to include patients on additional antihypertensive medications other than the investigational medicinal products. Again it is likely that this would need to be accounted for with techniques such as pre-specified subgroup analysis or adjustment in statistical testing. A treatment escalation algorithm would need to be devised to minimise the risk of unintentional intervention group crossover during follow-up (which may need to be longer than in this trial), whilst allowing for treatment intensification in order to achieve secondary prevention BP targets. Finally, as beat-to-beat BPV is increased in patients with AF compared to control [281], and beta blockers are frequently used as part of a rate control treatment strategy for AF [282], the potential for data confounding by including participants with AF may outweigh any benefit of improved recruitment. However, automated oscillometric BP measurement devices have been shown to be reliable in AF provided multiple measurements are taken as per guideline recommendations [92, 283]. Therefore, if any future trial used BPV derived from enhanced CBPM or ABPM to judge the impact of the intervention, rather than beat-to-beat BPV, it may be possible to include these patients. Further safeguarding could be achieved by specifying data validation criteria for patients with AF, for example by stating an acceptable range for HRV across BP measurements used to derive BPV that would minimise the impact of uncontrolled AF on the BP data.

Although, owing to the findings of the primary trial outcome, the trial was considered not to be feasible in its current format, there were some positives amongst the secondary feasibility outcomes. These findings must be interpreted in the context of the small sample size, but they may give grounds for cautious optimism. Firstly, retention in the trial was reasonable, with 9/14 (64.3%) randomised participants completing three-month follow-up. Secondly, compliance with the intervention and with BP measurements was good, with the reduced rate of completed daytime ABPM measurements mainly due to a technical issue at one of the trial sites. Thirdly, there were no major safety issues in either trial arm and only one participant discontinued treatment due to side effects. Fourthly, although it was not possible to draw any

conclusions about differences between the intervention arms in terms of BPV reduction, functional outcomes, or cognitive outcomes, a reduction in BPV was demonstrated over the three-month follow-up period. This indicates that if sufficient numbers of participants could be recruited, it should be possible to detect a differential effect of different antihypertensive medication classes on BPV if one exists. Further work is now required to estimate the reduction in BPV that is attributable to each intervention as this will be required to estimate the necessary sample size in a future trial, and has not been adequately established in this patient group.

There are no directly comparable trials for the results of this study and so, even though insufficient data were obtained for the secondary exploratory outcomes, its novelty and merits should be noted. Firstly, it should be highlighted that the primary objective of investigating feasibility was achieved, and this represents a strength of the study design and underlines the value of conducting preliminary trials such as this one. Secondly, the data gathered has also allowed for recommendations to be made that may improve recruitment if a future trial is pursued. Thirdly, the trial has proven the concept that it is possible to measure a change in BPV in the months following an ischaemic cerebrovascular event, indicating that a future trial with modified eligibility criteria could successfully test the hypothesis that BPV reduction will not be equal between groups treated with different antihypertensive medication classes. The trial also has limitations that are worthy of consideration. Firstly, only a small proportion of eligible patients who declined to take part in the trial offered a reason for their decision and this represents a missed opportunity for improving the trial design. Secondly, owing to the small sample size limited data regarding participant retention and reasons for withdrawal were obtained. Obtaining more data in both of these areas would have been useful for judging the feasibility of any similar future trial. Thirdly, it was not possible to demonstrate a differential effect on BPV between the two intervention arms. In part this was due to the small sample size, but it cannot be excluded that the use of antihypertensive agents in some participants prior to their recruitment in the trial could have influenced their BPV as recorded in the trial. Unfortunately, as it is accepted standard care to treat raised BP for secondary stroke prevention it would not be ethical to incorporate a complete washout period into the

trial design. Therefore, follow-up in any further trials may need to be prolonged, or previous antihypertensive use may need to be adjusted for in the statistical analysis.

8.8 Summary

- With the current design this RCT must be deemed not feasible owing to the large proportion of patients screened who were not eligible for inclusion.
- However, the trial did demonstrate that it is possible to measure a change in BPV over three months post stroke and compliance with trial procedures by those recruited was good.
- The main reasons for ineligibility were similar across trial sites, suggesting that modifying the eligibility criteria may allow for improved recruitment in any similar future trial.
- Modifications including a longer window of eligibility following symptom onset, including patients with previous stroke/TIA, and allowing for patients who require multiple antihypertensive agents should be considered.
- It may also be possible to include patients with AF, though this would probably depend on the method(s) chosen to measure BPV and would require careful data collection and inspection to minimise the risk of confounding.

9 General Discussion

As summarised in chapter two of this thesis, the idea that an individual's BP can vary from reading to reading, even when multiple readings are taken concurrently, is not new. Multiple factors can contribute to this variability, some of which are natural (e.g. circadian rhythm or emotional state) or situational (e.g. WCH or MH) [90], yet an increasing body of evidence has emerged indicating that BPV may also be pathological. Early suggestions that BPV may not be a benign phenomenon came from work by Rothwell et al. where limitations to the accepted concept of "usual BP" were noted [126], and secondary analyses of several major stroke trials showed that long-term visit-to-visit variability (after adjustment for mean BP levels) was a stronger predictor of recurrent stroke than mean BP [131]. Further work in the wake of these publications has shown that increased BPV is associated with markers of damage to multiple organ systems, for example microalbuminuria and proteinuria [134-136], cerebral small vessel disease and micro-haemorrhages [137, 138], and left ventricular hypertrophy [136]. Furthermore, several meta-analyses of reports on the prognostic significance of BPV indicate that increased long-term variability is an independent risk factor for mortality, coronary heart disease, and stroke [14, 128, 152, 153]. The same is probably also true of short-term variability, though the evidence is less robust [128]. It should be noted that analyses of the prognostic significance of BPV have used statistical adjustment for mean BP levels. This illustrates that it is not possible to consider BPV in isolation from mean BP. Firstly, both are measured using the same device(s) and (where the device is programmed to take multiple measurements) at the same time. Secondly, the two measurements are linked, with data indicating that BPV has a positive linear relationship with mean BP [130, 251]. Thirdly, although BPV is an independent cardiovascular risk factor, the application of this in clinical practice is likely to be in combination with the prognostic information provided by mean BP. In other words, the prognostic value of BPV is likely to be additive to that of mean BP rather than separate. Finally, it may be that both are altered by the same interventions, though the extent to which antihypertensive medications alter BPV is uncertain. In relation to ischaemic stroke, it has been suggested that BPV may be of particular relevance, with the ischaemic penumbra theoretically vulnerable to fluctuations in BP in the context of abnormal cerebral autoregulation and a possible

pathophysiological link with post stroke autonomic dysfunction [13, 181]. Compared to controls, BPV is increased in patients with ischaemic stroke [100]. Furthermore, increased BPV in this patient group is associated with adverse clinical features, such as secondary haemorrhagic transformation and END [185-189], and worse long-term functional recovery as assessed by mRS at three months [98, 197-199]. However, the literature on BPV is complicated by heterogeneity in terms of BPV measurement and calculation, a lack of understanding as to whether alternative measurement methods and timescales of BPV are equivalent or if any one method is superior, and a lack of established "normal" values for BPV.

The aims of this thesis were to further the investigation of BPV in patients with ischaemic cerebrovascular disease with specific regard to: (i) its measurement and calculation, and (ii) its potential as a therapeutic target following an ischaemic cerebrovascular event. In summary, the experimental chapters presented in this thesis have indicated the following with regard to these aims. Firstly, there were significant differences in mean BP values as assessed by daytime ABPM and contemporaneous HBPM in patients with a recent ischaemic stroke or TIA, which has implications for the measurement of BPV using these methods. Mean daytime ABPM values were in the order of 7/2mmHg lower than HBPM values and this difference was consistent over time, but not reproducible within individuals. Secondly, there were no significant relationships between different timescales of BPV as assessed by comparison of BPV values derived from beat-to-beat BP measurements and those derived using other methods. This was the case even when the difference between timescales was small (i.e. within-hour daytime ABPM data compared with beat-to-beat BP data) and suggests that different BPV measurements are not interchangeable. Thirdly, there were significant relationships between ischaemic stroke severity, as measured by NIHSS or OCSP classification, and baseline short-term BPV derived from daytime ABPM, indicating increased BPV in patients with LACS compared to other stroke subtypes. However, similar relationships were not demonstrated for short-term BPV from enhanced CBPM or beat-to-beat BPV, and no relationship between BPV and affected cerebral hemisphere was demonstrated. Fourthly, there were no significant differences in baseline BPV for patients with a recent ischaemic stroke or TIA treated with a CCB or ACEI/ARB based antihypertensive regimen compared to controls.

However, this study did show a possible, but non-significant contrasting effect on short-term BPV from daytime ABPM for those treated with a CCB or ACEI/ARB. Finally, to test whether different classes of antihypertensive medication alter BPV to varying degrees, a feasibility RCT was developed to compare the effects of a CCB or ACEI/ARB based antihypertensive regimen on BPV following an acute ischaemic stroke or TIA. However, the trial design as tested was proven to be unfeasible due to the high rate of patient ineligibility, which resulted in poor recruitment. However, participant retention in the trial was acceptable and the interventions were safe. Furthermore, the trial demonstrated that it is possible to determine a change in BPV in the months following an acute ischaemic cerebrovascular event. These findings will now be discussed further, taking the two broad aims in turn, with consideration given to how gaps in the evidence have been addressed, and any implications for future research on this topic.

9.1 Studies Investigating the Measurement of Blood Pressure Variability Post Stroke

As summarised above, chapters four and five were concerned with the measurement of BP and BPV following a recent ischaemic stroke or TIA. Chapter four investigated differences in the measurement of mean BP between alternative out-of-office measurement methods, namely daytime ABPM and HBPM. Chapter five investigated the relationships between very short-term BPV from beat-to-beat BP measurements and variability derived over longer timescales from more commonly used BP measurement methods. For the adequate treatment of hypertension to be possible we must first understand the relevance of raised BP to future cardiovascular events, and second, establish the threshold value at which the benefit of intervention outweighs the risk/side effects of treatment. Both of these factors rely on having an accurate and reproducible method for measuring BP. Furthermore, these same factors apply when considering the clinical importance of BPV and it is unlikely that BPV can be considered in isolation from BP. At present there is no standardised methodology for measuring BPV and the threshold values of variability for increased cardiovascular risk, including risk of first or recurrent stroke, have not been established [90, 155, 156]. Even in the treatment of mean BP levels, which is widely accepted in comparison to the idea of targeting treatment at BPV, there remains uncertainty about the optimum target

value, especially for prevention of recurrent stroke and cognitive decline [55, 62, 284, 285], and debate about which measurement method represents the gold standard [156]. This uncertainty is reflected in recent guideline updates, with the AHA now recommending treatment at a lower threshold value than European guidelines [54, 91, 92]. Although all major guidelines agree that 135/85mmHg is the equivalent out-of-office BP value (measured by either daytime ABPM or HBPM) for a CBPM of 140/90mmHg, the AHA countenance that the difference is dependent on BP level, with no difference at a CBPM of 130/80mmHg or below and an increased difference with greater CBPM values [54, 91, 92]. That ABPM values tend to be lower than CBPM values is widely accepted [110]. However, the limited number of direct comparisons of ABPM and HBPM suggest that out-of-office methods may not be equivalent [112, 116, 118, 120, 121]. Clearly these discrepancies in BP measurement, if accurate, have implications for the treatment and monitoring of BP for both primary and secondary disease prevention, and the same may be true of BPV.

Evidence suggests that BPV is related to mean BP, with two studies indicating a linear positive relationship whereby BPV increases alongside mean BP level [130, 251]. A third study has suggested that the relationship may be 'U' shaped, with variability increasing either side of SBP in the range 120-140mmHg, though there was stronger evidence for the increase above SBP 140mmHg than below 120mmHg [286]. Therefore, discrepancies in the measurement of mean BP level are likely to have implications for the measurement of BPV, and by extension its treatment. If mean BP values obtained from different measurement methods are not equivalent, then we may expect variability derived using different methods to differ also, even before considering other methodological differences that may impact BPV measurement, such as the number of BP readings acquired and the time between readings. In addition, threshold values for the prognostic relevance of BPV may differ across measurement methods, as do threshold values for mean BP.

Chapter four of this thesis established that there are discrepancies in BP measurement between two commonly used methods for measuring out-of-office BP, for the first time demonstrating that a discrepancy exists in high-risk patients with a history of ischaemic cerebrovascular event. The findings were that daytime ABPM values were

on average 7/2mmHg lower than contemporaneous HBPM values, which is at odds with guideline recommendations. This difference was consistent over a six-month period, however, there were wide limits of agreement between the two methods indicating a large variance in their disagreement at an individual level. Furthermore, the difference for individuals was not reproducible over time. Overall the findings suggest that daytime ABPM and HBPM are not interchangeable methods of measuring BP and values from one cannot be used to infer values from the other. Rather, they may be better considered complementary methods of BP measurement [111]. Given the relationship between BP and BPV, it follows that daytime ABPM and HBPM are also unlikely to be interchangeable methods of measuring BPV and this assertion is supported by reports comparing BPV derived from the two methods [118, 160]. The findings from chapter four add to the existing evidence base regarding the equivalence (or otherwise) of daytime ABPM and HBPM, and are in agreement with the majority of similar studies that have enrolled lower risk populations [106, 112, 116, 121, 247]. However, there is inconsistency in the data, with other studies reporting no differences [115, 119], or daytime ABPM values greater than HBPM [118, 120]. Most of the studies to date, including the one presented in this thesis, are limited by relatively small sample size and may lack the necessary statistical power to reach a definite conclusion. The study by Mancia et al. is larger than the others, but is limited by the use of an HBPM protocol that is not consistent with guideline recommendations, being based on just two measurements taken on consecutive days [120]. Consequently, additional research is likely to be necessary to clarify this issue.

The study in chapter five demonstrated similar discrepancies between different timescales of BPV measurement in the same population. From comparison of the raw BPV values from different measurement methods it was clear that they were not the same, regardless of the technique of calculation. Further analysis demonstrated that there were no meaningful correlations between beat-to-beat and the other timescales of BPV assessed, and the agreement between methods was poor. The relationship between beat-to-beat and within-hour BPV was closer than for other comparisons, but the level of agreement remained insufficient to suggest that they could be considered equivalent. Beat-to-beat BPV has not previously been thoroughly compared with other timeframes of variability, despite evidence indicating that it may be of particular

prognostic significance post stroke regarding recovery and recurrent events [15, 98, 200], perhaps because beat-to-beat BP measurement is less commonly used in clinical practice. The findings of this chapter were in keeping with the existing literature. Although limited evidence suggests that the different statistical methods used to calculate BPV are strongly correlated when applied to the same set of BP measurements [157, 259], the same is not true of different timescales of BPV [118, 134, 160, 200]. All timescales of variability appear to be predictive of cardiovascular risk [128, 131, 200, 252-254], yet their prognostic value may not be equal [90, 131, 155]. Therefore, uncertainties remain about the clinical value and application of BPV. It is possible that all timescales of BPV are prognostically relevant, but that threshold values for abnormal variability differ according to the timescale of measurement (as threshold values for hypertension differ according to the method of measurement). Alternatively, it is also possible that BPV over different timescales is not a singular phenomenon, representing different underlying pathophysiological processes [134, 167, 170, 174, 256, 258], and that some timescales may be more relevant in certain patient groups than others. To further our understanding of this issue, additional research is required to establish which (if any) measurement of BPV is the most relevant to clinical outcomes as this will help with standardisation of BPV measurement and facilitate more robust research regarding therapeutic intervention targeted at BPV. How this might be achieved will be discussed further below.

9.2 Studies Investigating the Therapeutic Intervention in Blood Pressure Variability Post Stroke

Chapters six to eight investigated the potential of BPV as a therapeutic target following an ischaemic cerebrovascular event. Chapter six was primarily concerned with the question of who to treat, looking to see if there were relationships between BPV and stroke severity or affected cerebral hemisphere, whereas chapters seven and eight focussed on the possibility of using existing antihypertensive medications to reduce BPV. The findings from the previous experimental chapters indicated that different methods of measuring BP and BPV post stroke are not equivalent. Therefore, these studies incorporated multiple methods of measurement to see if any findings were consistent across timescales of BPV. There is currently a paucity of evidence

investigating the effect of treatments to reduce BPV post stroke/TIA. However, there is a growing body of data indicating that increased BPV in, both the acute and subacute periods following an ischaemic cerebrovascular event, is associated with clinical signs of poor prognosis, such as haemorrhagic transformation [184-187], or END [188, 189], and poor long-term functional outcome [98, 192, 194-199]. Importantly, it remains unclear whether interventions to reduce BPV would be beneficial in all patients with an ischaemic stroke, or what treatments would be most effective at reducing BPV.

Chapter six aimed to address the question of whether all patients with a recent ischaemic cerebrovascular event might benefit equally from treatment to reduce BPV by investigating whether there are relationships between baseline BPV and stroke severity, or the cerebral hemisphere affected by the ischaemic event. The study found that there were significant relationships, independent of mean BP, between short-term BPV from daytime ABPM and both NIHSS and OCSP classification. The relationships were consistent and, perhaps surprisingly, suggested that BPV was greater in patients with lower NIHSS and a classification of LACS. Interestingly there were no relationships demonstrated for BPV derived from enhanced CBPM or beat-to-beat BP measurements. Furthermore, no relationships between BPV and the affected cerebral hemisphere were found. The findings regarding BPV and stroke severity were consistent with the only other study to have reported on BPV in relation to OCSP classification, which also indicated that baseline BPV was greater in patients with LACS than PACS, TACS, or POCS [13]. As previously discussed in section 6.7, it is not possible to prove a causal relationship between LACS and increased BPV based on this cross-sectional analysis. It may be the case that having a lacunar infarct leads to increased BPV, but it is also possible that increased BPV may be more likely to cause lacunar as opposed to larger infarcts. This is possibly as a result of pulsatile haemodynamic stress on cerebral small vessels [269, 270], which could cause endothelial damage or vasospasm resulting in critically reduced CBF and/or blood-brain barrier dysfunction leading to stroke [266, 268]. These findings raise two interesting questions. Firstly, would treatment aimed at reducing BPV post stroke have the greatest potential benefit in patients with lacunar stroke? Secondly, would treatment aimed at reducing BPV for primary stroke prevention result in greater reductions in the rate of lacunar stroke compared to cortical stroke? The negative result in terms of affected

hemisphere may be due to a methodological issue with the study. Whilst there is debate that central nervous system input to autonomic function may be lateralized [63, 179][63, 180][63, 179][63, 180][63, 180][63, 176][63, 180][63, 180][63, 180][63, 180][63, 180][63, 179][63, 180][63, 180][63, 180][63, 180][63, 180][63, 180][63, 180][63, 180], it is likely that specific regions within each hemisphere, for example the insular cortex are relevant rather than the whole hemisphere itself [265]. It was not possible to classify participants in this cohort based on the cerebral regions involved in their ischaemic stroke beyond the left or right hemisphere due to the data that was available. Therefore, it is possible that this study was not adequately designed to demonstrate relationships between BPV and stroke location and further investigation of this is advised.

Given that the results of chapter six indicated an inverse relationship between increased BPV and stroke severity, and the findings from other studies demonstrating a link between increased BPV post stroke and adverse outcomes, the question of how BPV could be mitigated is pertinent. In chapter seven the possibility of differential effects on baseline BPV, post ischaemic stroke or TIA, of two commonly used classes of antihypertensive medications (CCB or ACEI/ARB) was investigated compared to control. This analysis was based on existing, but limited evidence of a possible difference in effect on BPV from different antihypertensive medication classes, with CCB reported to lower BPV and ACEI/ARB reported to be neutral or possibly increase BPV [201, 203, 211]. These two medication classes were also chosen for comparison as they are recommended first-line agents for the treatment of hypertension [91], and both have a role in secondary stroke prevention treatment. There is evidence that vasodilatory antihypertensives may be particularly effective for preventing recurrent stroke [219, 273], which supports the use of CCB (and thiazide-like diuretics) in this population. Similarly, there is evidence that ACEI/ARB can inhibit atherosclerotic processes [59], which suggests they may have benefits to stroke and cardiovascular disease risk in addition to BP lowering. Although this study did not show any differences in BPV when a CCB based regimen and an ACEI/ARB based regimen were separately compared to control, it did suggest a non-significant contrasting trend for the two groups in short-term BPV from daytime ABPM. The trend suggested that BPV was reduced compared to control in those participants taking a CCB whereas it was

increased in those taking an ACEI or ARB. This is consistent with the existing literature. I have already discussed that the analysis may have lacked sufficient statistical power to demonstrate a difference in the two comparison groups, and with beat-to-beat BPV only being recorded in a subgroup of participants this would have had a greater impact on this aspect of the study. Also, the use of a cross-sectional design, looking only at baseline BPV and not change in BPV over time, may have limited my ability to detect a difference. This design was chosen due to the constraints of the available data, with different follow-up periods in the trials that provided data preventing a coherent analysis of change in BPV over time, but pooling data from the three trials felt to be necessary in order to increase the sample size. Despite the overall negative findings of the study in chapter seven, the consistency of the findings from this and the preceding experimental chapter suggest that ABPM may be the most appropriate measurement technique for future investigations of BPV post stroke. Overall, there remains a need for dedicated prospective trials to investigate the use of existing antihypertensive medications to reduce BPV following stroke, and in other patient groups.

The CAARBS feasibility trial, described in chapter eight, attempted to address this gap. To the best of my knowledge it is the only prospective RCT investigating interventions to reduce BPV following ischaemic stroke. Unfortunately, this feasibility trial highlighted various issues that might hinder a definitive RCT if the protocol as initially proposed were scaled up, the main issue being the high rate of patient ineligibility with the chosen inclusion/exclusion criteria. However, there was some encouragement that a further trial could be successful as the retention rate of successfully randomised participants was reasonable, compliance with the treatment interventions and BP measurements was generally good, and the interventions were shown to be safe. Furthermore, descriptive analysis of the BPV data indicated that it was possible to measure a change in BPV over three months following an ischaemic cerebrovascular event, and there did appear to be a difference in the change in BPV between the two trial arms (though this was not formally tested). To be viable any future trial would clearly need to have modified eligibility criteria, yet as this remains a significant gap in the evidence regarding BPV and ischaemic stroke it is my opinion that it would be worth pursuing.

9.3 Future Research Directions

The findings from this thesis have advanced our understanding of the measurement of BP and BPV post stroke, have provided useful insights into how to further investigate the potential treatment of BPV, and indicate that certain subgroups of ischaemic stroke patients may particularly benefit from this treatment if proven to be successful. Uncertainties remain regarding the equivalence of out-of-office BP measurement methods, the optimum method for measuring BPV, and whether established antihypertensive medications might also be directed against BPV. Consequently, further research into these questions is necessary. With regard to the equivalence of daytime ABPM and HBPM in the assessment of mean BP, further large-scale direct observational comparisons taking ABPM as the reference standard may be useful. Likewise, further direct comparisons of different timescales of BPV may be helpful. This could be achieved with a large-scale cross-sectional cohort study, though without follow-up data over at least three months it would not be able to incorporate long-term visit-to-visit variability, which probably requires a minimum of four visits to be calculated accurately [123]. Ideally the cohort would recruit participants across a range of ages, with a balanced mix of gender and ethnicity, a mixture of higher/lower risk cardiovascular profiles, and treated/untreated for hypertension as these are factors which may influence differences between daytime ABPM and HBPM or BPV measurements [106, 113, 114, 130, 238, 251, 287]. This would also improve the generalisability of any findings. Alternatively, an independent patient data meta-analysis of existing studies may be another method to investigate differences between daytime ABPM and HBPM, though there may be insufficient studies to apply this method to the question of equivalence of BPV over different timescales. Whilst this may be quicker and more cost-effective than a de novo cohort study, it may be hindered by study heterogeneity. In particular, the lack of standardisation of BP measurement across existing studies and the use of HBPM protocols not consistent with current guidelines could make statistical meta-analysis difficult.

Rather than further cross-sectional comparisons, it may be more meaningful to generate outcome driven data for mean out-of-office BP and different timescales of BPV. Specifically, it would be useful to establish threshold values at which the risk of

cardiovascular disease events begins to rise, this need being echoed by the European Society of Hypertension statement on BPV [156]. One study has addressed this for HBPM [241], but outcome driven data for both ABPM and HBPM in the same cohort has not been acquired. Similarly, only one study has addressed this for BPV, using medium-term variability derived from HBPM [118]. Whilst it is possible that retrospective analyses of existing cohort or registry data may be able to fulfill this need, they may be limited by the number of potential participants available with good quality baseline data from both ABPM and HBPM, and they are unlikely to provide data for beat-to-beat BPV. Therefore, despite the obvious difficulties of the lengthy required follow-up for identification of cardiovascular events and the cost of such long-term follow-up, a prospective observational trial would probably generate more accurate and robust data. When reported, the primary outcomes from the BPV observational trial will address some of these issues in a population with stroke. Once it is clarified whether a particular timescale and/or statistical calculation for BPV has greater prognostic value, then it will be possible to provide guideline recommendations on the measurement of BPV for research and clinical practice, thereby standardising the approach.

Whether the relationship between increased BPV and lacunar stroke reported in this thesis is genuine, and whether there is evidence that lacunar stroke is a causal factor for increased BPV, could also be investigated in a further large-scale cohort study, provided a sufficient case-mix of stroke subtypes was recruited. Alternatively, it could also be addressed as a secondary outcome in a future prospective RCT investigating the possible treatment of BPV post stroke. The latter option would provide the advantage that longitudinal BPV could also be assessed in addition to baseline and there would be standardisation of BP treatment, which would minimise the impact of this as a confounding factor. To investigate a possible reverse causal relationship between lacunar stroke and BPV it may be simplest to retrospectively review registry data, first identifying patients with a variety of stroke subtypes and then looking back to see identify any between-group differences in variability preceding the qualifying stroke event. This may be limited to CBPM measurements (either within-visit or visit-to-visit variability over time), but could be sufficient to demonstrate the possibility of a relationship. Ultimately, this may remain a secondary question until it is proven that it

is possible to reduce BPV with treatment, and that this treatment has an impact on clinical outcomes in addition to reducing mean BP, hence pursuing the option of performing a secondary analysis of a future prospective RCT may be the most sensible.

As previously mentioned, it is my belief that a further prospective RCT to investigate the effect of existing antihypertensive medications on BPV post stroke would be of value. The experience of CAARBS indicates that any such trial would certainly need modified eligibility criteria. However, if these criteria were altered to retain a longer window of eligibility post symptom onset, allowed the inclusion of patients with recurrent stroke and possibly also AF, and allowed for the inclusion of patients on multiple antihypertensive agents, then there is the potential to substantially improve patient eligibility. The employment of minimisation criteria to ensure balanced trial arms and statistical adjustment for factors which may confound any effect on BPV of the chosen intervention would be necessary, with or without the pre-specification of subgroups for analysis (e.g. analysing patients with first vs. recurrent stroke separately). Using the same intervention arms for comparison remains reasonable, as CCB and ACEI/ARB are the most commonly used antihypertensive drug classes and so this will maximise the clinical relevance of any findings. Also, until such time as it is proven that one particular method of measuring BPV has greater prognostic value than others, or the measurement of BPV is standardised, it would remain advisable to employ multiple BP measurement techniques in any future trial. Finally, it was a secondary aim of CAARBS to try and establish estimates of intervention effect size that could be used to calculate the necessary sample size for a future definitive trial. Unfortunately this was not possible due the limited number of participants recruited and so it remains a crucial step in planning any further trials of this nature. To that end a further feasibility study may be required, which would have the advantage of being able to test the modifications to the inclusion/exclusion criteria suggested above. Alternatively, if sufficient funding could be secured, it may be possible to pursue a definitive RCT immediately, but with an embedded pilot study to allow for further adjustments of the recruitment target or eligibility criteria if necessary.

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Appendix A – Publications and presentations

Publications Related to this Thesis:

Davison WJ, Myint PK, Clark AB, Potter JF. Blood pressure differences between home monitoring and daytime ambulatory values and their reproducibility in treated hypertensive stroke and TIA patients. *Am Heart J* 2018; 207: 58-65.

Robinson TG, **Davison WJ**, Rothwell PM, Potter JF. Randomised controlled trial of a calcium channel or angiotensin converting enzyme inhibitor/angiotensin receptor blocker regime to reduce blood pressure variability following ischaemic stroke (CAARBS): a protocol for a feasibility study. *BMJ Open* 2019; 9(2):e025301. doi:10.1136/bmjopen-2018-025301

Conference Abstracts Related to this Thesis:

Davison W, Myint PK, Clark A, Langley M, Potter JF.
Comparison of within-individual blood pressure readings from self-monitoring and ambulatory blood pressure monitoring – data from the TEST-BP trial.
European Stroke Conference, Berlin, 2017.

Davison WJ, Myint PK, Potter JF.
A comparison of blood pressure variability assessed over varying time periods using different methods of measurement in patients with cerebrovascular disease.
European Stroke Organisation Conference, Gothenburg, 2018.

Davison WJ, Myint PK, Potter JF.
A comparison of different methods of assessing and calculating blood pressure variability post-stroke or TIA.
European Stroke Organisation Conference, Gothenburg, 2018.

Davison WJ, Myint PK, Potter JF.
Altered baroreceptor sensitivity and heart rate variability after stroke predict increased blood pressure variability.
European Stroke Organisation Conference, Gothenburg, 2018.

Davison W, Myint P, Potter J.
A comparison of beat-to-beat with other measurement methods estimating blood pressure variability in patients with cerebrovascular disease.
European Stroke Organisation Conference, Milan, 2019.

Davison W, Appiah K, Robinson T, Rothwell P, Myint P, Potter J.
Associations between blood pressure variability and stroke severity or subtype in patients with a recent ischaemic stroke.
European Stroke Organisation Conference, Milan, 2019.

Davison W, Appiah K, Robinson T, Rothwell P, Potter J.
Calcium channel blockers versus angiotensin converting enzyme inhibitors/angiotensin receptor blockers to reduce blood pressure variability following ischaemic stroke – a randomized feasibility trial (CAARBS).
European Stroke Organisation Conference, Milan, 2019.

Appendix B - National Institutes of Health Stroke Scale (NIHSS)

Category	Score/Description		Date/Time Initials
1a Level of Consciousness *(Alert, drowsy, etc)*	0 = Alert 1 = Drowsy 2 = Stuporous 3 = Coma		
1b LOC Questions *(Month, age)*	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect		
1c LOC Commands	0= Performs both correctly 1= Performs 1 correctly 2= Performs none correctly		
2 Best Gaze *(Eyes open – patient follows examiner's finger or face*	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation		
3 Visual Fields *(introduce visual stimulation/threat to pts visual field quandrants)*	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = bilateral hemianopia (Blind)		
4 Facial Paresis *(Show teeth, raise eyebrows and squeeze eyes shut)*	0 = Normal 1 = Minor 2 = Partial 3 = Complete		
5a Motor Arm - Left **5b** Motor Arm – Right *(elevate arm to 90º if patient is sitting, 45º if patient supine*	0 = No drift 1 = drift 2 = Can't resist gravity 3 =No effort against gravity 4 = No movement	Left	
		Right	
6a Motor Leg - Left **6b** Motor Leg – Right *(elevate arm to 90º if patient is sitting, 45º if patient supine*	0 = No drift 1 = drift 2 = Can't resist gravity 3 = 4 =	Left	
		Right	
7 Limb Ataxia *(finger-nose, heel down shin*)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs		
8 Sensory *(Pinprick to face, arm, trunk and leg – compare side to side*	0 = Normal 1 = Partial loss 2= Severe loss		
9 Best Language *(Name item, describe a picture & read sentences*)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute		
10 Dysarthria *(Evaluate speech clarity by patient: repeating listed words)*	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Near to unintelligible or worse X = Intubated or other physical barrier		
11 Extinction & Inattention	0 = No neglect 1 = Partial neglect 2 = Complete neglect		
TOTAL SCORE			

Appendix C – Modified Rankin Scale (mRS)

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

Appendix D – Consent forms for trials contributing data to this thesis

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Participant Trial Number:	Initials:
Date of Birth:	

Dr Phyo Kyaw Myint
Consultant Stroke Physician
Gunthorpe Acute Stroke Unit

CONSENT FORM– PERSON WITH STROKE/TIA

Title: **TEST-BP: Trial of the Effectiveness and cost effectiveness of Self-monitoring and Treatment of Blood Pressure in secondary prevention following Stroke or Transient Ischaemic Attack (TIA)**

Name of Chief Investigator: Dr Phyo Kyaw Myint

1. I confirm that I have read and understand the information sheet dated ----------(Version …….) for the above study, have had the opportunity to ask questions and had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Norfolk & Norwich Hospital or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records held in NHS hospital/GP surgery and/or private health provider. ☐

4. I understand that a researcher will periodically contact me, arrange to ☐

visit at home and ask me to fill in a number of questionnaires.

5. I agree to my GP being informed of my participation in the study. ☐

6. I understand that I may receive a number of home visits from a nurse to help me to be able to use BP monitors. ☐

7. I understand that, I may be invited to take part in an interview about how I have found my treatment and what impact it has had on me and give my permission for this to be audio recorded. If I am interviewed agree to my anonymous quotations being used for the project report and publications. ☐

8. I agree to take part in this study. ☐

_____ _____ _____

Name of Participant Date Signature

_____ _____ _____

Researcher Date

Signature

Original stored in Central Study File; 1 copy for the patient; 1 for filing in the participant's medical records

Prof John Potter

Professor of Ageing and Stroke Medicine

Older People's Medicine

Protocol reference : Version 3
Ethics Approval Reference: 15/EE/0061
Patient Identification Number for this trial:
Patient Hospital Identification Number:

PARTICIPANT CONSENT FORM

Trial title: SERVED Memory: Feasibility study of Screening & Enhanced Risk Management for Vascular Event related Decline in Memory

Short Title: SERVED Memory

Name of Principal Investigator: Prof John Potter

3. I confirm that I have read and understand the information sheet dated _____ (Version …….) for the above study and have had the opportunity to ask questions and had these answered satisfactorily. ☐

4. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Norfolk & Norwich Hospital or from regulatory authorities where it is relevant. I give permission for these individuals to have access to my records held in NHS hospital/GP surgery and/or private health provider. ☐

☐

4. I understand that a researcher will periodically contact me to arrange hospital visits and will ask me to fill in a number of questionnaires.

5. I agree to my GP being informed of my participation in the study. ☐

6. I understand that I my GP will be informed of my cognition status and will be informed of any vascular risk factors that I may have . ☐

7.I agree to take part in the SERVED Memory study. ☐

_____ _____ _____

Name of Participant Date Signature

_____ _____ _____

Researcher Date

Signature

Original stored in Central Study File; 1 copy for the patient; 1 for filing in the participant's medical records

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

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Stroke Services
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Norwich NR4 7UY
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trust website: www.nnuh.nhs.uk

BLOOD PRESSURE VARIABILITY:

DEFINITION, NATURAL HISTORY AND PROGNOSIS FOLLOWING ACUTE STROKE

(ACUTE STUDY)

PARTICIPANT CONSENT FORM

VERSION 4, DATED 11 February

2014

Principal Investigator: Professor John Potter

	Please Initial
I confirm that I have read and understand the Participant Information Sheet Version 4 dated 11th February 2014 for the above study, and have had the opportunity to ask questions.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without any medical care or legal rights being affected.	
I understand that my GP will be informed about my participation in this study, and by signing this consent form I am granting permission for this.	
I understand that relevant sections of my data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records.	

I understand that the research team will contact me by telephone, one, three and twelve months from now to gather information on my recovery, and of any new health problems. I give permission for a member of the team to contact me at these tome points. ☐

I agree to take participate in this research study. ☐

I understand that, before my discharge from hospital, I may be asked if i would like to participate in the follow up part to this study. I give permission for members of the research team to approach me to give me information regarding the follow up study. ☐

Patient Name		
Carer Name	Date	Signature
Researcher	Date	Signature

(File: 1 for patient, 1 for researcher, 1 for hospital notes)

PARTICIPANT CONSENT FORM
VERSION 1.0, DATED 30 JANUARY 2017

A Calcium channel or Angiotensin converting enzyme inhibitor /Angiotensin receptor blocker regime to reduce Blood pressure variability in acute ischaemic Stroke (CAARBS): A Feasibility Trial

Participant ID:_____

Please initial each box

1. I confirm that I have read and understand the Participant Information Sheet Version 1.1, dated 03 May 2017 for the above study, and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. ☐
3. I understand that my GP will be informed about my participation in this study, and by signing this consent form I am granting permission for this. ☐
4. I understand that relevant sections of my data collected during the study may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I understand that participating in this study will involve me being prescribed medication with the intention of lowering my blood pressure. ☐
6. I understand that my data will be transferred to the University of Leicester and the University of East Anglia for analysis. ☐
7. I agree to take participate in this research study. ☐

_____	_____	_____
Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

(File: 1 copy for patient, 1 copy for researcher, 1 copy for hospital notes)

Appendix E – Regulatory approvals for CAARBS

NHS
Health Research Authority
London - Central Research Ethics Committee
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 1048 007

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

05 September 2017

Professor Thompson Robinson
University of Leicester
Cardiovascular Research Centre, The Glenfield Hospital
Groby Rd
Leicester
LE3 9QP

Dear Professor Robinson

Study title:	**A Calcium channel or Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker Regimen to reduce Blood pressure variability in acute ischaemic Stroke (CAARBS): A Feasibility Trial**
REC reference:	**17/LO/1427**
Protocol number:	**0611**
EudraCT number:	**2017-002560-41**
IRAS project ID:	**216241**

The Research Ethics Committee reviewed the above application at the meeting held on 30 August 2017 and would like to thank your colleagues for attending the meeting to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Additional conditions

1. Please advise the duration of retention of personal data collected for the study and confirm that this is in line with the study sponsor's policy on this issue.

2. Please provide a written justification for the exclusion of people intending to donate blood during the study or confirm that this exclusion will be removed.

3. The information sheet should state that the study is being conducted for the purposes of an educational qualification.

4. The information sheet needs to include a sentence under the heading 'What is involved if I agree to participate?' to say 'Your family member or carer will be asked to complete a questionnaire about you.' The consent form should include a penultimate point to say 'I agree that a family member or carer can complete a questionnaire about me'.

Please notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites listed in the application taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Summary of discussion at the meeting

Recruitment arrangements and access to health information, and fair participant selection

It was asked why people intending to donate blood during the study would be excluded, and the researchers said this had been included as a precaution. They were asked to provide a written justification for this exclusion criterion for completeness, or confirm that it will be removed.

The reason for the limited time of up to four hours to consider taking part in the study was requested. The researchers said that the time is necessarily restricted because of the nature of the condition being investigated and they wish to recruit as many patients as are required for the study. They said that this process has been utilised successfully in the past. The impact of the inability to arrange interpreters/translators because of the limited time available was queried, and the researchers said that it is not expected that this will affect the recruitment to any great degree. This was accepted by the Committee.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

Reference was made to the NICE guidelines on treatment for this patient group, which indicate that ethnicity governs the appropriate medication. The researchers were asked to comment on the ethics of giving medication to someone in a particular ethnic group when the medication is known not be effective in this group. The researchers explained that the guidelines had been taken into account, and they are confident that the randomisation involved in the study will not cause any problems relating to efficacy with any participant.

It was pointed out that the personal data collected in the study should be retained for longer than the 6-12 months stated in the answer to question A43 of the application form for audit and publishing purposes. The researchers acknowledged this and agreed to amend the retention period in line with the sponsor university's policy on this issue.

As participants will be asked to complete a depression scale in the study, it was asked when the completed scales will be reviewed. The researchers said that they will be assessed immediately after completion and participants' GPs will be notified of any concerns.

It was asked whether taking part in the study would result in any delay in treatment and the researchers confirmed that it would not, and any patient requiring surgery will receive this at the earliest opportunity.

Informed consent process and the adequacy and completeness of participant information

The information sheets were found to be well-written.

The short consent time was not considered to be a concern as the study does not involve a major change from normal care for patients other than the taking of additional measurements and the completion of questionnaires, and participants could benefit from improved BP monitoring.

It was asked that the information sheet be amended to state that the study is being conducted for the purposes of an educational qualification.

As a family member or carer will be asked to complete a questionnaire about the participant, it was asked that the information sheet includes mention of this in the information sheet, and that an appropriate point is included in the consent form for participants to confirm agreement to this.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]		25 July 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor indemnity insurance certificate]		29 July 2016
GP/consultant information sheets or letters [GP Patient Entry Letter]	1.0	19 July 2017

GP/consultant information sheets or letters [GP Medication Change Letter]	1.0	19 July 2017
GP/consultant information sheets or letters [GP Trial Discharge Letter]	1.0	19 July 2017
Investigator's brochure / IMP Dossier [Amlodipine SmPC]	1.0	19 July 2017
Investigator's brochure / IMP Dossier [Lisinopril SmPC]	1.0	19 July 2017
Investigator's brochure / IMP Dossier [Ramipril SmPC]	1.0	19 July 2017
Investigator's brochure / IMP Dossier [Candesartan SmPC]	1.0	19 July 2017
Investigator's brochure / IMP Dossier [Losartan SmPC]	1.0	19 July 2017
IRAS Application Form [IRAS_Form_01082017]		01 August 2017
IRAS Checklist XML [Checklist_01082017]		01 August 2017
Letter from funder [Letter from funder]		12 December 2012
Letter from sponsor [Sponsor letter]		26 July 2017
Other [Sponsor clinical trials insurance certificate]		29 July 2016
Other [Albert's Lines]		
Other [Article on Albert's Lines test]		
Other [Modified Rankin Scale]		
Other [National Institute of Health Stroke Scale]		
Other [Oxford Stroke Classification]		
Other [TOAST classification]		
Participant consent form [Participant Consent Form]	1.0	19 July 2017
Participant information sheet (PIS) [Patient Information Sheet]	1.0	19 July 2017
Research protocol or project proposal [Research protocol]	1.0	19 July 2017
Summary CV for Chief Investigator (CI) [Prof Robinson CV]		16 February 2017
Summary CV for student [Dr Davison CV]	1.0	21 July 2016
Summary CV for supervisor (student research) [Prof Potter CV]	1.0	10 May 2017
Validated questionnaire [Montreal Cognitive Assessment]	7.1	
Validated questionnaire [MiND-B (Self-completion Version)]		19 July 2017
Validated questionnaire [MiND-B (Proxy Completion Version)]		19 July 2017
Validated questionnaire [Geriatric Depression Scale]		19 July 2017

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/LO/1427	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Elaine Hutchings

pp
Dr Andrew Hilson
Chair

E-mail: NRESCommittee.London-Central@nhs.net

Enclosures: *List of names and professions of members present at the meeting*

"After ethical review – guidance for researchers"

Copy to: *Dr Diane Delahooke, University of Leicester*
Mrs Carolyn Maloney, University Hospitals of Leicester NHS Trust

MHRA
Regulating Medicines and Medical Devices

MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom

mhra.gov.uk

Dr D Delahooke
UNIVERSITY OF LEICESTER
RESEARCH GOVERNANCE OFFICE, RESEARCH & ENTERPRISE DIVISION
FIELDING JOHNSON BUILDING, UNIVERSITY ROAD
LEICESTER
LE1 7RH
UNITED KINGDOM

21/09/2017

Dear Dr D Delahooke

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	22116/0023/001-0001
Eudract Number:	2017-002560-41
Product:	Amlodipine
Protocol number:	0611

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 20/09/2017.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare Products Regulatory Agency

NHS
Health Research Authority

Professor Thompson Robinson
University of Leicester
Cardiovascular Research Centre, The Glenfield Hospital,
Groby Rd
Leicester
LE3 9QP

Email: hra.approval@nhs.net

25 September 2017

Dear Professor Robinson

Letter of HRA Approval

Study title:	**A Calcium channel or Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker Regimen to reduce Blood pressure variability in acute ischaemic Stroke (CAARBS): A Feasibility Trial**
IRAS project ID:	**216241**
EudraCT number:	**2017-002560-41**
Protocol number:	**0611**
REC reference:	**17/LO/1427**
Sponsor	**University of Leicester**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **216241**. Please quote this on all correspondence.

Kevin Ahmed
Assessor

Telephone: 0207 104 8171
Email: hra.approval@nhs.net

Copy to: *Dr Diane Delahooke, Sponsor Contact, University of Leicester*
Mrs Carolyn Maloney, R&D Contact, University Hospitals of Leicester NHS Trust