

**HAEMODYNAMIC PARAMETERS IN
HYPERTENSIVE PATIENTS FOLLOWING
ACUTE STROKE
AND
EARLY OUTCOME**

Doctor of Medicine Thesis

University of Leicester

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Table of contents

<i>Title page</i>	<i>i</i>
<i>Table of contents</i>	<i>ii</i>
<i>List of figures</i>	<i>xi</i>
<i>List of tables</i>	<i>xiii</i>
<i>List of abbreviations</i>	<i>xv</i>
<i>Study declaration</i>	<i>xvii</i>
<i>Ethical declaration</i>	<i>xviii</i>
<i>Acknowledgements</i>	<i>xix</i>
<i>Abstract</i>	<i>xx</i>

1	INTRODUCTION	1
1.1	Background	2
1.1.1	Epidemiology and incidence of stroke	2
1.1.2	The burden of stroke	2
1.2	Blood pressure and stroke	5
1.2.1	Primary stroke prevention	5
1.2.2	Secondary stroke prevention	12
1.2.2.1	Dutch-TIA	14
1.2.2.2	Tenormin after stroke and TIA (TEST)	15
1.2.2.3	The Heart Outcome Prevention Evaluation Study (HOPE)	15
1.2.2.4	Post-stroke Antihypertensive Treatment Study (PATs)	15
1.2.2.5	Perindopril Protection Against Recurrent Stroke Study	

	(PROGRESS)	15
1.2.2.6	Morbidity and mortality after stroke, Eprosartan compared with Nitrendipine for secondary prevention (MOSES)	16
1.2.3	On-going secondary prevention trial	18
1.2.3.1	Ongoing Telmisartan alone and in combination with Ramipril global endpoint trial (ONTARGET) and the Telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease (TRANSCEND)	18
1.2.3.2	Prevention regimen for effectively avoiding second strokes (PRoFESS)	19
1.3	Blood pressure changes in acute stroke	20
1.3.1	Blood pressure and stroke outcome	21
1.3.1.1	Short-term outcome	24
1.3.1.2	Long-term outcome	27
1.4	Acute stroke blood pressure management trials	31
1.4.1	Completed trial	31
1.4.1.1	Acute Candesartan Cilexetil therapy in stroke survivors (ACCESS)	31
1.4.1.2	Intravenous Magnesium Efficacy in Stroke trial (IMAGES)	32
1.4.1.3	Glucose-potassium-insulin infusions in the management of post-stroke hyperglycemia: the UK Glucose Insulin in Stroke Trial (GIST-UK)	33
1.4.1.4	National Institute of Neurological Disorders and Stroke Trial (NINDS)	33

1.4.2	Current guidelines	34
1.4.3	On-going acute BP intervention studies	36
1.4.3.1	Controlling Hypertension and Hypotension Immediately	
	Post- Stroke Trial (CHHIPS)	36
1.4.3.2	Efficacy of nitric oxide in stroke (ENOS)	37
1.4.3.3	Scandinavian Candesartan Acute Stroke trial (SCAST)	37
1.4.3.4	Continue Or Stop post-Stroke Antihypertensive Collaborative	
	Study (COSSACS)	37
1.5	Importance of cardiovascular autonomic control	39
1.5.1	Autonomic changes and stroke	39
1.5.1.1	Baroreflex anatomy	40
1.5.1.2	The arterial baroreflex	41
1.5.1.3	Mechanisms regulating baroreceptor action	44
1.6	Measuring Baroreceptor sensitivity	45
1.6.1	Background	45
1.6.2	Traditional methods	47
1.6.2.1	Oxford method	47
1.6.2.2	The Valsalva manoeuvre	47
1.6.2.3	Neck suction method	48
1.6.3	Non invasive methods	49
1.6.3.1	The sequence or spontaneous method	52
1.6.3.2	The spectral analysis method (frequency domain analysis	
	based on Fast Fourier Transformation – FFT)	54
1.6.3.3	Control breathing method	56
1.6.4	Commonly used terminology to describe different methods	57

1.6.4.1	Autoregressive (AR) Modeling	57
1.6.4.2	Autoregressive Moving Average (ARMA) Modeling	57
1.6.4.3	Broadband Spectral Analysis	58
1.6.4.4	Fourier Transform	58
1.6.4.5	Fast Fourier Transform	58
1.6.4.6	Time-Varying Spectral Analysis	58
1.6.4.7	Transfer Function	58
1.7	Heart rate variability	59
1.8	Blood pressure variability	61
1.9	Arterial stiffness	63
1.9.1	Background	63
1.9.1.1	Traditional methods	64
1.9.1.2	Recent methods	65
1.9.2	Pulse pressure	65
1.9.3	Pulse wave analysis	66
1.9.3.1	Principles of Sphygmocor™ device	66
1.9.4	Arterial stiffness and stroke	71
1.9.4.1	Measures of arterial stiffness	71
1.9.4.2	Pulse Wave Analysis (PWA): Measurement of Wave Reflection	72
1.9.4.3	Wave Reflection	72
1.9.4.4	Augmentation index (AIx)	73
1.9.4.5	Generalized Transfer Function: The Principle of PWA	74
1.9.5	Effects of diseases on PWA	76
1.9.5.1	Prognostic Value of Central Blood Pressure and AIx	76

1.9.6	Pulse Wave Velocity (PWV)	76
1.9.6.1	Methodology of PWV	77
1.9.6.2	Prognostic Value of PWV	77
1.9.7	Relationship between arterial function and cardiovascular risk factors	78
1.9.7.1	Ageing	78
1.9.7.2	Heart Rate	80
1.9.7.3	Perspectives	80
2	Methodology	82
2.1	Study methodology	83
2.1.1	Study Design	83
2.1.1.1	Study Population	83
2.1.1.2	Study Treatment Plan	83
2.1.1.3	Inclusion Criteria	84
2.1.1.4	Exclusion Criteria	84
2.1.2	Pre-randomisation	85
2.1.3	At randomisation	87
2.1.4	At day 14	88
2.1.5	At 6-month intervals	88
2.2	Study Measurements	88
2.2.1	Primary Efficacy Measures	88
2.2.2	Secondary Efficacy Measures	89
2.2.2.1	Early Secondary Efficacy Measures	89
2.2.2.2	Late Secondary Efficacy Measures	89
2.2.3	Safety Measures	90

2.3	The Data and Safety Monitoring Committee	90
2.4	Data Management	91
2.5	Statistical Considerations	91
2.5.1	Sample Size Calculation	92
2.6	Patient Data Protection	92
2.7	Ethics	92
2.7.1	Good Clinical Practice	92
2.7.2	Patient Information and Consent	93
2.7.3	Study Monitoring	93
2.7.4	Sponsorship	94
2.7.5	Funding	94
2.7.6	Medicines and Healthcare products Regulatory agency (MHRA)	94
3	Haemodynamic Predictors of early Outcome Following Acute Stroke in Treated Hypertensive Patients	95
3.1	Background and aims	96
3.2	Methods	97
3.2.1	Subjects	97
3.2.2	Ethics	98
3.2.3	Inclusion criteria	98
3.2.4	Exclusion criteria	99
3.2.5	Pre-randomisation	99
3.2.6	At randomisation	99
3.2.7	Within 24 hours	99
3.3	Outcome	102

3.4	Data Analysis	102
3.4.1	Cardiac BRS	102
3.4.2	Casual BP	103
3.4.3	BP Variability (BPV)	103
3.4.4	PI variability	103
3.5	Statistical Analysis	103
3.6	Results	105
3.7	Discussion	110
3.7.1	BP and outcome	110
3.7.2	Pre-existing antihypertensive therapy	111
3.7.3	Cardiac BRS and outcome	111
3.8	Limitations and future prospects	112
3.9	Conclusion	112
4	Central Arterial Pressure Predicts Early Outcome Following Acute Stroke in Treated Hypertensive Patients	113
4.1	Background	114
4.2	Subjects and Methods	116
4.2.1	Subjects	116
4.2.2	Methods	116
4.2.3	Protocol	117
	4.2.3.1 Applanation tonometry	117
	4.2.3.2 Pulse wave analysis (PWA) and pulse wave velocity measurement	118
	4.2.3.3 Central BP	119
4.2.4	Outcome	119

4.2.5	Statistical Analysis	119
4.2.6	Results	120
4.3	Discussion	125
4.3.1	Blood pressure and outcome	125
4.3.2	Cerebral autoregulation	125
4.3.3	Stroke sub-type	126
4.3.4	Arterial Stiffness and outcome	126
4.4	Limitations	127
4.5	Conclusion	127
5	Relationship of Cardiac Baroreceptor Sensitivity and Arterial Stiffness Following Acute Stroke in Treated Hypertensive Patients	128
5.1	Background	129
5.2	Methods	131
5.2.1	Subjects	131
5.2.2	Cardiac BRS	132
5.2.3	Blood pressure (BP)	132
5.2.4	Arterial stiffness	132
	5.2.4.1 Applanantion tonometry	132
	5.2.4.2 Pulse wave analysis (PWA) and pulse wave velocity (PWV) measurement	133
5.2.5	Statistical analysis	133
5.3	Results	134
5.4	Discussion	142
5.4.1	Cardiac BRS	142
5.4.2	Arterial stiffness	143

5.5	Limitations	143
5.6	Conclusions	143
6	Discussion and Summary	144
6.1	Summary	145
6.1.1	Cerebrovascular autoregulation	146
6.1.2	BP and outcome	146
6.1.3	Pre-existing antihypertensive therapy	147
6.1.4	Arterial stiffness	148
6.1.5	Cardiac BRS	150
6.1.6	Stroke sub-type	150
6.2	Implications	150
6.3	Limitations	151
6.4	Prospects for further work	151
6.5	Conclusion	152
7	Appendices	153
Appendix:1	Stroke severity and functional assessment tools	154
Appendix:2	Oxfordshire Community Stroke Project classification (OCSP)	158
Appendix:3	International Stroke Trial (IST) questionnaire	159
Appendix: 4	European Quality of Life questionnaire (EuroQOL)	159
Appendix:5	TOAST classification of ischaemic stroke	161
Appendix: 6	COSSACS sub-study ethics, data and consent forms	162
Appendix:7	Publications arising from this thesis	177
8	References	178

List of figures

Figure: 1.1	Predicted bed-day impact of shorter stay and reduced stroke cases	4
Figure: 1.2	Coronary heart disease and stroke mortality in England	5
Figure: 1.3	The relative risk of stroke for five categories of blood pressure	6
Figure: 1.4	Results of meta-analysis of primary prevention trial	8
Figure: 1.5	Effects of antihypertensive therapy in patients with prior stroke or TIA on subsequent stroke (fatal or nonfatal)	17
Figure: 1.6	Relationship between SBP level on admission in acute ischaemic stroke and stroke outcome	23
Figure: 1.7	Major areas involved with baroreflexes	41
Figure: 1.8	Diagram of baroreflex arc	43
Figure: 1.9	Sigmoid relationship between carotid pressure and R-R interval	46
Figure: 1.10	The neck chamber, developed by Ernsting and Parry	49
Figure: 1.11	Finapres TM 2300, Ohmeda for non-invasive estimation of finger arterial BP	51
Figure: 1.12	A schematic representation of the selection of spontaneous baroreflex sequences	53
Figure: 1.13	Example of ECG, pulse interval tachogram, power spectrum and spectral component	55
Figure: 1.14	Assessment of BRS using time domain analysis during controlled breathing	57
Figure: 1.15	Tracings from Marey's publication on sphygmogram	64
Figure: 1.16	The Sphygmocor TM system	68
Figure: 1.17	The Sphygmocor TM output	69

Figure: 1.18	Principle of applanation tonometry	70
Figure: 1.19	Aortic pressure waveform, and the pressure amplification at an arterial branch	73
Figure: 1.20	Derived aortic pressure waveform displaying time to reflected wave (Tr) and augmentation index (AIx)	74
Figure: 1.21	The Sphygmocardiograph: computerized report on analysis of radial artery and synthesized aortic pressure waves	75
Figure: 1.22	The vicious cycle of large arterial disease	79
Figure: 2.1	A & D automatic digital blood pressure monitor UA767	86
Figure: 3.1	Equipment used to acquire cardiac BRS data	101
Figure: 5.1	Age and PWVcf correlation	140
Figure: 5.2	Cardiac BRS (spectral) and PWVcf	140
Figure: 5.3	Cardiac BRS (sequence) and PWVcf	141
Figure: 5.4	Kaplan-Meier survival curve	142

List of tables

Table: 1.1	Summary of trials of BP lowering in hypertensive patients for primary stroke prevention	10
Table: 1.2	Summary of randomised controlled trials of BP lowering in patients with a history of stroke or TIA (non-acute)	13
Table: 1.3	High acute stroke BP and poor short-term outcome	25
Table: 1.4	High acute stroke BP and good short-term outcome	26
Table: 1.5	Lower acute stroke BP and poor short-term outcome	26
Table: 1.6	Lower acute stroke BP and good short-term outcome	27
Table: 1.7	Higher acute stroke BP and poor long-term outcome	29
Table: 1.8	Higher acute BP and good long-term outcome	30
Table: 1.9	Lower acute BP and poor long-term outcome	30
Table: 1.10	Indications for acute stroke blood pressure reduction: current guidelines	35
Table: 3.1	(A) Demographic details of patients	106
Table: 3.2	(B) Demographic details of patients	107
Table: 3.3	Relationship of baseline variables and 2-week outcome in regression analysis	108
Table: 3.4	Change in mRS at 2 weeks for a Δ increase in a risk factor, holding other risk factors fixed	109
Table: 4.1	Baseline of patients	122
Table: 4.2	Casual BP and arterial stiffness parameters	123
Table: 4.3	Results from a final model, adjusted for age, baseline mRS, baseline NIHSS, type of stroke and central SBP	125
Table: 5.1	Baseline characteristics	136

Table: 5.2	Baseline haemodynamic parameters	137
Table: 5.3	Spearman's Correlation with PWVcf	138
Table: 5.4	Age, NIHSS and mRS adjusted Spearman correlation with PWVcf	139

List of abbreviations

ACEI	Angiotensin-Converting Enzyme Inhibitor
AIx	Augmentation Index
ANS	Autonomic Nervous System
ARB	Angiotensin Receptor Blocker
BP	Blood Pressure
bpm	Beats per Minute
BPV	Blood Pressure Variability
BRS	Baroreceptor Sensitivity
CCB	Calcium Channel Blocker
COSSACS	Continue Or Stop post-Stroke Antihypertensives Collaborative Study
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
FFT	Fast Fourier Transformation
GTF	Generalised Transfer Function
HF	High Frequency
HR	Heart Rate
HRV	Heart rate variability
HRV	Heart Rate Variability
LACS	Lacunar Strokes
LF	Low Frequency
LF/HF	Low-to-High Frequency ratio
MAP	Mean Arterial Pressure
mRs	Modified Rankin Score

NIHSS	National Institute of Health Stroke Scale
PACS	Partial Anterior Circulation Stroke
PI	Pulse Interval
PIV	Pulse Interval Variability
POCS	Posterior Circulation Stroke
PP	Pulse Pressure
PSA	Power Spectral Analysis
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
PWVcf	Pulse Wave Velocity carotid femoral
PWVcr	Pulse Wave Velocity carotid radial
SBP	Systolic Blood Pressure
TACS	Total Anterior Circulation Stroke
TIA	Transient Ischemic Attack
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
Tr	Time to Reflected wave
WHO	World Health Organisation

Study declaration

In fulfilment of the requirement of an MD thesis, this study declaration summarises the extent to which the work contained in this thesis is my own work.

The design and funding for the study were organised by Professor Tom Robinson, Professor of Ageing & stroke Medicine, University of Leicester and Professor John Potter, Professor of Ageing & Stroke Medicine, University of East Anglia, Norfolk. I coordinated this multi-centre study and I was involved in the process of ethical approval for subsequent protocol amendment.

The recruitment and study of all subjects reported in chapter 4 and 5 was performed by myself. I recruited 80% of subjects reported in chapter 3, though I am grateful to my colleagues, Dr Paul Johnson, Clinical Research Fellow (Exeter) and Dr Toby Black, Clinical Research fellow (Bournemouth) for 10% of recruitment each.

The data handling and statistical analysis in this study was performed by me.

Professor Ronney Panerai, Professor of Medical Physics, University of Leicester developed the software that is used for recording, calibration, editing and analysing digitalised beat-to-beat blood pressure and heart rate recordings. This software is used for calculating cardiac baroreceptor sensitivity, blood pressure and pulse interval variability described in chapters 3 and 5.

Dr Nick Taub, Research Fellow in Medical Statistics, and Ms Julia Chernova, Trial statistician, Trent Research and Development Support Unit, provided assistance for statistical analysis of the data reported in chapters 3 and 4.

Ethical declaration

All studies reported in this thesis were approved by the Multi-centre Research Ethics Committee (MREC) and Local Research Ethics Committee (LREC). Verbal and written information was provided to study subjects and informed, written consent was obtained from the subjects (relative assent obtained for subjects who lacked capacity). The patient information, consent forms and ethical approval for the study are outlined in Appendix 6.

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Finally, I am indebted to all the patients who kindly participated in the study.

Abstract

Background

Stroke remains the third commonest cause of death in adults and second cause of death amongst over 60 years of age. It is the commonest cause of severe disability. Stroke outcome remains poor in the United Kingdom compared to Western Europe. Currently, manipulating modifiable risk factors, namely hypertension, diabetes mellitus etc, remains the focus of interest in acute stroke research. With the better understanding of haemodynamic parameters it is known that cardiac baroreceptor sensitivity (BRS) plays an important part in the short-term blood pressure control. It is recognised that impaired cardiac BRS, measured 72-hours post-ictus, predicts poor death/dependency in long-term. There is a suggestion that increased arterial stiffness affecting baroreceptors in aortic arch and carotid artery may account for impaired cardiac BRS in acute stroke. However, the role of cardiac BRS and arterial stiffness in predicting early (2-week) death/dependency following acute stroke in subjects on pre-existing antihypertensive therapy is not known.

Hypothesis

Central, rather than peripheral, arterial compliance is a better predictor of cardiac BRS. There is relationship between baseline cardiac BRS and central arterial stiffness and both are independent predictors of early (2-week) outcome following acute stroke.

Methods

This thesis evaluates their predictive role for early outcome in a subgroup of an ongoing trial, the Continue Or Stop post-Stroke Antihypertensive Collaborative Study (COSSACS).

Findings

Cardiac BRS and arterial stiffness are negatively correlated, though this relationship is not significant when adjusted for common confounders. Lower beat-to-beat mean arterial pressure (MAP) and central systolic blood pressure (SBP) in acute phase of stroke (<48 hours), but not cardiac BRS or arterial stiffness predict early outcome.

Conclusions

These findings have important implications for the management of acute stroke hypertension, including the continuation or discontinuation of pre-existing antihypertensive therapy, given the presence of cerebrovascular dysautoregulation following acute stroke. Randomised, controlled, intervention studies are ongoing to inform the management of this common problem.

1 INTRODUCTION

1.1 Background

1.1.1 Epidemiology and incidence of stroke

Worldwide, 15 million people suffer a stroke annually. Of these, 5 million die and another 5 million are left permanently disabled. The incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure, and reduced levels of smoking. However, the absolute number and burden of stroke continues to increase because of the rapid rise in the elderly population in both the developed and developing world(1;2).

Approximately, 130,000 people in the United Kingdom have a stroke annually. Most people affected are over 65. Despite recent evidence of a decline in stroke incidence, stroke remains the third most common cause of death in the UK, but the leading cause of death above the age of 60 years.

1.1.2 The burden of stroke

The lifetime cost of first ever stroke occurring in 1990 in the United States of America, based on medical and nursing care was estimated to be \$123 565 (£69 000) for intra-cerebral haemorrhage, \$90 981 (£49 000) for ischaemic stroke, and \$103 576 (£56 000) for all stroke subtypes. Direct cost accounted for 45.0% of acute-care, the rest is accounted for long-term care. Indirect costs, based on non-productivity, accounted for 58.0% of lifetime costs(3). However, the additional burden, particularly the strain placed on the carers of stroke patients, remains unrecognised.

Stroke burden is projected to rise from around 38 million Disability-adjusted life years (DALY- combined years of potential life lost due to premature death with years of productive life) in 1990 to 61million DALYs in 2020(1).

In the UK, stroke is the single most common cause of adult disability and dependency, associated with suffering to both patients and their carers, leading to great human and financial expense to society. Stroke patients occupy around 20 per cent of all acute hospital beds and 25 per cent of long term beds. The cost of stroke to the NHS is estimated to be over £2.3 billion consuming 5% of NHS expenditure, twice that for CHD. It is estimated that the total cost of stroke care will rise by around 30 per cent by the year 2023(4).

In Spring 2006, the UK Department of Health produced Action on Stroke Services: An Evaluation Toolkit for Providers (ASSET1) to help hospital trusts appraise performance on stroke. It considered the merits of making four specific improvements: increasing their acute stroke unit capacity, rapid access TIA services, rapid scanning to enable thrombolysis, and early supported discharge arrangements.

If all services made these changes, then each year in England 840 strokes would be prevented and 3,900 stroke victims would regain their independence (who would otherwise have died or experienced long-term dependency). The chart (Figure 1:1) shows the predicted cumulative bed-day impact of shorter lengths of stay and fewer strokes across each Strategic Health Authority.

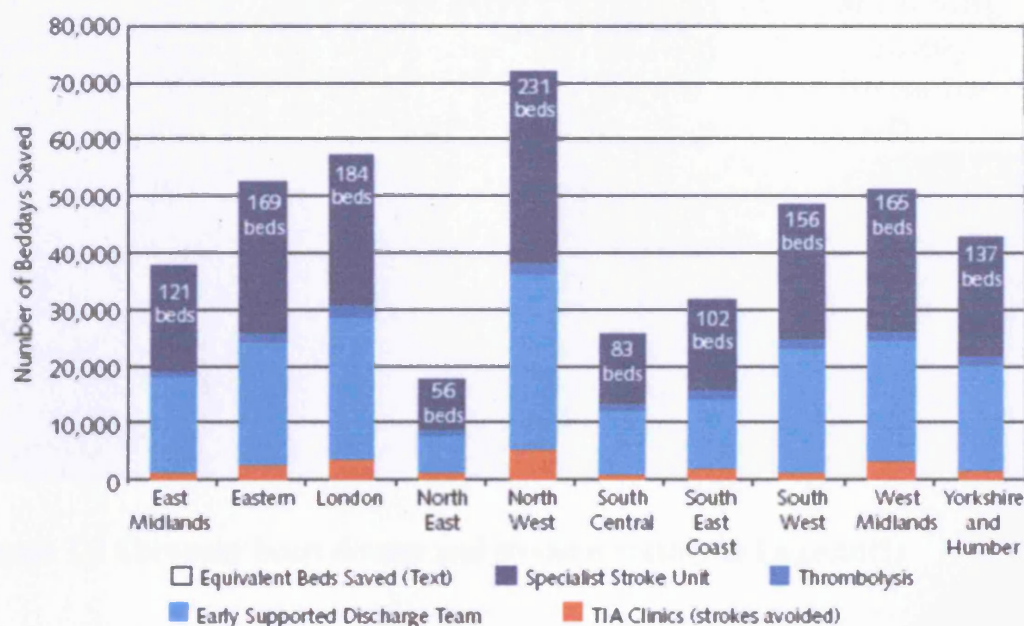


Figure 1:1 Predicted bed-day impact of shorter stay and reduced stroke cases

Although there is similarity in patho-physiology of stroke and coronary artery disease there is a significant difference in their mortality. The incidence of, and mortality rates for, stroke and coronary heart disease have declined in recent years, although stroke mortality has declined at a slower rate. Between 1992 and 2002 stroke death rates in those aged under 75 declined by 30 per cent, and heart disease death rates declined by 44 per cent. However for stroke patients the chance of dying from their stroke has remained constant (at around 24 per cent) over that time, while for heart attack patients the chance of dying from their heart attack has declined by about 1.5 per cent each year⁽⁵⁾. (Figure 1:2).

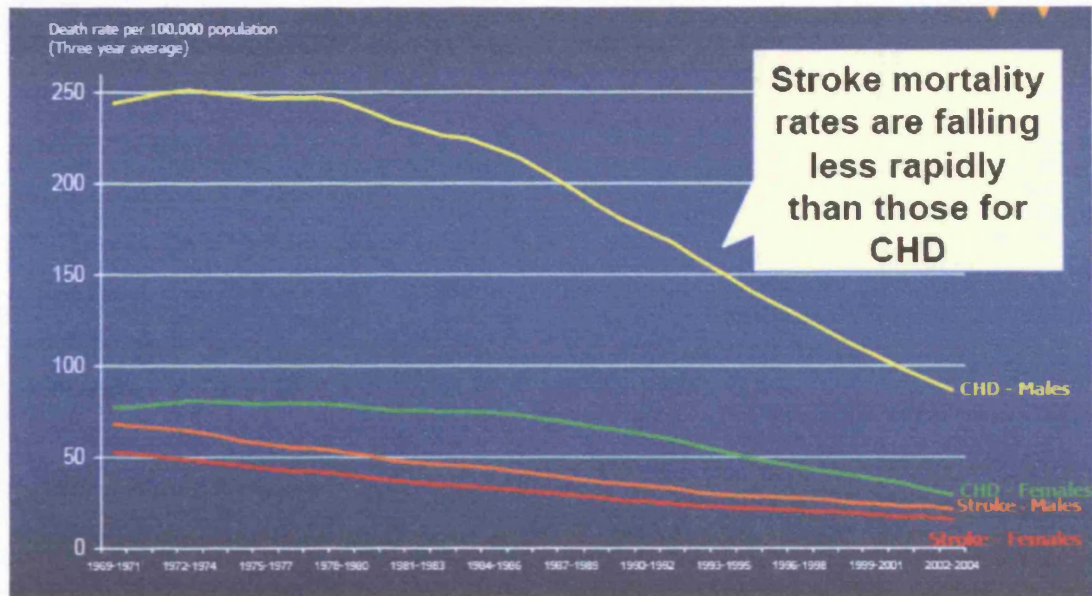


Figure 1:2 Coronary heart disease and stroke mortality in England(5)

1.2 Blood pressure and stroke

1.2.1 Primary stroke prevention

The single most important modifiable cause of stroke is high blood pressure; for every ten people who die of stroke, four could have been saved if their blood pressure had been controlled(1). The relationship between BP levels and the risk of first-ever stroke is now well established(6;7). It appears to be log-linear(8;9) (Figure 1:3).

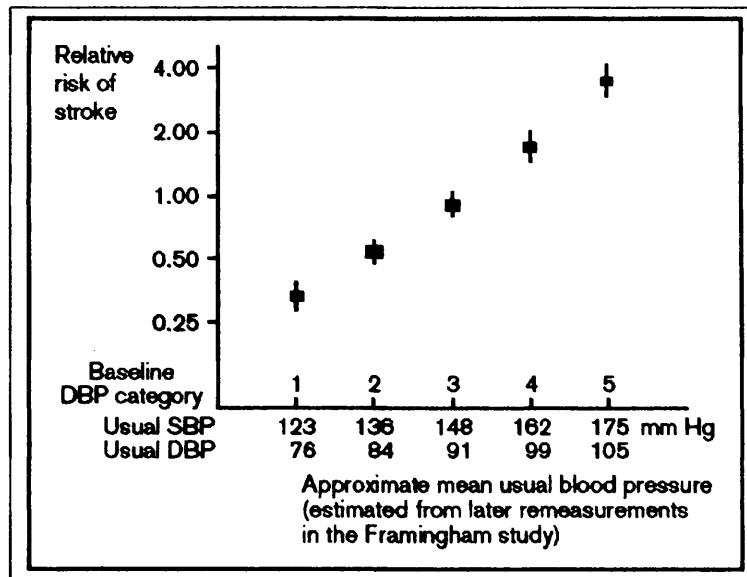


Figure 1:3 The relative risks of stroke for five categories of blood pressure(8)

Despite the advent of treatment of selected patients with acute ischaemic stroke with intravenous tissue-plasminogen activator and the promise of other acute therapies, effective prevention remains the best treatment for reducing the burden of stroke(10-12). Primary prevention is particularly important because ~70% of strokes are first events(13). The age-specific incidence of major stroke in Oxfordshire, UK, has fallen by 40% over the past 20 years in association with an increased use of preventative treatments including antihypertensive therapy and general reductions in other risk factors(14).

Research has confirmed the benefit of BP reduction in the primary prevention of stroke. A reduction in BP of 15/6 mmHg will decrease stroke incidence by nearly 50% in younger and about 34% in older people with similar benefit in those with combined or systolic hypertension(6). A meta-analysis of the results of the 4 largest, and combined results of 13 smaller unconfounded, randomised trials, including all ages and using mostly thiazide diuretics and β -blockers is shown in (Figure 1:4)

indicating a highly significant reduction in stroke with antihypertensive treatment of $38\pm 4\%$ (95%CI 31-45%)(15). A decade later, Li et al confirmed this in a prospective population-based study of 27,936 subjects, of whom 60% had hypertension. Ninety percent of first ever stroke occurred in subjects with uncontrolled hypertension ($>140/90$ mmHg)(16) strengthening the fact that hypertension control remains the most important primary preventative measure in the general population. In a review of all antihypertensive treatment trials, despite the differential lowering in DBP, antihypertensive treatment reduced all cardiovascular events and the risk of stroke and coronary events to a similar extent in the young (39 to 49 years), old (60 to 79 years) and very old (> 80 years). Moreover, for combined fatal and nonfatal end points, absolute benefit increased with higher age and with a lower ratio of DBP to SBP lowering(17).

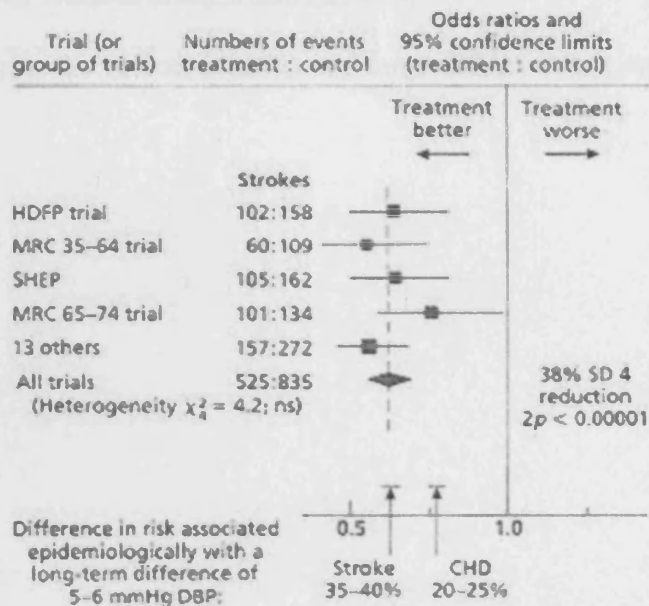


Figure 1:4 Results of meta-analysis of primary prevention trials.

It includes 4 largest, and combined results of 13 smaller unconfounded, randomised trials including: the Hypertension Detection and Follow-up Program (HDFP) (chlorthalidone)(18), MRC 35-64 trial(19) (bendrofluazide or propranolol), Systolic Hypertension in the Elderly trial (chlorthalidone+atenolol (or reserpine)) MRC 65-74 trial(20) (atenolol or hydrochlorothiazide), 13 combined trials(15) (diuretic, β blocker).

More recent trials have focused on alternative agents. Staessen et al reviewed the effects of new [calcium-channel blockers, alpha-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB)] vs old (diuretics or beta-blockers) antihypertensive agents with respect to stroke prevention(21;22). Old and new drugs provided similar protection against total cardiovascular mortality. Calcium-channel blockers (-10%, $P = 0.02$), as well as ARB (-24%, $P = 0.0002$) resulted in better stroke prevention than did the old drugs. Again, these studies confirmed the benefit of BP reduction on stroke prevention with newer

agents. Though BP reduction remains the most important issue for stroke prevention, BP still remains under treated(23).

All trials with respect to stroke reduction and target BP levels are summarised in (Table 1:1).

Trial (Publication year)	N (% of stroke)	BP target	BP difference SBP/DBP mmHg	Treatment arms	Follow- up (years)	RRR fatal & non- fatal stroke	P
HDFP (1982)(18)	10,940 (2.5%)	DBP<90	Not stated	Stepped care(diuretic, anti-adrenergic, vasodilator) and referred care (community treatment)	5	34.5% in stepped care participants	<0.01
MRC 35- 64 (1985)(19)	17,354	DBP<90	72%/71% had DBP<90 at 5 year	Diuretic/propranolol/ placebo	5.5	42% in active treatment group	0.002
SHEP, (1991)(24)	4736	ISH	12/4	Chlorthalidone/ placebo	4.5	36% in active treatment group	0.0003
MRC 65- 74 (1992)(20)	4396	SBP<150 or 160	0/0	Diuretic/ atenolol/ placebo	5.8	31% in active treatment group	0.04
HOT (1998)(25)	18,790	DBP≤90,≤85 and ≤80	0/2/4 mmHg in DBP ≤90, ≤85, ≤80	CCB, ACE, betablocker or diuretic in step-wise method	3.8	43% reduction in stroke in patients with IHD	0.046
HOPE (2000)(26)	9297 (11%)	Not stated	4/3	Ramipril/placebo	5	32% with Ramipril	<0.001
LIFE (2002)(27)	9193 (8%)	<140/90	1/-2	Losartan/atenolol	4.8	25% with Losartan	0.001
ANBP2 (2003)(28)	6083 (5%)	<140/90	1/0	ACE/diuretic	4.1	Fatal stroke more common with ACE (HR 1.91, CI 1.04 to 3.50), though non- fatal stroke similar in both groups	0.04
SCOPE (2003)(29)	4964 (3.9%)	<160/90	3/2	Candesartan/placebo	3.7	28% with Candesartan	<0.04
VALUE (2004)(30)	15,245 (20%)	140/90	2/1	CCB/ARB	4.2	Less stroke in CCB group	0.08
ASCOT- BPLA (2005)(31)	19,257 (11%)	<140/90 (non- diabetic), <130/80 (diabetic)	3/2	New (CCB, ACE) vs Old (diuretic, betablocker)	5.5	23% with new antihypertensives	0.0003

Table 1:1 Summary of trials of BP lowering in hypertensive patients for primary stroke prevention

BP : Blood pressure, SBP :systolic BP, DBP : diastolic BP, ISH :isolated systolic hypertension, RRR : relative risk reduction, CI: 95% confidence interval, HR : hazards ratio, CCB: calcium channel blocker, ACE : angiotensin converting enzyme inhibitor, IHD : ischaemic heart disease, ARB : angiotensin receptor blocker inhibitor

Despite convincing evidence of the benefit of BP lowering in primary stroke prevention, only a small proportion of treated hypertensives achieve good BP control of less than 140/90 mmHg(32-34). In an analysis of first ever stroke and level of BP control in the preceding year, there was a significantly higher SBP (151 vs 144 mmHg) in treated hypertensive stroke subjects than in controls of <70 years(7). Recently, in a large observational study (ForLife)(35), involving 12,792 hypertensive patients (7% of the cohort had previous stroke or TIA), only 18 % achieved good BP control - <140/90 mmHg. In the same cohort hypertension was the most important contributing risk factor (43%) for development of calculated risk of stroke over 10 years in both the treated and untreated group.

Summary and Gaps

- The benefit of hypertension treatment for primary prevention of stroke is clear.
- Choice of a specific regimen must be individualized, but reduction in blood pressure is generally more important than the specific agent used to achieve this goal.
- Hypertension remains undertreated in the community, and programs to improve treatment compliance need to be developed and supported.

1.2.2 Secondary stroke prevention

The need for prevention of recurrent stroke in hypertensive patients who have already suffered from stroke or transient ischaemic attacks has been recognised for a long time. Indeed, in the Oxford Vascular Study (OXVASC) the risk of stroke after a transient ischaemic attack was ~ 10% within 1 week and 18% within the first 3 months(14). Similar to the primary prevention of stroke, 32% (95% CI, 14 – 45%) of recurrent strokes were attributable to uncontrolled BP(36). However, for the secondary prevention of stroke, recent guidelines recommend the prescription of blood pressure-lowering drugs to normotensive and hypertensive patients with previous cerebrovascular complications(33;37). The evidence for this will now be discussed.

As early as the late 50s in up to 500 patients with 5 to 10 year follow up, it was noted that stroke recurrence rate was as low as 16% in well-controlled hypertensives compared to up to 59% in those with poor BP control(38-40). In the early 60s, Marshall gave long-term hypotensive therapy to 39 stroke survivors for 3 years and compared stroke recurrence with that of 42-control subjects. He recorded 66% survival in hypertensive patients compared to 96% in non-hypertensives(41). These early observations led to further randomised control trials, which are summarised in (Table 1:2).

Trial (publication year)	N	Post- ictus	Entry BP	BP reduction SBP/DBP mmHg	Treatment arms	Follow- up (years)	Odds Ratio- stroke recurrence (95% CI)	Odds Ratio – vascular events (95% CI)
Carter (1970)(42)	97	>2 w	SBP>160 &/or DBP>110	?	Thiazide, Methyldopa/ untreated	4	0.33 (0.13– 0.81)	
HSCS (1974)(43)	452	> 4 w	167/100	26/13	Deserpidine and diuretic/ placebo	3	0.80 (0.49-1.29)	0.69 (0.45-1.06)
Dutch TIA (1993)(44)	1473	< 3 m	158/91	6/3	Atenolol/ placebo	2.6	0.84 (0.57-1.23)	1.04(0.77-1.41)
TEST (1995)(45)	720	>1 w	161/89	4/3	Atenolol/ placebo	2.3	1.01 (0.71-1.44)	0.85 (0.61-1.19)
PATS (1995)(46)	5665	> 4 w	154/93	5/2	Thiazide diuretic/ placebo	3	0.71 (0.58-0.88)	0.77 (0.63-0.94)
HOPE (2000)(26;47)	1013	> 4	139/79	3/2	Ramipril/ Placebo	4.5	0.85 (0.56-1.30)	
PROGRESS- ACEI +/-D (2001)(48)	6105	2 w–5 y	147/86	12/5	ACEI + Diuretic (3544)/ placebo	4	0.55 (0.45-0.68)	0.58 (0.48-0.69)
				5/3	ACEI(2561) /placebo		0.94 (0.75-1.19)	0.95 (0.78-1.16)
MOSES (2005)(49)	1405	< 24 m	151/87	13/3	ARB (681)	2.5	0.75(0.58-0.97)	0.79(0.66-0.96)
				16/7	CCB (671)			

Table 1:2 Summary of randomised controlled trials of BP lowering in patients with a history of stroke or TIA (non-acute)

BP: Blood pressure, SBP: systolic BP, DBP: diastolic BP, ISH: isolated systolic hypertension, CI: 95% confidence interval, CCB: calcium channel blocker, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

Two randomized clinical trials(42;43) specifically designed to address these issues found that lowering BP in stroke survivors under the age of 65 years (within a year of ictus in Hypertension-Stroke Cooperative Study group [HSCS] group(43), and within 2 weeks of ictus in the Carter study(42)) was beneficial. The antihypertensives used were methyldopa, bethanidine or debrisoquine and thiazide diuretics. Overall, there was no significant reduction in stroke and cardiovascular events except for congestive cardiac failure, in which active treatment showed a significant reduction.

The apparent lack of benefit could be explained on the basis of relatively lower initial BP in the study group (mean BP 167/100) and the small number of patients.

1.2.2.1 Dutch-TIA

A total of 1,473 aspirin-treated patients with transient ischaemic attack or non-disabling ischaemic stroke (within 3 months post-ictus) were randomised to 50 mg atenolol daily or placebo. The mean follow-up was 2.6 years. The study data neither confirm nor rule out that atenolol prevents important vascular events in patients after transient ischaemic attack or non-disabling ischaemic stroke. For patients on atenolol, the adjusted hazard ratio was 1.00 (95% CI, 0.76-1.33) for death from vascular events. The adjusted hazard ratio for fatal or nonfatal stroke was 0.82 (95% CI, 0.57-1.19). Given the modest effect on blood pressure with atenolol (6/3 mm Hg), the restrictions in patient selection, and the limited number of patient-years, the trial remains neutral(44).

1.2.2.2 Tenormin after stroke and TIA (TEST)

This Swedish multicentre, randomised, double blind study recruited a total of 720 subjects within 3 weeks post-ictus. They were randomised to atenolol or placebo and followed up for a mean of 2.3 years. No difference in either stroke recurrence or vascular events was found. However, the number of patients recruited was smaller than projected number of 1900, and most of the patients had a high functional level which could be related to lower risk of stroke recurrence(45).

1.2.2.3 The Heart Outcomes Prevention Evaluation Study (HOPE)

In a group of 1013 stroke patients (within 4 weeks post-ictus) from the HOPE study, ramipril significantly reduced stroke in a broad range of high-risk patients who were not known to have a low ejection fraction or heart failure (OR 0.85(95% CI, 0.56 – 1.30)(26).

1.2.2.4 Post-Stroke Antihypertensive Treatment Study (PATS)

PATS was the first large (n = 5665) randomised trial of secondary stroke prevention. It demonstrated that a 5 mmHg SBP reduction reduced stroke recurrence by 29% compared with placebo when a thiazide diuretic(Indapamide) was started within 4 weeks of ictus(46).

1.2.2.5 Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS)

This large, randomised controlled secondary prevention study, further showed that compared with placebo, angiotensin converting enzyme (ACE) inhibitor-based therapy (antihypertensive therapy started within mean 8 months of ictus- range 2 weeks to 5 years) decreased recurrent cardiovascular complications, including

stroke recurrence in hypertensive as well as normotensive stroke survivors(48).

Over 6,000 patients with a previous history of stroke or TIA were recruited with a mean follow up period of 3.9 years. The study demonstrated that active treatment reduced the risk of total major vascular events by 26% and that there was a similar reduction in risk of stroke in hypertensive as well as non-hypertensive subgroups. Combination therapy of Perindopril + Indapamide reduced the BP by 12/5 mmHg and stroke risk by 43%. Single therapy reduced BP by 5/3 mmHg with no discernable stroke risk reduction.

This was a sufficiently powered study to demonstrate the benefits of BP lowering in non-hypertensive and hypertensive stroke patients for secondary prevention.

1.2.2.6 MORbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention (MOSES)

This secondary prevention trial recruited 1,405 high-risk hypertensive stroke patients (cerebral events during the last 24 months). They were randomised to Eprosartan or Nitrendipine. The mean follow-up was 2.5 years; Primary end points were total mortality and all cardiovascular and cerebrovascular events including recurrent events. This study demonstrated that in high-risk hypertensive stroke patients, an early normotensive and comparable blood pressure could be achieved in both treatment groups, but the combined primary end points (composite of total mortality, all cardiovascular and cerebrovascular events) were significantly lower in Eprosartan group(49).

A review of trials suggested that antihypertensive treatment decreased stroke recurrence by 28%(50). These findings were supported again in another recent meta-analysis(51) (Figure 1:5).

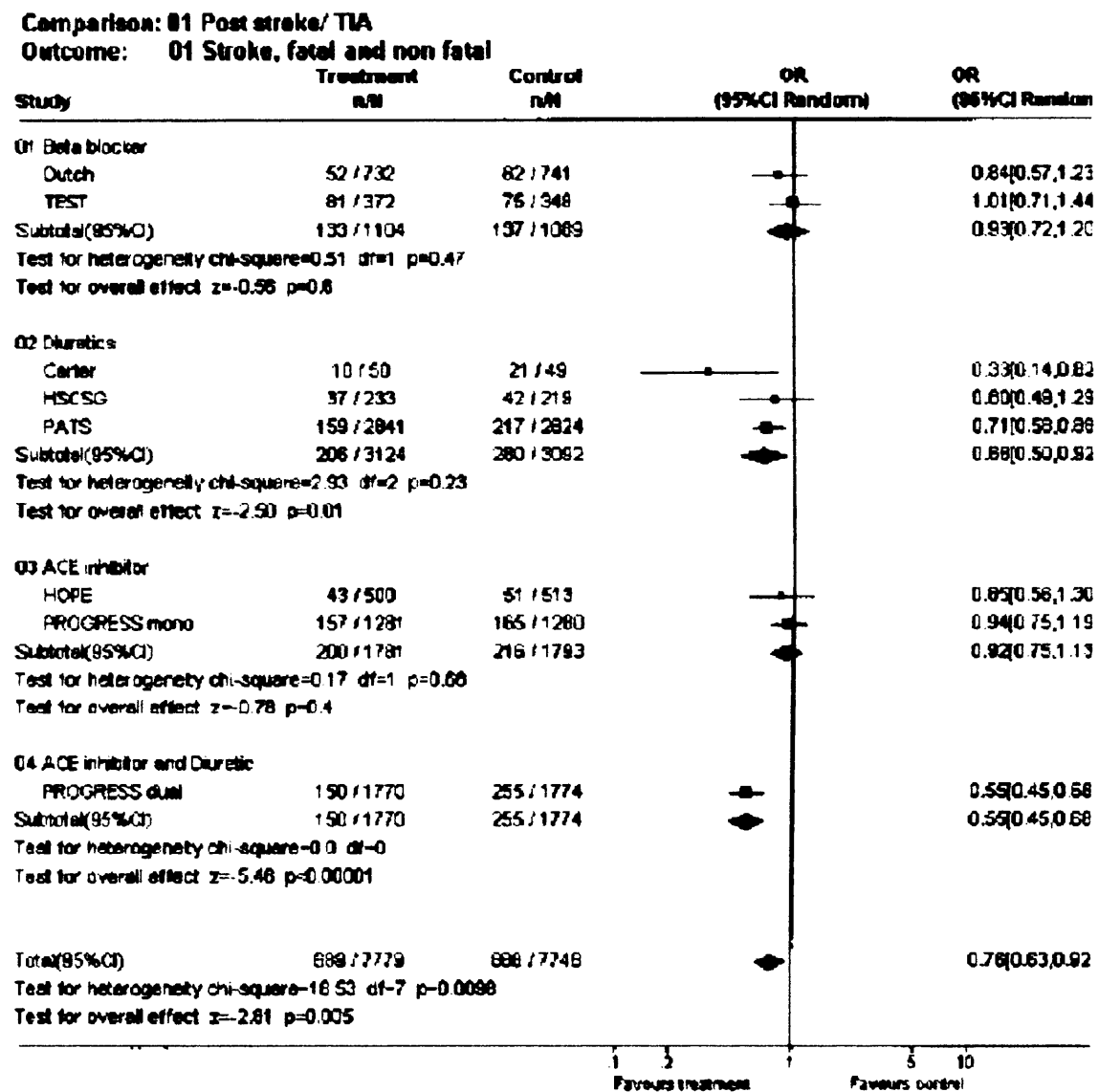


Figure 1:5 Effects of antihypertensive therapy in patients with prior stroke or TIA on subsequent stroke (fatal and nonfatal)(51)

1.2.3 On-going secondary prevention trials

1.2.3.1 ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and The Telmisartan Randomized Assessment Study in ACE iNtolerant subjects with cardiovascular Disease(TRANSCEND)

The ONTARGET is designed to clarify whether an ARB (telmisartan), an ACE inhibitor (ramipril) or a combination of both confers blood pressure-independent cardioprotection in high-risk patients whose blood pressure is well controlled. The TRANSCEND trial has the same endpoints, but will compare telmisartan with placebo in patients who are intolerant to an ACE inhibitor. Primary endpoints for both trials are the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for heart failure. A total of 25 620 patients will be randomised in ONTARGET and 5926 in TRANSCEND. Both trials are parallel, randomized, double-blind clinical trials with follow up of 3.5 to 5.5 years. Baseline patient characteristics are similar to those in the Heart Outcomes Prevention Evaluation (HOPE) study(26), except that the current trials have greater ethnic diversity (including an important cohort from Asia). The subjects are slightly older and mean blood pressure at randomisation is again normal, but slightly lower than in HOPE. The use of beta-blockers and lipid-lowering therapy, known to reduce mortality and morbidity, is also higher in ONTARGET/TRANSCEND. These trials are the largest comparisons to date of ARB and ACE-inhibitor therapy in high-risk patients with controlled blood pressure, and the results will contribute to the future treatment of cardiovascular disease(52-54).

1.2.3.2 Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS)

This is a multi-national, double-blind study of Aggrenox® (aspirin 25 mg + extended release dipyridamole 200 mg BD) vs clopidogrel + aspirin, with and without telmisartan. The primary outcome is time to first recurrent stroke.

Secondary outcome of “vascular events” defined as time to the first of stroke (non-fatal or fatal) or MI (non-fatal or fatal) or vascular death or worsening Chronic Heart Failure, and new onset diabetes. Over 20,000 neurologically and clinically stable patients over 55 years of age who had stroke within at least 90 days were recruited world wide. Recruitment stopped in year 2007 but follow-up is ongoing and results are awaited(55;56).

Despite clear evidence supporting the role of BP control in secondary stroke prevention, a significant number of stroke survivors have uncontrolled BP. Indeed, North East Melbourne Stroke Incidence Study (NEMSIS) examined control of hypertension in a community-based population of 5-year stroke survivors found that 82% of their patients had hypertension that was uncontrolled (BP >140/90 mm Hg) in more than one third of patients(57).

Summary and gaps

- The benefit of lowering BP for secondary stroke prevention is clear even in non-hypertensives.
- Angiotensin converting enzyme inhibitor and diuretic use has evidence-based support.
- There is lack of evidence for immediate post-stroke hypertension treatment.

1.3 Blood pressure changes in acute stroke

High blood pressure (BP > 140/90 mmHg, as defined by the World Health Organisation, the International Society of Hypertension and British Hypertension Society) occurs in up to 82% of stroke patients(58-61) when measured within 48 hours of ictus. Subsequently BP settles during the first week, Harper et al demonstrated 12/7 and 22/12 mmHg fall in SBP/DBP at 24 hours and 7 days following hemispheric stroke, respectively(62;63). The greatest fall in BP being associated with the highest baseline BP levels(64).

Furthermore, 24 hour BP monitoring following stroke has demonstrated a loss of circadian rhythm following stroke. In a prospective, small study of 50 patients, analysis of continuous BP within 120 hours following stroke showed a loss of circadian rhythm (loss of night time dipping of > 10%) in over 85% of cases(65). Another study from our department also demonstrated a significant reduction in diurnal BP changes especially in cortical, subcortical and primary intracerebral haemorrhage groups compared to age and sex matched controls(66). Further study of 173 acute stroke patients (<24 hours of onset), examined 24-hour SBP pattern. It found various patterns of BP changes during the first 48 hours - 15% dippers (fall in SBP <20%); 2 % extreme dippers (fall >20%); 46 % non-dippers (fall<10%); and 37% reverse dippers (a rise in mean nocturnal SBP compared to mean daytime SBP) (67).

These changes are thought to be multifactorial and are related to previous hypertension, activation of the neuroendocrine system (sympathetic nervous system,

renin-angiotensin axis and glucocorticoid system), increased cardiac output and “white coat hypertension”(68-72). Raised intracranial pressure in relation to stroke also provokes a pressor response via the Cushing reflex. An observation in 843 acute stroke patients admitted within 41 hours post-ictus (median delay 5 hours, maximum delay 168 hours), demonstrated that BP levels were similar on admission whether patients entered hospital early or late after onset of symptoms. Therefore, proposing that the acute mental stress of admission to hospital may be a major contributor to high BP(68).

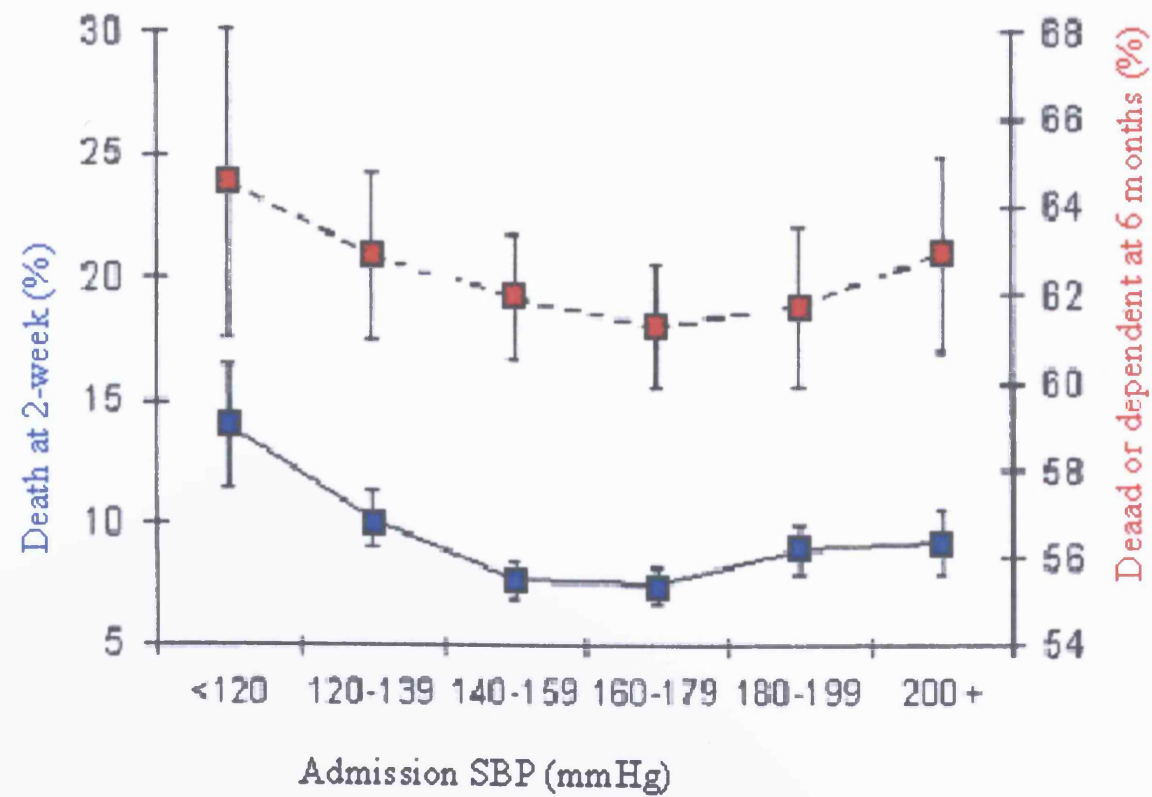
1.3.1 Blood pressure and stroke outcome

Though the relationship of BP during the acute phase of stroke and outcome has been extensively studied, the prognostic influence of acute stroke BP is still a matter of controversy. It is thought that acutely elevated BP might be a protective mechanism in maintaining cerebral perfusion pressure and promoting blood flow to the ischaemic penumbra, but the effects of post-stroke hypertension on neurological outcome give conflicting results(73) Some workers have associated high BP levels with poor outcome(74;75), whereas others have found good prognosis(76;77) or no influence(78). This discrepancy could be explained by a U-shaped relationship between BP and outcome measure.

In the International Stroke Trial (IST) (Figure 1:6), high or low SBP was associated with worsened short (14 day) and long-term (6month) outcome in a ‘U-shaped’ relationship. For every 10 mmHg rise in SBP above 150 mmHg, the risk of early death increased by 3.8%, there was an increase in the frequency of early stroke recurrence by 4.2% and a non-significant increase of 1.1% in 6-month death or

dependency, independent of age, level of consciousness, time to BP measurement and presence of atrial fibrillation. For each 10 mmHg decrease in SBP below 150 mmHg there was a corresponding 17.9% increased risk of early death and an increased risk of death or dependency at 6 months of 3.6%. In addition, a single and non-standardised casual BP measurement might have under-estimated the strength of the BP relationship with outcome in IST(60).

Figure 1:6 Relationship between SBP level on admission in acute ischaemic stroke and stroke outcome.
Data from the International Stroke Trial⁽⁶⁰⁾



1.3.1.1 Short-term outcome

For the purposes of this review death and dependency or early neurological deterioration (from 24 hours post-ictus up to 30 days) following stroke constitutes short-term outcome.

During the past three decades many workers tried to establish a relationship between acute BP levels and stroke outcome. The work of these studies is presented in the Table 1:3, Table 1:4, Table 1:5 and Table 1:6.

Trial (publication year)	N (stroke type)	BP measurement	Results
Ahmed et al (2001)(79)9)	92 (all ischaemic)	< 24 hours	OR for 21-day death/ dependency >160/ 90: 4.8 (1.2 – 19.3) >170/ 95: 4.4 (1.1 – 17.8) >180/100: 12.7 (2.2 – 74.7) >190/ 105: 5.6 (1.1 – 30.0)
Abboud et al (2006)(80)0)	230 (all ischaemic)	< 24 hours	OR for 10-day death/dependency SBP≥165 OR 2.91 (1.52 – 5.59), DBP per 10 mmHg ↑ OR 1.18 (0.95 – 1.47)
Britton et al (1990)(81)1)	388 (26 ICH)	< 1 week	Greater in-hospital mortality in severely hypertensives (30 vs. 14%)
Davalos et al (1990)(82)2)	98 (all ischaemic)	<8 hours	Elevated SBP associated with neurological deterioration within first 48 hours
Dunne et al (1987)(83)3)	75 (all ICH)	Not stated	SBP >200mmHg associated with increased in-hospital mortality
Harmsen et al (1972)(84)4)	97 (29 ICH)	>1 week	Greater in-hospital mortality in patients with BP >160/ 95mmHg (35 vs. 24%)
Hatano (1976)(85)5)	6395 (23% ICH)	Not stated	Increased 'early' mortality in patients with BP >200/ 115mmHg
Qureshi et al (1995)(86)6)	182 (all ICH)	Not stated	MAP >140mmHg associated with increased 24-hour mortality OR 2.1 (1.1 – 3.9)
Robinson et al (1997)(87)7)	136 (11 ICH)	<72 hours	30-day death and dependency associated with each 10mmHg increase in 24-SBP OR 1.88 (1.27 – 2.78)
Tuhrim et al (1988)(88)8)	82 (all ICH)	Not stated	SBP >150mmHg associated with increased 30-day mortality
Wong et al (2005)(89)9)	186 (15% ICH)	<48 hours	30-day death/dependency associated with DBP≥90 mmHg

Table 1:3 High acute stroke BP and poor short-term outcome

BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; MAP: mean arterial pressure;
OR: odds ratio; CI: confidence Interval; ICH: intracerebral haemorrhage

Trial (publication year)	N (stroke type)	BP measurement	Results
Rodriguez-Garcia et al (2005)(90)	434 (all ischaemic)	< 24 hours	Death and dependency associated with 24-h SBP >160 mmHg (OR 2.35, 95% CI 1.10 to 5.52). Whereas a decrease in SBP on day 7 associated with less death/dependency (OR 0.46, 0.24 to 0.88)
Semplicini et al (2003)(91)	92 (all ischaemic)	Not stated	SBP 140 – 220, DBP 70 – 110 mmHg had best 7-day neurological outcome

Table 1:4 High acute stroke BP and good short-term outcome

BP: blood pressure; SBP: systolic BP; MAP: mean arterial pressure; OR: odds ratio; CI: confidence Interval; ICH: intracerebral haemorrhage

Trial (publication year)	N (stroke type)	BP measurement	Results
Castillo et al (2004)(92)	304 (all ischaemic)	< 24 hours	fall of >20 mmHg in SBP in first 24- hours associated with 48 hour neurological deterioration
Jorgensen et al (1994)(76)	868 (46 ICH)	<1 week	Lower SBP in patients with stroke-in-progression at 1 week (156 vs. 170mmHg)
Okumura et al (2005)(93)	2101 (52% ICH)	<24 hours	RR of 30-day death 2.69 (95% CI, 1.43- 5.07) for lowest SBP and 3.49 (95% CI, 1.58-7.74) for lowest DBP after acute infarction. Patients with previous hypertension had better outcomes at higher admission BP level than did normotensive patients.
Vlcek et al (2003)(94)	372 (all ischaemic)	< 48 hours	A DBP fall from preadmission level of > 25% within 24 hours after admission associated with day 5 dependency. Adjusted OR 3.8 (95% CI: 1.2 to 12.1)

Table 1:5 Lower acute stroke BP and poor short-term outcome

BP: blood pressure; SBP: systolic BP; MAP: mean arterial pressure; OR: odds ratio; CI: confidence Interval; ICH: intracerebral haemorrhage, RR: relative risk

Trial (publication year)	N (stroke type)	BP measurement	Results
Bhalla et al (2001)(95)	72 (not stated)	< 24 hours	24-SBP lower in group with 1-week functional/ neurological recovery (149 vs. 162 mmHg)
Chamorro et al (1998)(96)	481 (all ischaemic)	<24 hours	Improved functional recovery at 1 week in patients with MAP reduction by day 2
Dandapani et al (1995)(97)	87 (all ICH)	<8 hours	MAP <145mmHg associated with reduced 30-day death and disability
Table 1:6 Lower acute stroke BP and good short-term outcome			

BP: blood pressure; SBP: systolic BP; MAP: mean arterial pressure; OR: odds ratio; CI: confidence Interval; ICH: intracerebral haemorrhage.

Table 1:4, Table 1:5 and Table 1:6 taken and modified from Age & Ageing⁽⁹⁸⁾

The majority of studies have demonstrated that poor outcome is associated with a high acute BP(79-89) and only a couple have shown good outcome(90;91). The relationship between lower acute BP and short-term outcome remains neutral.

1.3.1.2 Long-term outcome

For the purposes of this review, death and dependency or poor functional/neurological recovery after 30 days post –stroke is considered long-term outcome.

From the early 60's until recently, there have been conflicting data on the prognostic values of admission BP parameters, most showing an association of higher SBP and or DBP with poor outcome, some with good outcome, and some demonstrating poor outcome with lower SBP, DBP and PP (Table 1:7, Table 1:8

and Table 1:9). However, in both short and long-term studies, there were a number of methodological issues:

- All were observational studies.
- Various components of BP were correlated with the outcome.
- Outcome definition varied in each study.
- Spontaneous fall over the first days following stroke was not controlled for.

It is therefore difficult to make any definite conclusions from these studies, and the modulation of BP in acute stroke remains an area of active research(99).

Trial (publication year)	N (stroke type)	BP measurement	Results
Acheson et al (1971)(100)	497 (not stated)	1st clinic attendance	DBP >120mmHg associated with increased mortality compared to DBP <90mmHg over 4.6 year follow-up
Aslanyan et al (2003)(101)	1455 (not stated)	< 6 hours	A 30% increase from baseline MAP associated with poor functional/neurological outcome at 1 and 3-month
Candelise et al (1986)(102)	462 (all ischaemic)	<3 months	Hypertension associated with increased mortality over 4-year follow-up period
David et al (1960)(103)	100 (all ischaemic)	Not stated	Severe hypertension associated with increased mortality over 2- year follow-up period
Henon et al (1995)(104)	152 (all ischaemic)	<24 hours	Increased MAP (113mmHg) associated with increased 3-month death/ disability compared to MAP 106mmHg
Howard et al (1963)(105)	100 (all ischaemic)	Not stated	SBP >140mmHg associated with increased 3-year mortality (50% vs. 30%)
Marshall et al (1961)(106)	106 (all ischaemic)	Not stated	DBP >110mmHg associated with increased 3-year mortality
Robinson et al (2001)(74)	136 (11 ICH)	<72 hours	24-hour SBP >160mmHg associated with increased 3-year mortality compared to SBP <140mmHg: HR 2.41 (1.24-4.67)
Schmidt et al (1988)(107)	1538 (11.9% ICH)	<24 hours	Increased BP associated with higher 7-year mortality (>200/115mmHg (68.9%) vs. 160- 180/ 95-104mmHg(53.5%))
Sorensen et al (1988)(108)	203 (all ischaemic)	<1 month	SBP >160mmHg associated with increased mortality over 106- month follow-up period
Sprigg et al (2006)(109)	1484 (all ischaemic)	< 48 hours	Poor 6-month death/dependency associated with high SBP, DBP, MAP and PP
Tsivgoulis et al (2005)(110)	339 (21% ICH)	< 24 hours	Every 10 mmHg rise in 24 hour PP associated with stroke recurrence at 1-year (Relative risk 1.323, 1.019 to 1.718, p=0.036)

Table 1:7 Higher acute stroke BP and poor long-term outcome

BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; MAP: mean arterial pressure; PP: pulse pressure; OR: odds ratio; HR: hazards ratio; ICH: intracerebral haemorrhage

Trial (publication year)	N (stroke type)	BP measurement	Results
Bruell et al (1960)(111)	80 (not stated)	Not stated	High SBP group (mean 165mmHg) less likely to exhibit long-term recovery compared to low group (147mmHg)
Osaki et al (1998)(112)	28 (all ischaemic)	<24 hours	Increased BP associated with increased odds of 3-month neurological recovery: OR 1.06 (1.00 – 1.12)
Table 1:8 Higher acute BP and good long-term outcome			

BP: blood pressure; SBP: systolic BP; OR: odds ratio

Trial (publication year)	N (stroke type)	BP measurement	Results
Allen (1984)(77)	137 (25 ICH)	< 24 hours	Low SBP(mean 147 mmHg) had increased 2-month death/dependency compared to high SBP (mean 162 mmHg)
Merrett et al (1966)(113)	465 (all ischaemic)	< 1 week	BP < 185/110 mmHg associated with increased 2-month mortality
Oliveira-Filho et al (2003)(114)	115 (not stated)	< 24 hours	Lower diastolic blood pressure on admission was associated with poor functional outcome at 3-month
Stead et al (2005)(115)	357 (not stated)	Not stated	SBP<155, DBP<70, MAP<100 were significantly associated with 90-day mortality
Table 1:9 Lower acute BP and poor long-term outcome			

BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; MAP: mean arterial pressure; ICH: intracerebral haemorrhage

Table 1:7, Table 1:8 and Table 1:9 taken and modified from Age & Ageing⁽⁹⁸⁾

1.4 Acute stroke blood pressure management trials

1.4.1 Completed trials

There is a limited evidence base to support/ inform the management of acute (< 1 week) stroke hypertension.

1.4.1.1 Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS)

The ACCESS study was designed to assess the safety of modest blood pressure reduction by candesartan cilexetil in the early treatment of stroke. A 7-day course of candesartan vs placebo started within 72 hours of acute ischaemic stroke significantly improved cardiovascular morbidity and mortality. Moreover, the same favourable effect was not achieved when candesartan was started 7 days after an acute stroke. The 12-month mortality and the number of vascular events differed significantly in favour of the candesartan cilexetil group (odds ratio, 0.475; 95% CI, 0.252 to 0.895)(116).

However, there are a number of issues with this trial:

- The study population was very hypertensive (196/103 mmHg). Though the improvement in cardiovascular mortality could have been due to acute BP control, there was no difference in BP levels between active treatment and placebo groups making it difficult to interpret BP dependent effects.
- After 7 days any antihypertensive plus ARB was given. Therefore, long-term ARB therapy might have influenced outcome.
- There was no difference in primary outcome (case fatality and disability at 3 month)

There is also some indirect evidence of the acute effects of BP lowering from other trials of acute treatment in stroke.

1.4.1.2 Intravenous Magnesium Efficacy in Stroke trial (IMAGES)

Though this trial was designed to demonstrate the effects of intravenous magnesium given within 12 hours of stroke onset on 90-day death or disability, SBP and DBP were reduced slightly in the magnesium group throughout the study infusion ($p < 0.0001$ compared with placebo). However, no difference in blood pressure was noted by 48 h. Mean blood pressure reduction between baseline and 24 h was 4/3 mmHg lower than placebo but there was no difference in 90-day death/disability in either active treatment or placebo group. Interestingly, poor outcomes were significantly reduced in non-cortical stroke syndromes (OR 0.75, 95% CI 0.58–0.97, $p=0.026$)(117). Further analysis of IMAGES patients demonstrated a good functional outcome in patients with non-cortical strokes in treatment group. Stroke patients who were younger, had a higher MAP or DBP, and did not have a history of ischaemic heart disease especially benefited from magnesium treatment(118). However, whether the treatment effect of magnesium is mediated via lowering of BP or whether the BP effect is simply the manifestations of magnesium treatment is unclear.

The interaction between baseline BP and treatment was present in both the main IMAGES and the lacunar stroke subset analysis.

1.4.1.3 Glucose-potassium-insulin infusions in the management of post-stroke hyperglycemia: the UK Glucose Insulin in Stroke Trial (GIST-UK)

This trial tried to determine whether treatment with a glucose-potassium-insulin (GKI) infusion immediately after the acute stroke reduces death at 90 days. Though GKI infusion significantly reduced plasma glucose concentrations, it was not associated with significant clinical benefit, although the study was underpowered. In addition, there was a significant SBP reduction of 9 mmHg (95% CI 5.3 to 12.7, $p < 0.0001$) in GKI group although, the effect of GKI on blood pressure may be the consequence of the potassium component of the GKI infusion or conversely the result of a relative pressor effect of saline moderating the normal fall in blood pressure after stroke. However, there was no significant reduction in 90-day mortality (OR 1.14, 95% CI 0.86 to 1.51, $p = 0.37$)(119).

1.4.1.4 National Institute of Neurological Disorders and Stroke Trial (NINDS)

In this randomised controlled trial, recombinant tissue plasminogen activator (rt-PA) was given within three hours post-stroke. The 3-month death/disability (global outcome) was in favour of rt-PA (OR 1.7; 95 %, 1.2 to 2.6, $p = 0.008$)(120). On further analysis rt-PA use favoured good 3-month outcome even when adjusted for baseline NIHSS (OR 2.11, 95% C I: 1.33 to 3.35, $p < 0.002$ for up to 90 minute group and OR 1.69, 95% C I: 1.09 to 2.62, $p = 0.02$ in the 91 to 180 minute group)(121). Interestingly, subjects with BP > 185/110 were excluded from study and those randomised, underwent acute BP manipulation to keep BP at pre-specified level. In particular, 9% of patients in the placebo arm of the NINDS were hypertensive (>185/ 110mmHg) and received bolus intravenous labetalol therapy. The odds ratio for death at 3 months was significantly reduced compared to

hypertensive patients in the placebo group who did not receive labetalol therapy (OR 0.1, 95% CI 0.1 to 0.7).

1.4.2 Current guidelines

Therefore, there is a lack of current evidence to inform the best management of acute stroke hypertension. Indeed, there are multiple, inconsistent, and conflicting 'authoritative' guidelines. For example, the European Stroke Initiative (EUSI) recommends the initiation of BP lowering therapy for acute stroke when BP is >220/120 mmHg, with a target of 180/100-105 for known hypertensives and 160-180/90-105 for non-hypertensives(122). The American Stroke Association recommends the initiation of antihypertensive treatment when BP is > 200/120 mmHg for acute stroke without thrombolysis, but >180/105 during and after thrombolysis, with a target to reduce BP below these levels(123). Whilst, the Japanese, British, Australian and New Zealand recommendations are similar for acute ischaemic stroke, but they recommend starting treatment at a somewhat lower BP for acute haemorrhagic stroke(124).

Thus, the most recent Cochrane Collaboration Stroke Review concludes that it is not clear whether high BP should be lowered in acute stroke, nor whether antihypertensives should be continued or stopped(125).

Therefore, current guidelines suggest therapeutic intervention for only a few specific indications(126;127) (Table 1:10), and there remains debate over how quickly anti-hypertensive therapy can be safely initiated following acute stroke.

<p>Hypertensive encephalopathy</p> <p>Cardiac/vascular urgencies</p> <p>Aortic dissection</p> <p>Acute myocardial infarction</p> <p>Unstable angina</p> <p>Severe left ventricular failure</p> <p>BP >200/120mmHg in association with intracerebral haemorrhage</p> <p>Thrombolysis</p>
<p>Table 1:10 Indications for acute stroke blood pressure reduction: current guidelines</p>

Whilst in a majority of patients, a decline in blood pressure occurs within the first hours after stroke even without any specific medical treatment(92), several questions about the management of arterial hypertension in the setting of acute stroke remain unanswered(128-130):

- Should patients previously taking antihypertensive medications continue taking them during the first hours after stroke?
- Are some of these medications contraindicated or indicated?
- Should new antihypertensive agents be started?
- What level of blood pressure would mandate initiation of new antihypertensive treatment?
- Which medication should be administered in this situation?

On-going and recently completed acute trials are designed to address some of these questions.

1.4.3 On-going acute BP intervention studies

1.4.3.1 Controlling Hypertension and Hypotension Immediately Post-Stroke Trial (CHHIPS)

A pilot study from our department has established the safety of ACE inhibition immediately following acute stroke (CHIPS)(131), and has led to a further pilot but larger, multicentre study CHHIPS(132). The CHHIPS Pilot Trial is a UK based multi-centre, randomized, double-blind, placebo-controlled, titrated dose trial. It will assess the effects of depressor therapy started within < 36 hours of stroke on death and dependency at day 14.

The secondary objectives are:

- to establish the safety of acute depressor (0–36 h post-stroke) BP manipulation in stroke patients, as assessed by the absence of early (<72 h) neurological deterioration, or death at 3 months
- to investigate whether beneficial or detrimental effects of BP manipulation are influenced by stroke type (ischaemic versus haemorrhagic)
- evaluate the effectiveness of such therapy on manipulating BP levels
- to assess whether alternative non-oral modes of antihypertensive drug administration, including sublingual lisinopril and intravenous labetalol, are effective
- to investigate whether effects of BP manipulation are influenced by the time to treatment.
- to identify the incremental cost effectiveness of labetalol versus placebo, lisinopril versus placebo and labetalol versus lisinopril in hypertensive patient

1.4.3.2 Efficacy of nitric oxide in stroke (ENOS)

An ongoing trial assessing the safety and efficacy of transdermal glyceryl trinitrate in acute stroke (< 48 hours) on 3-month death and disability following stroke(133). ENOS study is a collaborative, international, multicentre, prospective, randomised, single-blind, blinded endpoint, parallel-group, controlled trial. It will also examine the effects of continuing or temporarily stopping prior anti-hypertensive medication. Preliminary data on 168 patients (mean age 70 years, male 54%, severity [Scandinavian Stroke Scale] 41, BP 167/90 mmHg) demonstrated that the mean differences in BP between patients randomised to continue vs stop prior antihypertensive medication on day 7 was -8.6/-2.3 mmHg (SBP, $p=0.002$; DBP, $p=0.047$)(134).

1.4.3.3 Scandinavian Candesartan Acute Stroke trial (SCAST)

An ongoing multicentre randomised, placebo-controlled, double-blind trial assessing the effectiveness of BP reduction in acute stroke (< 30 hours of onset, SBP \geq 140) on 6-month death and dependency and combined vascular death in 6 months(135).

1.4.3.4 Continue Or Stop post-Stroke Antihypertensive Collaborative Study (COSSACS)

This will be considered in more detail later on (see section 2.1).

Therefore, there are a number of important questions still to be answered:

1. At least 40% of acute stroke patients are already taking antihypertensive therapy on hospital admission(136) , and it remains uncertain if pre-existing therapy should be continued or stopped. The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) and ENOS(134) will establish the efficacy and safety of BP manipulation in the acute stroke period by the continuation or stopping of preexisting therapy.

The CHHIPS, ENOS and SCAST trials will address the safety and efficacy of BP manipulation in acute stroke settings.

2. Are there any physiological measures of cardiovascular autonomic control, which may influence acute stroke BP manipulation and be responsible either fully or partly, for the changes in the 2-week death/dependency?

Summary and gaps

- Blood pressure changes, particularly hypertension, are common post-stroke.
- Post-stroke hypertension may be associated with increased morbidity and mortality.
- The benefits and risks of blood pressure manipulation following acute stroke are not clearly established.
- Ongoing trials will address these issues for stroke patients on pre-existing antihypertensive therapy (COSSACS, ENOS) and for hypertensive (CHHIPS, ENOS and SCAST) stroke patients.
- The role of acute stroke haemodynamic parameters in predicting 2-week outcome are not clearly established, and may influence the safety of acute stroke BP manipulations.

1.5 Importance of cardiovascular autonomic control

1.5.1 Autonomic changes and stroke

Short and long-term mortality following stroke is high(137;138). The majority of deaths are related to non-stroke events, in particular cardiac death(138). Various studies have reported between 30 and 40% mortality at 1-year, and up to 43% of cardiac events (death or nonfatal myocardial infarction) during long-term follow up(139;140).

Cardiovascular autonomic control plays an important part in controlling BP via Baroreceptor Sensitivity.

The baroreflex loop is driven by the sympathetic and parasympathetic arms of the autonomic nervous system (ANS) and is the most important loop for cardiovascular control. Through the action of the ANS it adjusts the pulse interval to compensate for arterial pressure changes. The state of the baroreflex loop is often assessed using cardiac baroreceptor sensitivity (BRS), which is the ratio of changes in RR interval to changes in systolic pressure levels. BRS is considered an important parameter as it is strongly related to ANS modulation, vessel distensibility and cardiac control.

1.5.1.1 Baroreflex anatomy

During embryonic development, the aortic and carotid baroreceptor areas arise from the third and fourth brachial arches(141). The baroreceptors are dense in the arch of the aorta(142), the carotid sinus(141;143), and other areas, including the common carotid, subclavian and innominate arteries. Almost all baroreflex control is thought to be exerted by receptors in the carotid sinus and aortic receptor areas(144). The central areas involved in baroreflex control are closely related complex pathways involving the hypothalamus, parabrachial nucleus, trigeminal nucleus, rostral ventrolateral medulla, ambiguus nucleus, and solitary tract nucleus (nucleus tractus solitarius - NTS)(145) (

Figure 1:7).

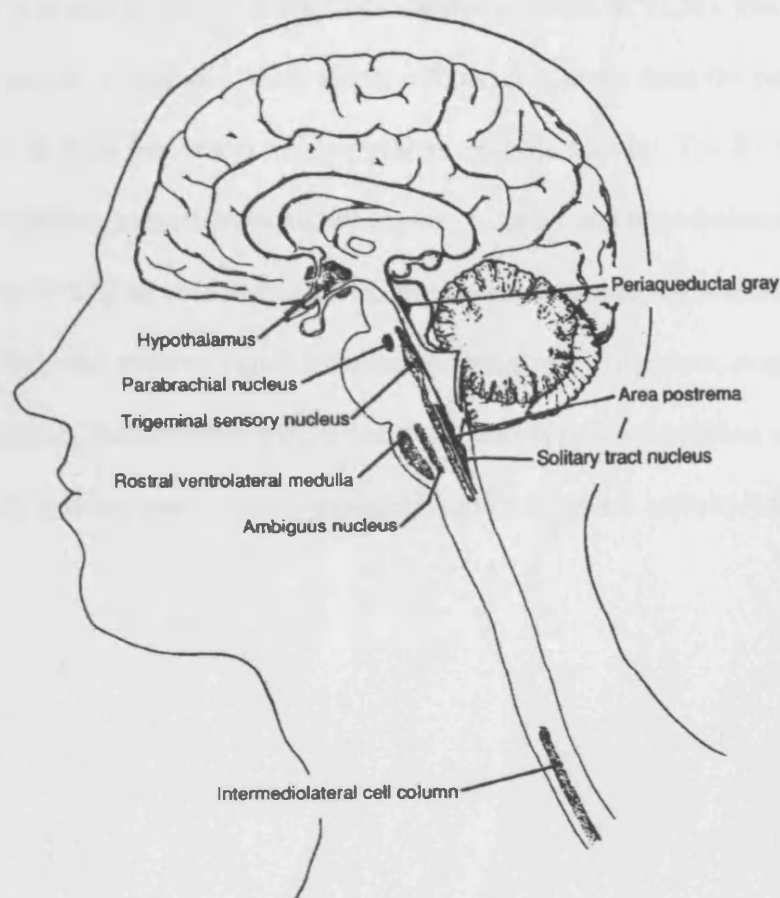


Figure 1:7 Major areas involved with baroreflexes(145)

1.5.1.2 The arterial baroreflex

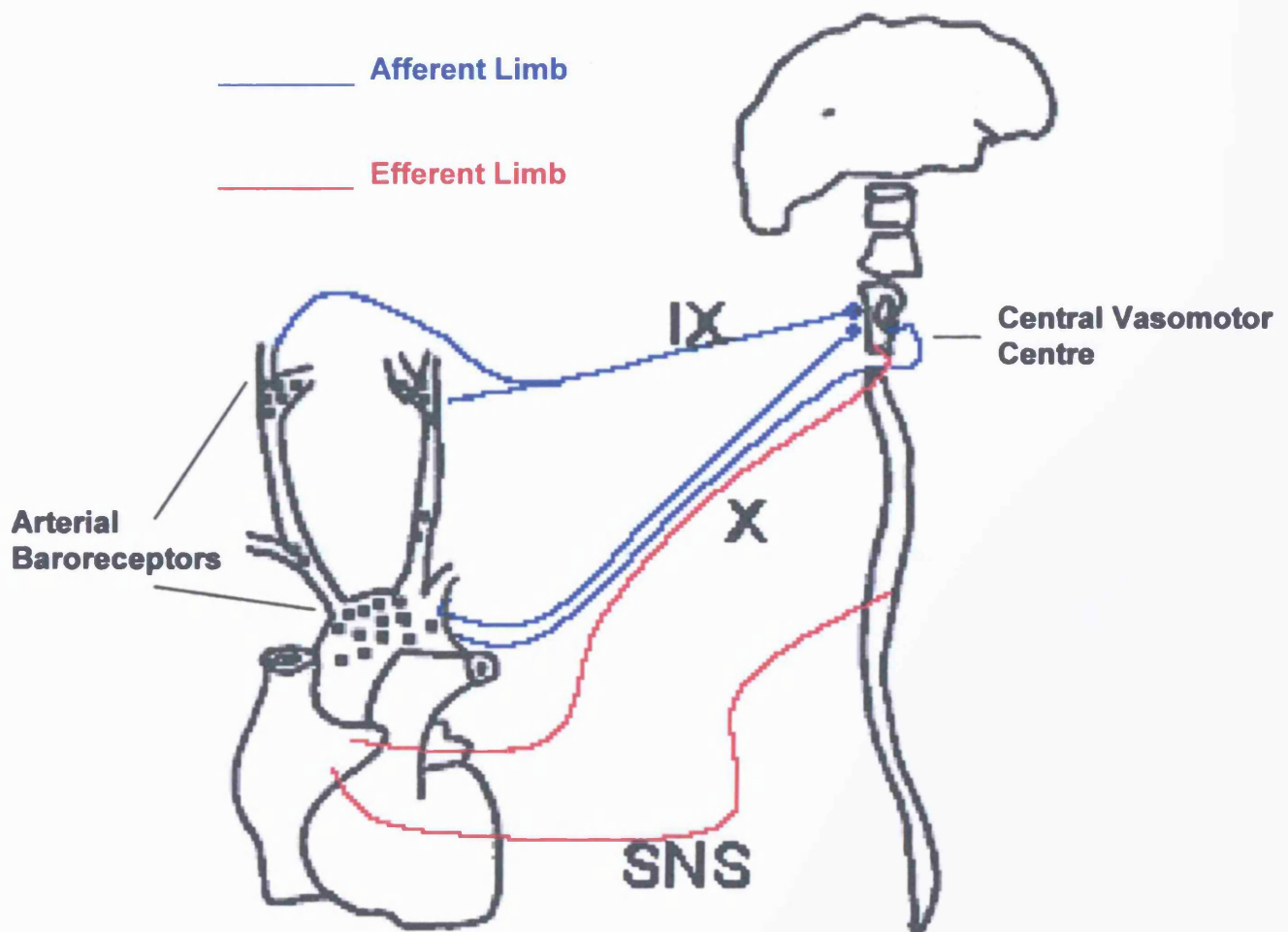
The arterial baroreflex is the principal neural reflex controlling the beat-to-beat homeostasis of arterial BP. A schematic diagram is shown in (Figure 1:8).

Baroreceptor sensory nerve endings lie in the adventitial layer of the carotid sinus and aortic arch. In response to stretch, as a result of an increase in luminal pressure, they activate and rapidly adjust to ensure steady BP levels. Baroreceptors are sensitive to dynamic changes in BP levels occurring over seconds to minutes.

Afferent impulses from the baroreceptors via the glossopharyngeal nerve (from the carotid sinus) and vagus nerve (from the aortic arch) reach the nucleus tractus solitarius (NTS) in the medulla, often called the vasomotor centre. The excitatory

inputs from the NTS go to the caudal ventrolateral medulla (CVLM) from where inhibitory impulses go to the rostral ventrolateral medulla (RVLM). The RVLM contains excitatory neurons, which along with other neurons from the pons and hypothalamus form precursors of sympathetic nervous activity. The RVLM also receives inhibitory signals from higher centers – cortex and hypothalamus. Both the CVLM and RVLM receive and send neuronal connections to the ventral respiratory neurons. They also receive inputs from cardio-pulmonary receptors, responsible for BP homeostasis. Baroreceptor afferent activity causes reflex inhibition of sympathetic and increase in parasympathetic nervous system activity(146).

Figure 1:8 Diagram of Baroreflex arc



IX – Glossopharyngeal nerve

X – Vagus nerve

SNS – Sympathetic nervous system

1.5.1.3 Mechanisms regulating baroreceptor action

Several mechanisms are proposed as follows:

1) Glioeelastic vessel relaxation: Arterial pressure increase causes distension of the vascular wall and distortion of the BRS nerve endings. As soon as the maximum pressure is achieved, glioeelastic relaxation reduces the tension on the nerve endings(147).

2) Activation of Na⁺ pump: Inhibition of the Na⁺ pump significantly reduces the post-excitatory depression and the resetting of baroreceptors following arterial pressure increase(148).

3) Activation of K⁺ channels: K⁺ channel inhibition reduces adaptation of the baroreceptors(149).

4) Hormones and chemical agents:

Norepinephrine: may either reduce the action of baroreceptors, by vasoconstriction, or increase their sensitivity, acting directly on the nerve endings(150).

Prostacyclin: seems to directly affect the baroreceptors, as a prostacyclin injection in the carotid sinus increases BRS, without changing the diameter at the carotid sinus. Decreased BRS in hypertension and atherosclerosis may be due to reduced prostacyclin production that characterizes such diseases(151).

Nitric Oxide (NO): when injected into carotid sinus reduces BRS irrespective of its vasodilating action(152).

Oxygen free radicals: act only on atheromatous vessels(153).

Agents secreted by activated platelets in the carotid sinus: these agents activate baroreceptors leading to reflex abolition of sympathetic nervous system and hypotension(154).

All of the above mechanisms make the baroreceptor reflex a powerful tool for regulation of arterial pressure. In turn, this reflex normalizes its changes. This is achieved directly by the reflex activation of the parasympathetic nervous system, inhibition of the sympathetic nervous system and increased vascular resistance and HR, and indirectly by renin and vasopressin secretion.

1.6 Measuring Baroreceptor Sensitivity

1.6.1 Background

As early as 1866, Cyon and Ludwig(155) showed that electrical stimulation of the aortic depressor nerve caused deceleration of heart rhythm and arterial pressure in rabbits. The origin of this reflex was thought to be myocardial until 1902, when Koester et al(156) introduced the concept that the arterial system contains pressure sensitive areas. In 1923, Hering was the first to discover the carotid sinus reflex and demonstrated that the responsible nerve fibres are in the carotid sinus and common carotid artery bifurcation. He showed that afferent stimulation is located in a branch of the glossopharyngeal nerve (Hering's nerve) and stimulation of this specific nerve causes deceleration of pulse interval and hypotension independent of accompanying bradycardia(157).

Koch(141) subsequently used the isolated blind carotid sinus preparation to open the carotid sinus baroreflex loop to define the reflex consequences of variation in

carotid sinus pressure. He showed that as carotid pressure is raised in steps at 20 seconds intervals from low to high levels, R-R intervals inscribe a sigmoid function (Figure 1:9).

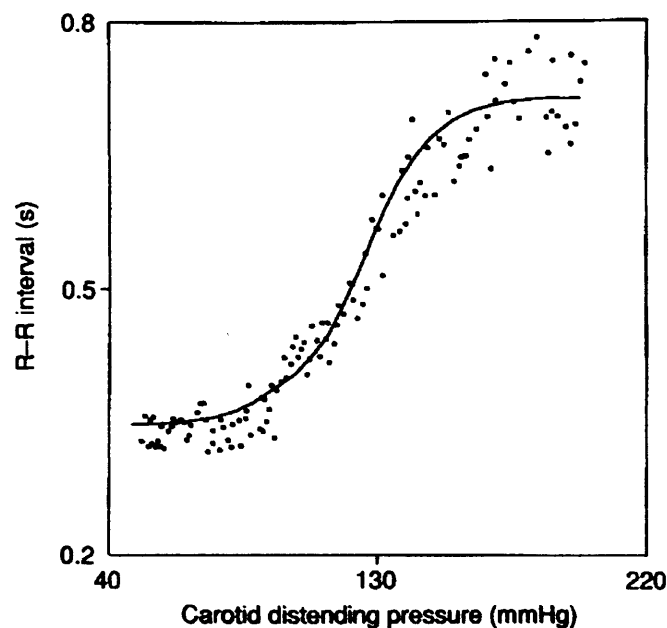


Figure 1:9 Sigmoid relationship between carotid pressure and R-R interval(141)

However, by the middle of twentieth century, methods available for study of baroreflex mechanisms in humans lacked the precision and reproducibility of methods available for animal research. Two developments changed this.

First, Ernsting and Parry, flight lieutenants in the British Royal Air Force, developed a neck chamber (see section 1.6.2.3) to counteract neck distension during the positive pressure breathing used to treat pilots(158;159).

Second, Smyth in 1969, showed that when arterial pressure is raised with bolus injections of a pressor drug, the R-R interval prolongation that occurs can be related, to preceding systolic pressures with linear regression analysis(160). With this background knowledge subsequent new techniques to measure BRS have evolved.

Several methods have been used to measure cardiac BRS in humans.

1.6.2 Traditional methods

1.6.2.1 Oxford method

Arterial pressure measurements were carried out invasively with insertion of an intra-arterial catheter. Cardiac BRS was estimated by evaluating changes in RR interval following administration of vasoactive drugs that induced significant changes in BP. Smyth et al first described the intravenous injection of pressor agents – angiotensin or phenylephrine – to assess cardiac BRS(160). However, the invasive nature of the procedure limits the wide spread use of this technique.

1.6.2.2 The Valsalva manoeuvre

This manoeuvre has a strong influence on the cardiovascular system. It consists of transient voluntary increase in intrathoracic and intra-abdominal pressures provoked by straining. It is divided into four phases. The fourth stage of the procedure, where arterial pressure increases and HR reduces, can be used for BRS calculation(161). This technique causes significant changes in venous return as well as baroreceptor stimulation.

Though this method is safe and does not need sophisticated equipment, there are a number of issues regarding its use. These mainly relate to the methodological part, especially the mouth pressure and duration of straining, and whether normal or maximal inspiration precedes straining(162). This procedure has a high failure rate as patients find it difficult or satisfactory arterial pressure is not achieved at the end of manoeuvre. It has very low reproducibility(163).

1.6.2.3 Neck suction method

Ernsting and Parry(158) were the first to apply suction on a neck air chamber to selectively activate the carotid baroreceptors and to cause HR slowing. Short-lasting external suction or pressure is applied to the region of the carotid sinus in the neck via an airtight chamber. External suction increases the transmural pressure in the carotid sinus, activating the baroreceptors, whilst external pressure unloads the baroreceptors. This method is better tolerated than a pharmacological one since it is less aggressive and applies a rapid stimulus directly on the neck. It can even be used when patients hold their breath, which avoids the influence of breathing on the BRS measurement. However, this method requires very specialised equipment (Figure 1:10).

Also, there are other problems with this technique. Firstly, the stimulus is only delivered to the carotid sinus, and other baroreceptors tend to diminish the reflex responses(162). Secondly, the pressure changes may be incompletely transmitted to the carotid sinus, resulting in changes in carotid sinus intramural pressure(164).

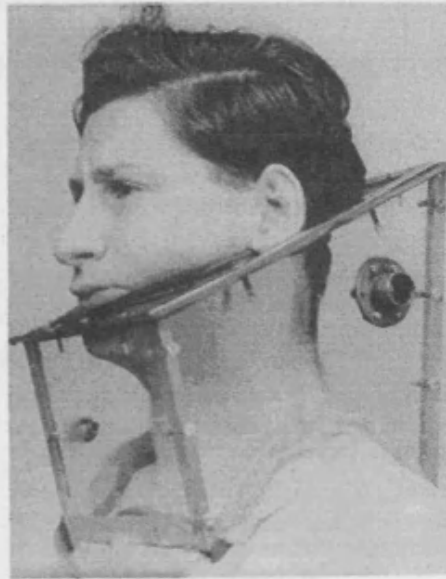


Figure 1:10 The neck chamber, developed by Ernstring and Parry(158)

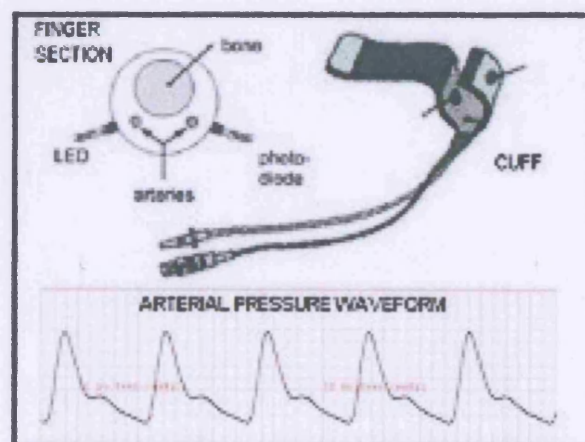
1.6.3 Non invasive methods

These methods use a noninvasive assessment of BP and HR. The FinapresTM or Portapres device can be used for non-invasive BP measurement. FinapresTM is a photoplethysmographic device involving an inflatable cuff (Figure 1:11), wrapped around the middle phalanx of a finger. On starting the device, the finger artery is fully unloaded, and then loaded to arterial occlusion with stepwise increasing pressure automatically applied to the cuff. An infrared signal is transmitted through the finger pulp from one side of the cuff to the other. The changes in infrared transmission are correlated to cuff pressure using this initial calibration technique (Physiocal). The finger arterial BP waveform is derived by the degree of inflation of the cuff required to keep the infrared signal constant, ie, to keep finger volume constant. This method of measuring finger arterial BP was first described as the volume clamp method in 1973 by Penaz(165). The system has a fast acting servo allowing rapid changes in finger volume, occurring with each cardiac cycle. Non-

invasive measurements obtained using this device have been shown to correlate well with intra-arterial measurements in a wide groups of subjects, including the elderly(166;167), and in particular in monitoring beat-to-beat BP changes(168) .

Subsequent analysis to calculate cardiac baroreceptor sensitivity (BRS) includes either of the following methods(169)

Figure 1:11 Finapres™ 2300, Ohmeda for non-invasive estimation of finger arterial BP



1.6.3.1 The sequence or spontaneous method

First described by Bertinieri et al in 1985(170). A brief 5 – 10 min period of arterial pressure and RR interval are used. A software program then identifies

Periods of three or more consecutive beats during which SBP is increased by at least 1 mmHg per beat, while RR interval progressively prolongs (pressor/up)

Periods of three or more consecutive beats during which SBP is decreased by at least 1 mmHg per beat, while RR interval progressively shortens (depressor/down)

The sequences associated with BP and PI changes in opposite directions are also noted though the cause of these is presently unclear.

These periods are presented graphically and the gradient of the linear curve constitutes BRS (Figure 1:12).

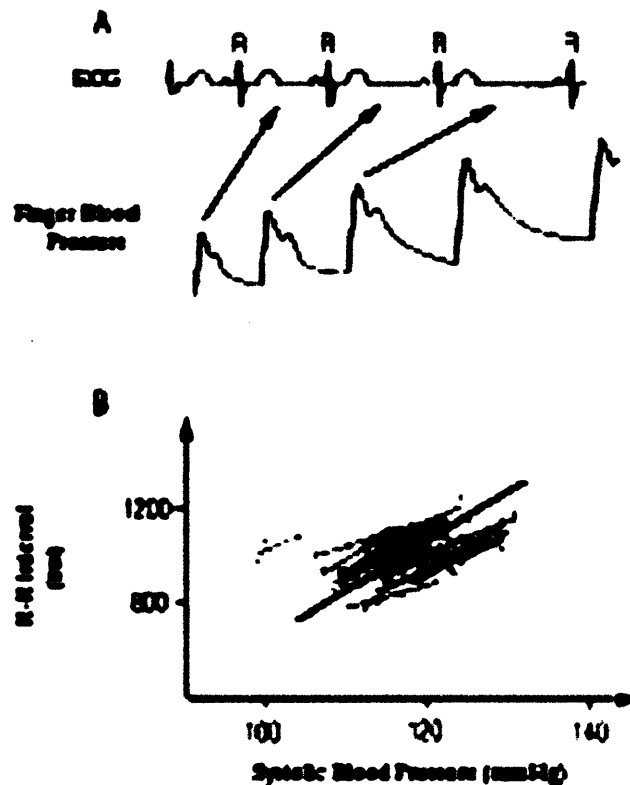


Figure 1:12 A schematic representation of the selection of spontaneous Baroreflex sequences.

It shows 3 beats of consecutively increasing SBP associated with prolonging RR interval. The average regression slope (heavy line) is termed the spontaneous baroreflex sensitivity(171). BRS values may be calculated from up and down sequences(172).

Parlow and colleagues assessed BRS in a group of healthy young volunteers with pharmacological and sequence methods, and found similar values for BRS by both methods(173).

A further study from our department, involving hypertensive and elderly subjects, compared BRS, derived from up and down sequence analysis, with pressor and depressor pharmacological techniques, showed acceptable agreement between the two methods(174).

However, there are some limitations with sequence analysis as with other methods. Typically, a sequence length of 3 or more beats is used, though studies have shown that BRS is inversely related to sequence length(172;174). Short sequences are more typical of physiological state but may not calculate BRS accurately, whereas, longer sequences of pharmacological methods may not represent the true picture. Nonetheless, with the advent of reproducible, reliable and noninvasive methods of continuous BP recordings, there is increased potential for the use of this technique.

1.6.3.2 The spectral analysis method (frequency domain analysis based on Fast Fourier Transformation - FFT)

BRS is measured by the α -index that is the square root of the ratio between the RR interval variability and the arterial pressure in the frequency zone. Spectral methods of calculating cardiac BRS have several advantages over conventional invasive pharmacological methods and give similar BRS values(174). Power spectral analysis involves the detection of rhythmicity in computer-derived tachograms of beat-to-beat recordings of BP and PI; various algorithms can then be used to assess the number, frequency and amplitude of the oscillatory components. However, the analysis requires prior selection of frequency bands for BP and PI. Previous studies favoured either the low-frequency band (0.05 – 0.15 Hz) or the combined low- and high-frequency bands (0.15 – 0.35 Hz)-the α value(169;173;175-178).

The frequency and amplitude spectra may contain 3 spectral peaks in different frequency ranges (Figure 1:13) : very low frequency 0.01-0.05 Hz (VLF), low frequency 0.05-0.15 Hz (LF) and high frequency 0.15-0.4 Hz (HF). The power in a frequency band represents the square of the variability of the parameter at that

frequency, equivalent to the standard deviation. Power spectral analysis estimates of PI and SBP variability were obtained by taking the square root of the powers of PI and SBP respectively for the VLF, LF and HF bands. Simultaneous spectral analysis of SBP and PI allow the gain of the baroreceptors to be represented by an 'α' index:

$$\alpha \text{ index} = \sqrt{\frac{(\text{Power of spectral components PI (HF, LF or combined HF+LF)})}{(\text{Power of spectral components SBP (HF, LF or combined HF+LF)})}}$$

Cardiac BRS assessed in this way compares well with estimation of gain of the baroreceptor using the phenylephrine method(177).

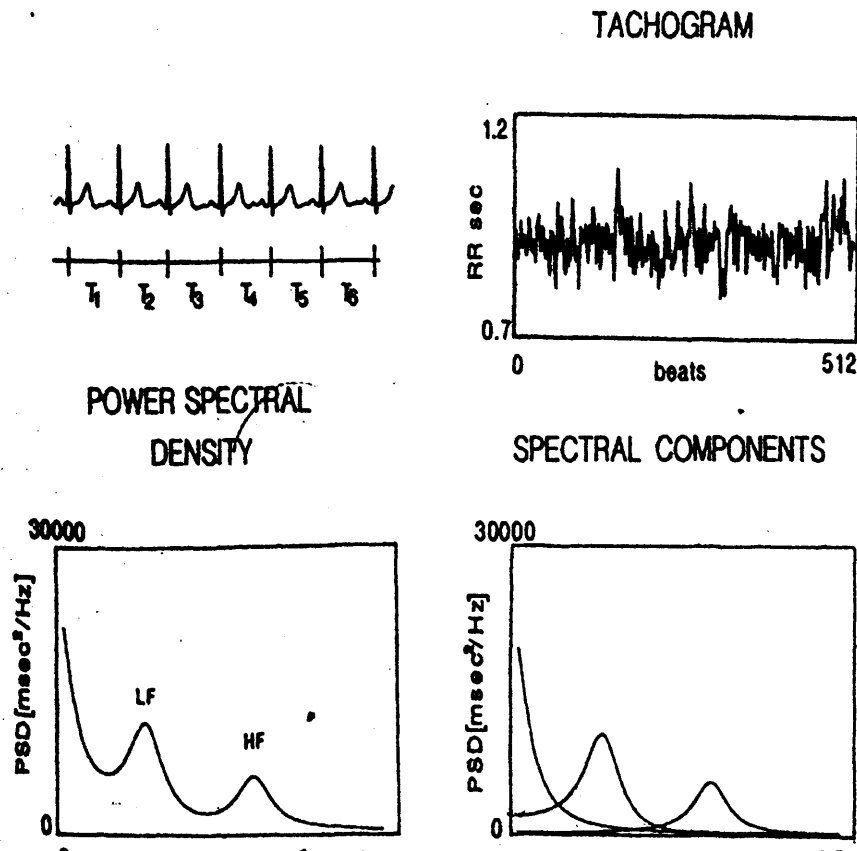


Figure 1:13 Example of ECG, Pulse Interval Tachogram, Power Spectrum and Spectral Component(177).

Two other measures are important in spectral analysis: phase and coherence. Phase is the time relationship between changes in SBP and PI. A negative phase implies changes in SBP leading to changes in PI, reflecting a baroreceptor-mediated

sequence. A positive phase implies PI leading SBP changes and reflects system noise or non-baroreceptor-mediated sequences. Coherence is a measure of input-output coupling. It assesses the statistical significance between the dynamic changes in arterial BP and the resulting changes in PI.

1.6.3.3 Control breathing method

Controlled breathing improves the correlation between α -index and BRS values that are calculated with the administration of phenylephrine. Based on these data, Davies et al described a new method of BRS calculation, using a controlled breathing protocol(179). The patients breathe at a rate of 0.1 Hz. The arterial pressure and RR signals are then passed through a simple digital filter (time domain) where time processing takes place and part of the signal in the frequency that interests us (0.1 Hz) is taken. BRS calculated with this method, is equal to the ratio of the mean range of RR intervals' variation to the mean range of arterial pressure variation (Figure 1:14). This method is simple, has best reproducibility and the lowest failure rates(179).

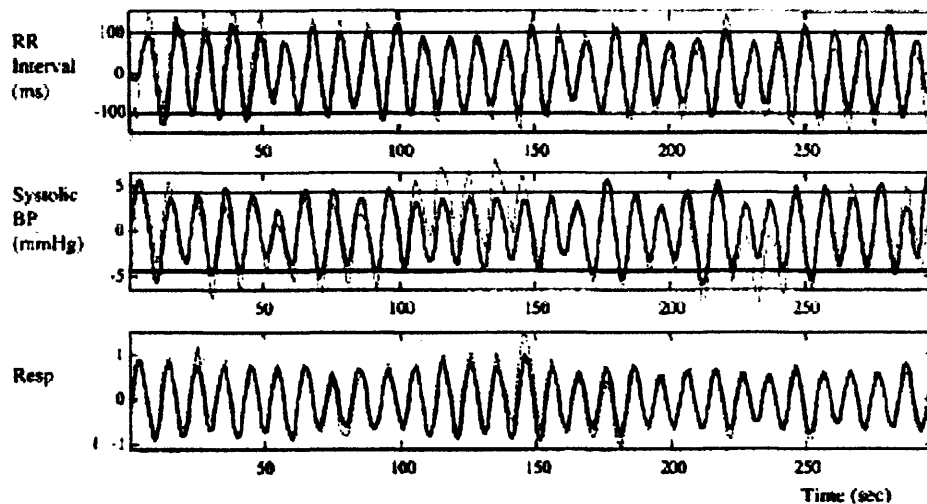


Figure 1:14 Assessment of BRS using time domain analysis during controlled breathing.

The dotted line shows the measured signal and the continuous line the filtered signal(179)

1.6.4 Commonly used terminology to describe different methods

1.6.4.1 Autoregressive (AR) Modeling

Technique for mathematical modeling of signals. This approach is based on the assumption that the value of a signal depends on the previous value of the same signal plus “noise”. Once the AR model of a signal is estimated, the spectrum of the input signal can be computed from a manipulation of the mathematical model.

1.6.4.2 Autoregressive Moving Average (ARMA) Modeling

Technique for mathematical modeling of signals. It is based on the assumption that the value of the output signal depends on either the previous values of the same signal (AR component) and on the present and previous values of a different input signal (moving average component), with the addition of a “noise” factor.

1.6.4.3 Broadband Spectral Analysis

Spectral analysis providing a spectral estimation over a wide range of frequencies. By this approach, a single spectrum is obtained from a relatively long-lasting input data record.

1.6.4.4 Fourier Transform

Decomposition of a given signal into a series of sine and cosine waves having frequencies that are multiples of the fundamental frequency (the reciprocal of the time length of the input data record). The spectral power of the input signal can be derived from the magnitude of these sine and cosine waves.

1.6.4.5 Fast Fourier Transform

Algorithm for the fast estimation of the Fourier transform. It requires that the number of samples derived from the input signal be powers of 2.

1.6.4.6 Time-Varying Spectral Analysis

A set of analysis procedures that describes how the spectral characteristics of the input signal change as a function of time.

1.6.4.7 Transfer Function

Mathematical relationship between the input and output of a system as a function of the frequency.

1.7 Heart rate variability

It is clearly established that abnormal cardiovascular autonomic regulation, as measured by heart rate variability (HRV) and cardiac baroreceptor sensitivity (BRS), are independent predictors of death after myocardial infarction(180;181).

HRV is estimated as the standard deviation of pulse interval (PI) or square root power of PI taken from simultaneous ECG readings obtained from intra-arterial or non-invasive ambulatory recordings.

In all observational studies of patients after myocardial infarction, a depressed HRV measured over a 24-h period as well as from short-term recordings has been consistently associated with an increased risk of cardiac and overall mortality(181-185). Either time or frequency domain measures were assessed in these studies. In another study, reduced spectral components, mainly reduction in the power of very-low and low frequency spectral components were found to be the best predictor of arrhythmic mortality in a post myocardial infarction group(184).

Galinier et al described the prognostic value of low-frequency power of HRV in identifying risk of sudden death in 190 chronic heart failure patients during a 22 months follow up period. Independent predictors of sudden death were ischaemic heart disease and daytime low frequency power $<3.3 \text{ ms}^2$ (RR=2.8, 95% CI 1.2–8.6). However, patients with conditions potentially associated with higher mortality were excluded from the study, which might introduce bias in result interpretation(186).

The findings from prospective studies that reduced HRV predicted clinical outcome after myocardial infarction and in heart failure has been extended to other conditions. In cross-sectional studies of hypertensive(187) and diabetic(188;189) patients, a reduced HRV was associated with a higher death rate. Indeed, there are direct survival consequences from the reduced HRV even in normal ageing. This was described in The Framingham Heart Study cohort of 736 elderly subjects (follow-up ~ 4 years) where low-frequency power of HRV was associated with an increased mortality of 70 % when adjusted for age, sex and other clinical risk factors(190).

Furthermore, HRV has been shown to be reduced as a consequence of both hemispheric(191;192) and brain stem(193) cerebral infarction by using conventional time and frequency domain analysis. Impaired HRV was seen even after 6(194) and 9(195) months post-stroke. However, the relationship between HRV and post-stroke outcome was not established until 2004, when Makikallio et al showed that abnormal β -slope (< -1.5) of ultra low frequency and low frequency of HRV power (assessed within 24 hours post-ictus) independently predicted post-stroke mortality even after adjusting for age (Hazards ratio: 3.8, CI 1.8 to 8.2, $p < 0.001$)(196).

Heart rate variability indices such as the ratio of the LF/HF power or the fractional LF power have been used to describe sympathovagal balance(177;197). They have been correlated with poor cardiovascular outcome in patients with myocardial infarction and cardiac failure(180;198).

1.8 Blood pressure variability

The occurrence of BP fluctuations over time was first described at the beginning of 18th century by Stephen Hales (1733), but the assessment of blood pressure variability (BPV) in a clinical setting was only made possible by the end of 19th century.

Assessment was done with the help of a sphygmomanometric technique introduced by the Italian scientist Scipione Riva Rocci(199). In the 1960s, the development of Oxford system, achieved a further step forward in BPV assessment in humans(200). More recently, noninvasive ambulatory BP monitoring technique, based on automated oscillometric arm-cuff BP readings, have become increasingly available(201). As these methods yield BP values every 15 to 30 minutes, they are unable to quantify short-lasting BP changes. Though they allow better assessment of BP behaviour over a 24 hour period, they prevent a detailed assessment of BPV due to the discontinuous nature of BP sampling. This limitation has been overcome by the introduction of noninvasive techniques of BP assessment at the finger level by the FinapresTM or Portapres devices as previously described (see section 1.6.3)(202).

BPV is estimated as the standard deviation of beat-to-beat BP readings obtained from intra-arterial or non-invasive ambulatory recordings. Increased BPV is associated with increased target organ damage and cardiovascular mortality in a hypertensive population (203-205). In a general population in the Ohasama study(206), increased BPV and reduced HRV from ambulatory BP monitoring confirmed increased cardiovascular mortality. Sander et al(207) addressed this issue

in a hypertensive population, and demonstrated that increased daytime SBP variability was the best predictor of progression of carotid atherosclerosis even after adjusting for other risk factors. It was also associated with increased cardiovascular events.

Finally, BPV is affected in a stroke population as well. In an observational study by Stead et al in 71 ischaemic stroke patients (<24 hours post-ictus) demonstrated that a wide fluctuation in SBP and DBP within the first 3 hours of admission was significantly associated with increased 90-day mortality. Wide fluctuation in DBP compared to SBP fluctuation ($p<0.001$, Wilcoxon sum test vs $p=0.047$) was significantly associated with 90-day mortality independent of stroke severity, age and gender(208).

Summary and gaps

- Cardiac BRS plays an important role in autonomic control following stroke.
- An impaired cardiac BRS following stroke predicts long-term mortality.
- An increased BPV in hypertensive as well as stroke population is associated with increased mortality.

1.9 Arterial stiffness

1.9.1 Background

Arterial pulse assessment is an important part of the clinical examination. It has long been recognized that any changes in pulse character suggested the presence of disease.

“The pulse ranks first among our guides; no surgeon can despise its counsel, no physician shut his ears to its appeal. Since then, the information the pulse affords is of so great importance, and so often consulted, surely it must be to our advantage to appreciate fully all it tells us, and to draw from it all that it is capable of imparting”

– F A Mahomed, 1872

The sphygmogram (Figure 1:15) was the first diagnostic instrument ever introduced into clinical practice to record pulse waveforms. Despite difficulties in its use, it gained clinical popularity between 1860 and 1920. Although Vierordt built the first instrument in Germany, it could not record pulse waveform detail and was too bulky to use. Marey constructed the first practical instrument (Figure 1:15) in Paris in 1860s(209). In subsequent years with its refinement by Mahomed(210), Broadbent(211) and Mackenzie(212), the art of sphygmocardiography (study of the dynamic interaction of the left ventricle and systemic arterial system through analysis of the arterial pressure waveform) began.

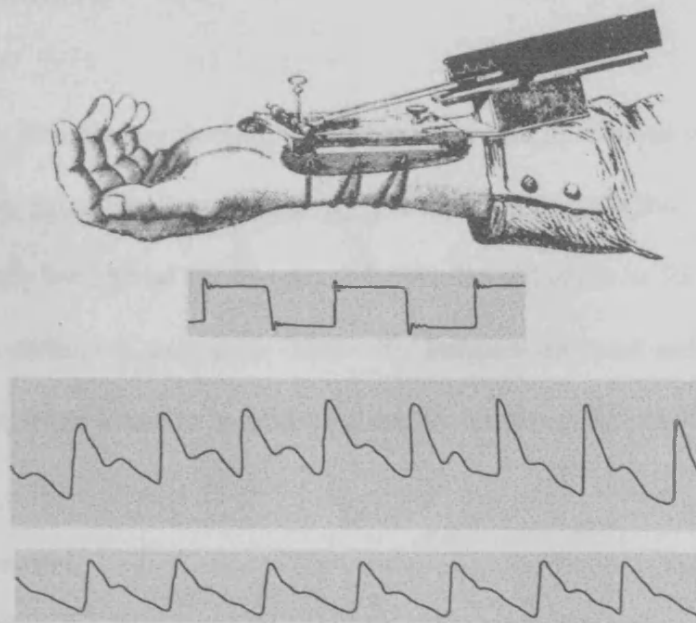


Figure 1:15 Tracings from Marey's publication on the sphygmogram(213).

The original instrument at the top, 'square wave test' to establish frequency response and instrumental artefact and tracings in young man showing pattern typical of radial artery

1.9.1.1 Traditional methods

In the 1870s Frederick Akbar Mahomed (1849 – 1884) – a medical student at Guy's Hospital in London – developed a sphygmogram whereby the peripheral pulse contour could be recorded(210). Mahomed was the first to describe the characteristic features of the peripheral arterial pulse in association with ageing commenting on the accentuated systolic and the depressed diastolic component of the waveform. The pressure changes described by Mahomed are explained through increased arterial wall stiffness. In 1920, Bramwell and Hill showed that arterial wall stiffness in man was the principle determinant of the pulse wave velocity (PWV)(214).

1.9.1.2 Recent methods

At the turn of the 20th century the sphygmomanometer was introduced which measured stiffness parameters non-invasively. Due to its simplicity this device was used predominantly for arterial BP assessment. Systolic and diastolic BP variables became the main method of measuring interaction between the heart and arteries. Subsequently they were found to be powerful cardiovascular prognostic markers.

1.9.2 Pulse pressure

Pulse pressure (PP) is the difference between SBP and DBP. It has been recognized as a prognostic marker for cardiovascular disease mortality. The Framingham Heart study suggested that hypertension related mortality and morbidity correlated best with PP(215). Benetos(216) reported a high PP as an independent predictor of coronary mortality in 19,000 French men. This prediction value is seen across the whole range of population. A recent observational study involving 25-year follow-up in seven countries of 12,763 men confirmed a 22% increased hazards ratio of cardiovascular mortality with every 10-mmHg increase in PP(217). As this observation was carried out only in a middle-aged male population, generalizing the findings for female and older population cannot be made.

In addition to hypertensives and the general population, PP is a prognostic marker in stroke. In 339 acute first ever stroke subjects (<24 hours of onset), high 24 hour PP along with increasing age and diabetes mellitus predicted stroke recurrence(110).

Nonetheless, the prognostic value of PP is not consistent across a range of population. In the Israeli ischaemic heart study(218), PP along with mean arterial pressure (MAP) predicted stroke mortality, but in hypertensive subjects, it did not. In another large cohort study (Chicago Heart Association Detection Project in Industry), among 36 314 participants (mean age: 39 years; 43% women) who were free of cardiovascular disease and not receiving antihypertensive treatment at baseline, there were 11 452 deaths: 745 were attributed to stroke, and PP had inferior predictive utility for cardiovascular events than SBP and DBP(219). In TAIST (Tinzaparin in Acute Ischaemic stroke Trial)(109), all BP parameters including higher PP predicted 6 month poor functional outcome.

1.9.3 Pulse wave analysis

With the advent of new non-invasive methods, arterial wall function can be assessed through changes in arterial pulse wave contour and its speed of conduction at various sites of the arterial tree. This in turn, gives new circulatory function indices.

1.9.3.1 Principles of SphygmocorTM device

The Sphygmocor system (Figure 1:16 and Figure 1:17), used in the investigations in this thesis, is a portable system based on the technique of applanation tonometry. It consists of a computer and interface board coupled to a high-fidelity piezo-electric transducer mounted in the tip of a hand-held wand. This generates a low voltage electrical current according to the pressure applied at the tip and, when applied to an artery underlying skin such that the arterial wall is flattened, circumferential pressure is equalised throughout and intra-arterial pressure equals transmural pressure at the tonometer tip (a similar principle is used when measuring intraocular

pressure by applanation tonometry). The technique can be successfully used at the site of any palpable artery to obtain the intra-arterial pressure waveform, but particularly where there is underlying bone to support the vessel being compressed (Figure 1:18).

Figure 1:16 The Sphygmocor™ system



Figure 1:17 The Sphygmocor™ output

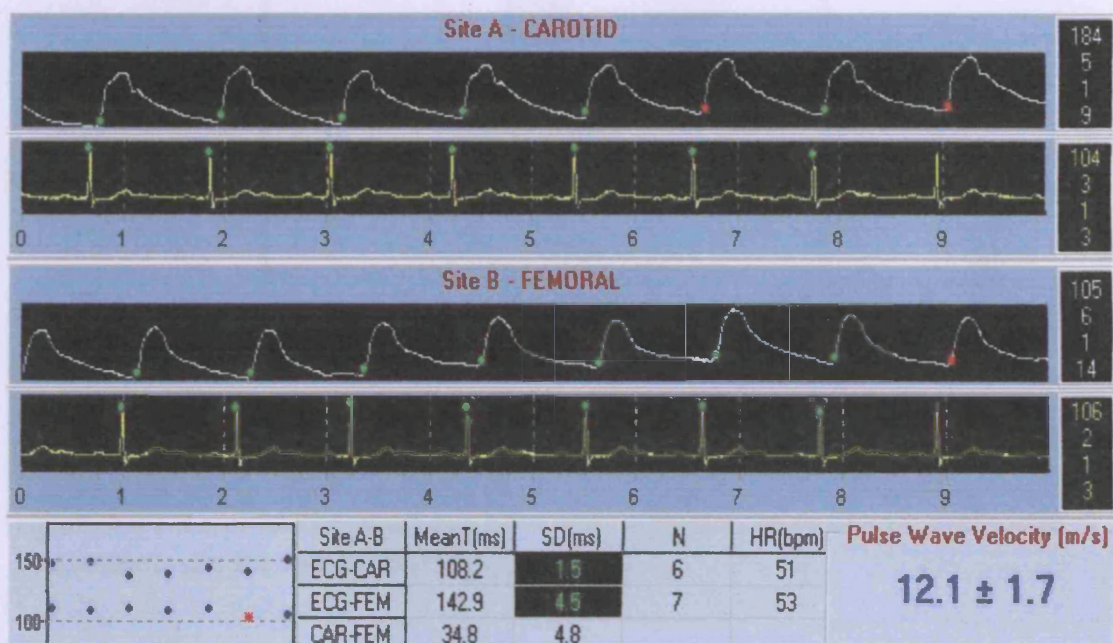
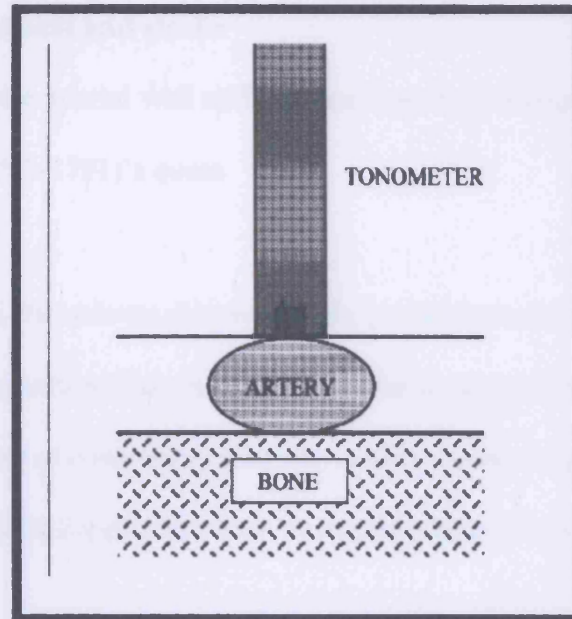


Figure 1:18 Principle of applanation tonometry.



The artery is gently compressed against the underlying bone, thus flattening it and equalizing circumferential pressures, allowing a high-fidelity pressure waveform to be recorded with the tonometer(220).

1.9.4 Arterial stiffness and stroke

The importance of the arterial wall stiffness has long been recognised as highlighted by John Wesley (1703-1791)'s quote

'In extreme old age, the arteries themselves, the grand instrument of the circulation, by the continual apposition of the earth, become hard, and as it were bony, till, having lost the power of contracting themselves they can no longer propel the blood, even through the largest channels, in consequence of which death naturally ensues.'

1.9.4.1 Measures of arterial stiffness

"However eloquent may be the words of a writer, he cannot in a page convey as clear an idea of the rhythm of the heart as a simple pulse-tracing, and if writers had given us more pulse-tracings, their works would have been greatly enhanced in value."

(James Mackenzie, 1902)

Although the importance of a simple pulse-tracing was described a century ago, over the past few years, it has been extensively studied in different population groups. The arterial stiffness and wave reflections have been widely investigated in hypertensives and in particularly, older subjects for various reasons. First, in the past DBP was considered a better guide to determine disease severity, but many large prospective, cross-sectional studies have shown that end-organ damage in hypertensive people is more strongly associated with SBP than DBP(221;222),

Second, epidemiological data suggested that SBP gave more information on cardiovascular risk. Third, PP was found to an independent cardiovascular risk factor(223;224).

1.9.4.2 Pulse Wave Analysis (PWA): Measurement of Wave Reflection

The pulsatile components of brachial blood pressure (SBP and PP) obtained by several prospective studies have highlighted importance of non-invasive central pressure measurements for 2 reasons.

First, just the central pressure, not the brachial pressure, directly affects the target organs. Second, the brachial pressure does not always represent the central pressure. In young adults, the amplitude of the brachial or radial pressure pulse may be 50% greater than that in the ascending aorta, whereas these pressures are of nearly equal magnitudes in the elderly(225). This difference between the young and elderly can be readily explained on the basis of wave reflection.

1.9.4.3 Wave Reflection

The forward pressure wave in an artery, transmitted from the central aorta, is reflected back (wave reflection) and amplified toward the periphery at any point of impedance discontinuity, such as arterial branching and arterial-arteriolar junctions (Figure 1:19). As a result, the pressure waveform recorded in the ascending aorta (or brachial artery) can be described as the sum of the forward pressure wave generated by the heart and the backward reflected pressure wave from the body. In the elderly, the reflected pressure wave from the body returns during early systole in the ascending aorta due to the arterial stiffness and augments the aortic PP to a similar degree as the brachial (low amplification). In contrast, in the young, wave reflection

affects neither the aortic PP nor the brachial PP because the reflected pressure wave returns during late systole or early diastole in the artery. Therefore, it cannot contribute to an increase in the aortic PP, and consequently results in high amplification.

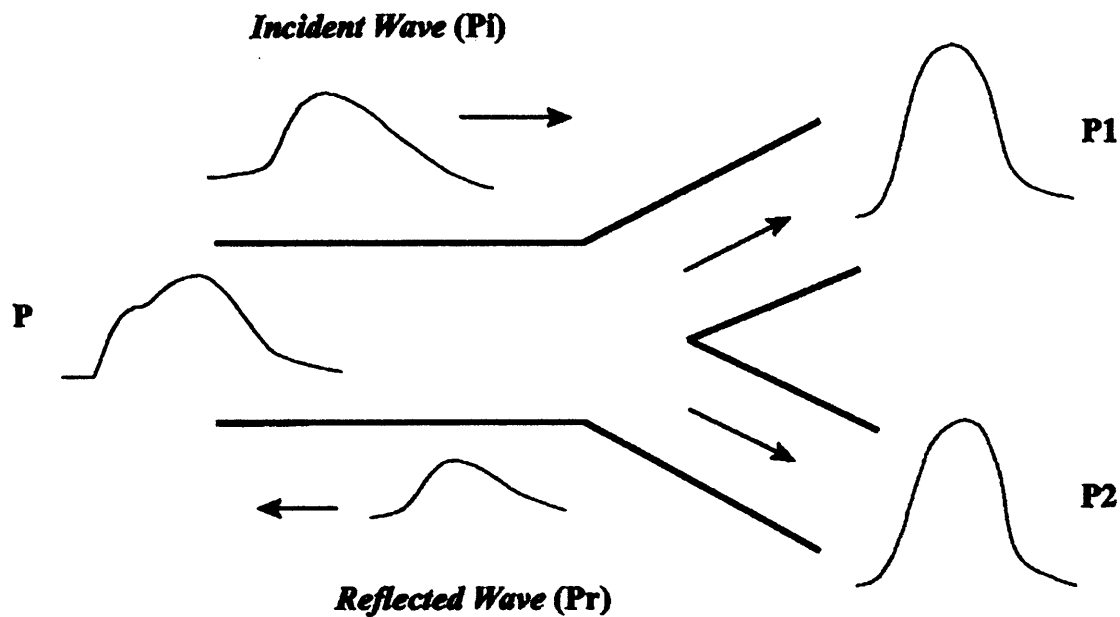


Figure 1:19 Aortic pressure waveform, and the pressure amplification at an arterial branch.

Backward pressure wave (P_r) reflected from the branch is superimposed with forward pressure wave (P_i) from the heart to generate the aortic pressure wave [$P = P_i + P_r$]. Incident pressure in the parent artery (P_i) is amplified by the impedance discontinuity. [$P_1 = P_2 = P_i + P_r$](226).

1.9.4.4 Augmentation index (AIx)

The augmentation index (AIx) is a representative surrogate of wave reflection and is defined as augmented pressure (magnitude of wave reflection) divided by PP (Figure 1:20). Fujii et al, for the first time, applied applanation tonometry to the non-invasive measurement of carotid AIx in clinical studies(227). Currently, from

PWA, it is possible to estimate the wave reflection in the aorta non-invasively and to generate central blood pressure from radial pressure waveforms with reasonable accuracy.

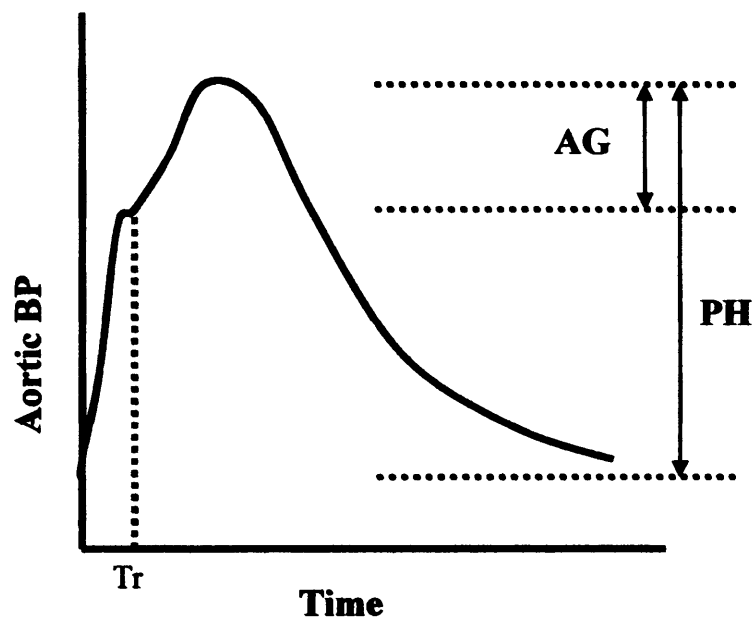


Figure 1:20 Derived aortic pressure waveform displaying time to reflected wave (Tr) and augmentation index (AIx).

PH (pulse height) is equivalent to pulse pressure, AG (augmentation) is the portion of pulse pressure resulting from the return of the pulse wave from distal reflecting sites. Aortic augmentation index = AG/PH (%) (226).

1.9.4.5 Generalized Transfer Function: The Principle of PWA

It is a known fact that any periodic wave can be divided into a set of sinusoidal waves, called the Fourier series, whose frequencies are all multiples of the frequency of repetition of the wave. Amplification of the central pressure, using Fourier analysis, is best expressed as the transfer function. The averaged transfer

function is named as the generalized transfer function and it accurately estimated the central systolic blood pressure (difference, $2.4 \pm 1.0 \text{ mmHg}$) (228). The central aortic measurements using a radial pressure waveform and the generalized transfer function (ie, PWA) have been validated by many studies and are regarded as a preferred method for non-invasive central blood pressure estimation (229-231). Figure 1:21 shows a representative trace of the radial pressure waveform recorded using high fidelity applanation tonometry and the reconstructed aortic pressure waveform using the generalized transfer function.

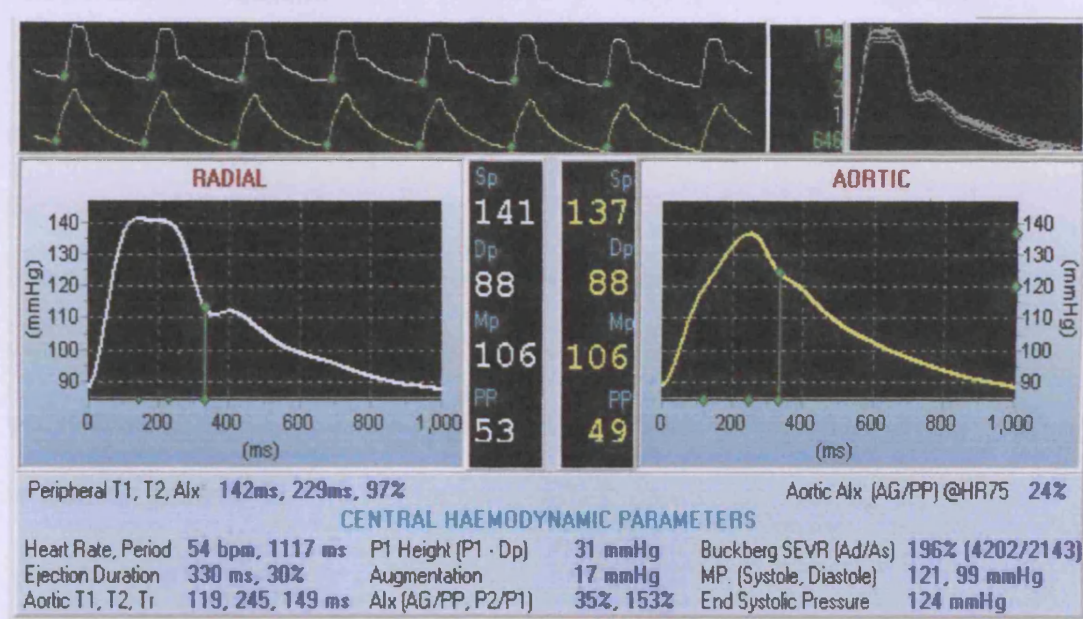


Figure 1:21 The Sphygmocardiograph: computerized report on analysis of radial artery and synthesized aortic pressure waves.

A series of radial artery pressure waves, recorded over a 10s period (upper continuous tracing) are used to synthesize a series of ascending aortic pressure waves (lower continuous trace) using a convolutional algorithm and a generalized transfer function. The radial waves are ensemble-averaged into a single wave (centre left), and the aortic waves into a single synthesized aortic wave (centre right), with the radial wave calibrated to brachial systolic and diastolic pressure, and integrated mean pressure taken to be identical at radial and aortic sites.

1.9.5 Effects of diseases on PWA

In most of the cardiovascular diseases (hypertension, diabetes mellitus and heart failure) PWA shows early wave reflection and late systolic pressure augmentation resulting in isolated high SBP and/or increased AIx(232).

1.9.5.1 Prognostic Value of Central Blood Pressure and AIx

There have been a relatively small number of prospective studies using PWA. Safar et al reported that carotid PP and AIx derived from the carotid pulse are independent risk factor for all-cause mortality in patients with end-stage renal disease (ESRD)(233;234). Weber et al reported the strong and independent association between the aortic AIx and the presence of coronary artery disease, and the prognosis after percutaneous coronary interventions(235;236). More recently, The Strong Heart Study confirmed that central PP is strongly associated with vascular hypertrophy, extent of atherosclerosis and cardiovascular events (HR 1.15 per 10 mmHg, $x^2 = 13.4$, $p < 0.001$)(237). However, AIx was not found to be high in diabetic group(238).

1.9.6 Pulse Wave Velocity (PWV)

There have been reports on the numerous indices of arterial stiffness; however, no single index has proved superior to the others. Of these indices, PWV is the most frequently used index in prospective studies.

1.9.6.1 Methodology of PWV

PWV is the measurement of the speed of the pressure waves that travel along the arterial segments(226). In practice, PWV was calculated as the distance/travelling time of the wave between 2 measuring sites of the pulse.

In addition to age, atherosclerosis and arteriosclerosis, PWV also increases with an increase in blood pressure but not influenced by wave reflection.

1.9.6.2 Prognostic Value of PWV

PWV was first identified as an independent risk factor for cardiovascular diseases in a prospective study conducted in France in 1999 that included patients with ESRD(239). In this study, the odds ratio for the subjects with $PWV \geq 12\text{m/s}$ was 5.4 when compared with the subjects with $PWV \leq 9.4\text{ m/s}$ for all-cause mortality.

Recent cohort studies confirmed the prognostic value of PWV in general clinical settings(240-243).

The value of central over peripheral pressure was confirmed in the Conduit Artery Function Evaluation (CAFE) substudy of the large Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)(244). ASCOT showed long-term superiority of new (amlodipine with or without perindopril) compared to old (atenolol with or without diuretic) therapy with respect to cardiovascular events. The modest reduction in brachial SBP of less than 1 mmHg with “new” therapy was 4 mmHg more when estimated for the central ascending aorta and similar to that found by Hirata et al(245) in their acute study. CAFE extends results of the pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd study (REASON)(246), which showed similar benefit of a perindopril/diuretic combination compared to atenolol

during a 12-month period. REASON showed a much greater decrease in calculated central (aortic and carotid) systolic pressure than in brachial pressure.

1.9.7 Relationship between arterial function and cardiovascular risk factors

Various factors like growth & development, ageing, exercise, body height, gender, and heart rate affect PWA, PWV and AIx. However, mechanism by which these 3 indices have an impact on the cardiovascular system is unclear. A vicious circle of large arterial disease is proposed (Figure 1:22), in which high central PP causes aortic dilatation and stiffening via elastin fiber fracture. Indeed, histological studies have confirmed thinning and fragmentation of elastin fiber in elastic arteries.

1.9.7.1 Ageing

Ageing is the dominant process affecting arterial stiffness, wave reflections and PP. Studies in normal subjects have shown a progressive increase in central PWV with age, indicating aortic stiffening(247-249). Furthermore arterial stiffness is accelerated in patients with hypertension(250) and ischaemic heart disease(251). Histological studies of elastic arteries show that, with increasing age, there is thinning and fragmentation of elastin fibres, smooth muscle cell degeneration and necrosis and collagen cross-linking on both elastin and collagen fibres(252). The amount of stiffer collagen in the human aorta doubles from age 20 to 70 years(253). These age-related changes in composition and structure of the elastic arterial media result in increase in arterial stiffness and PWV. The age-related changes in elastin and the increase in collagen are, however, not seen in muscular arteries where there is apparently no age-related increase in stiffness or PWV(226;254). An increase in central AIx and PP is also observed with increasing age. In contrast to the fact that

there is an increase in AIx of radial, carotid and aortic pressure with an increase in age(255), preliminary Framingham data, while confirming the age-related increase in central PWV, shows little age-related increase in carotid AIx(256).

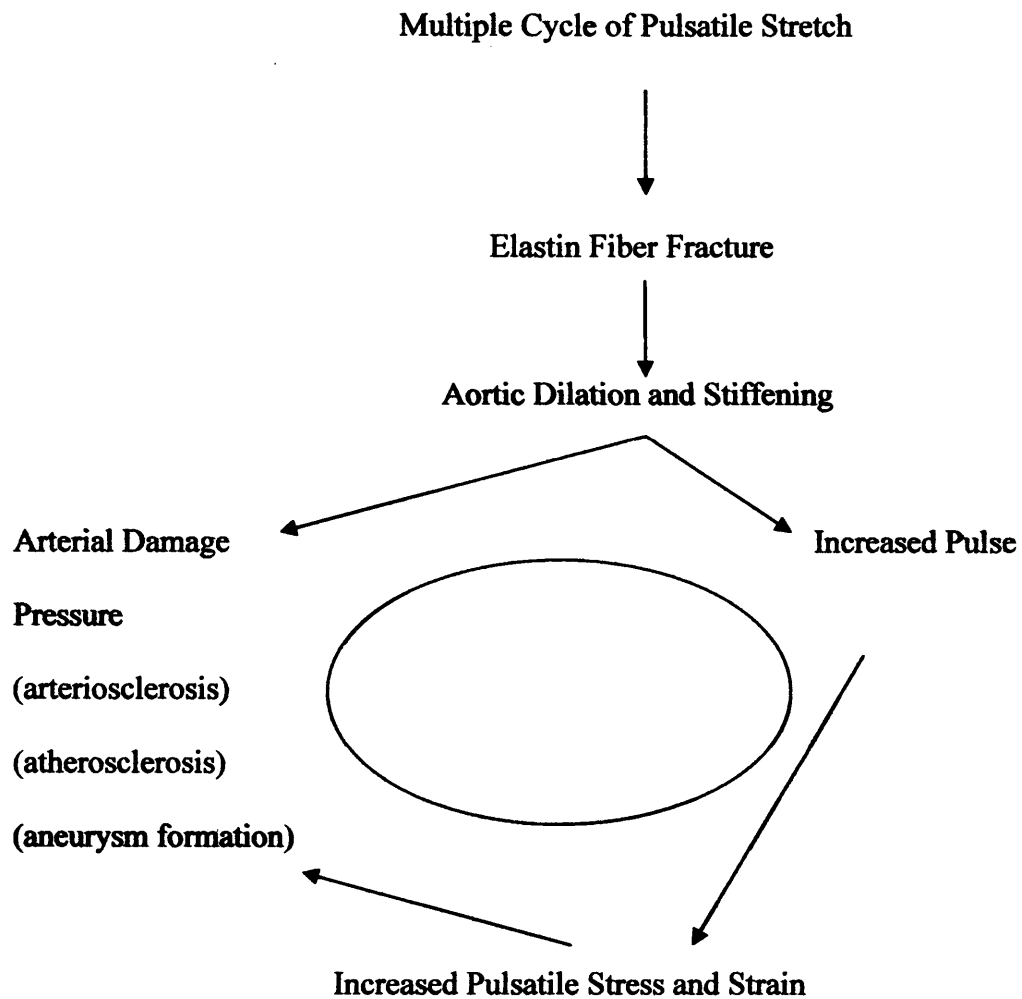


Figure 1:22 The vicious cycle of large arterial disease
Taken from Hirata et al 2006(257).

1.9.7.2 Heart Rate

Heart rate is linked to PP. However, there are conflicting data on relationship between arterial stiffness parameters and heart rate, showing positive association with PWV(258;259), no association with PWV and negative relationship with AIX(260). These findings may have implications when arterial stiffness is measured in subjects who take heart-rate limiting antihypertensives.

1.9.7.3 Perspectives

Despite the advances in understanding of global cerebrovascular disease risk factors it has been estimated that only half of cerebrovascular disease risk is explained by conventional risk factors alone(261). Although in their infancy and not utilised in routine clinical practice, researchers have suggested that arterial stiffness measures offer greater insight into the interaction between the heart and arteries and it might provide additional, and more powerful, cardiovascular prognostic information.

Despite non-invasive nature and simple to measure, AIX, PWV and central PP have not been studied in stroke population yet. It is known that cerebral autoregulation and cardiac baroreceptor sensitivity (BRS) are impaired following acute stroke(262;263). We have demonstrated that cardiac BRS and pulse wave velocity are inversely related following acute stroke when measured in < 48 hours of stroke onset(264) and an impaired cardiac BRS is associated with poor long-term mortality(262).

Summary and gaps

- **Applanation tonometry provides data on arterial function: the arterial waveform (pulse wave analysis), the arterial stiffness of vessel segments (pulse wave velocity) and central BP.**
- **Arterial stiffness of central arteries occurs in conditions that are associated with increased cardiovascular risk, e. g., ageing, hypertension, diabetes mellitus and smoking**
- **Arterial stiffness may mediate increased stroke risk through increase in central PP, but other mechanisms may also be involved.**

We postulate the following hypotheses

- 1) Cardiac baroreceptor sensitivity does predict early (2-week) outcome following acute stroke.**
- 2) Central, rather than peripheral, arterial compliance is a better predictor of cardiac baroreceptor sensitivity and is an independent predictor of outcome following acute stroke.**
- 3) There is relationship between baseline cardiac BRS and aortic PWV in treated hypertensive patients following stroke.**

2 METHODOLOGY

Studies presented in chapter three to five of this thesis represent sub-studies of the main COSSACS (Continue Or Stop post-Stroke Antihypertensive Collaborative Study) trial. The methodology of the main COSSACS trial will now be considered, with specific methodology related to the sub-studies presented in the relevant chapters.

2.1 Study methodology

2.1.1 Study Design

The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) is a United Kingdom multi-centre, prospective, randomized, open, blinded-endpoint (PROBE) study supported by Health Foundation to assess whether existing antihypertensive therapy should be continued or discontinued within the first 48 hours for the first two weeks following acute ischaemic and haemorrhagic stroke.

2.1.1.1 Study Population

2900 patients admitted to Acute Stroke Units/ Medical Units at United Kingdom Teaching and District General Hospitals within 48 hours of onset of suspected stroke and within 48 hours of last dose of medication with a recognized antihypertensive effect (see sample size calculation – section 2.5.1).

2.1.1.2 Study Treatment Plan

All routine aspects of the management of patients with suspected stroke with respect to investigation (including haematology, biochemistry, chest radiology and

electrocardiography), acute management and rehabilitation was continued as standard local practice. This includes four-time daily casual BP observations and the timing of introduction of antithrombotic therapy.

2.1.1.3 Inclusion Criteria

- Age >18 years.
- Stroke onset <48 hours. For patients waking with suspected stroke, time of onset will be taken as last time patient documented to be asymptomatic.
- Clinical diagnosis of suspected stroke, with neuroimaging before or following study entry to exclude non-stroke diagnoses and to define ischaemic and haemorrhagic stroke.
- Currently receiving antihypertensive therapy and within 48 hours of last dose (Classes of antihypertensive therapy include: thiazide diuretics, beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, angiotensin-II antagonists, alphablockers, and centrally acting agents).
- Informed patient consent, or relative/ carer or independent clinician assent for COSSACS.

2.1.1.4 Exclusion Criteria

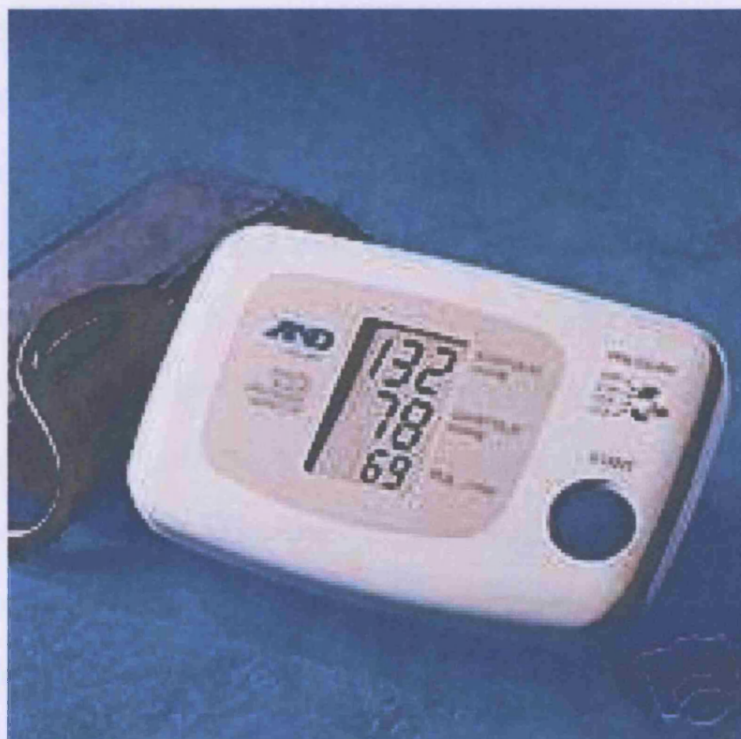
- Hypertensive encephalopathy (Indication for urgent introduction of antihypertensive therapy).
- Hypertension >200/ 120mmHg in association with intracerebral haemorrhage
- Co-existing cardiac or vascular emergency, e.g. aortic dissection

- Contraindications to stopping antihypertensive therapy, e.g. betablockers for angina, clonidine as risk of rebound hypertension.
- Impaired conscious level (National Institutes of Health Stroke Scale (NIHSS) Section 1a score >2).
- Dysphagia. Defined on the basis of a standardized bedside swallow assessment by appropriately trained personnel.
- Premorbid dependence (Modified Rankin Score (mRS >3)).
- Co-existing life-threatening condition with life expectancy <6 months.
- Females of child-bearing potential.
- Non-stroke diagnoses (on subsequent neuroimaging).

2.1.2 Pre-randomisation

Patients underwent two sets of three casual BP monitoring, using the mean of multiple BP recordings using the UA-767 PC monitor (Figure 2:1) with appropriate sized cuff in the supine position – two sets of 3 readings repeated 10-minutes apart. BP monitoring conducted by appropriately trained research staff at participating study centres. Patients with a mean SBP >100mmHg from all six readings and currently taking antihypertensive therapy were considered for entry into the study (see sample size calculation – section 2.5.1).

Figure 2:1 A&D Automatic Digital Blood Pressure Monitor UA767



2.1.3 At randomisation

For those patients who fulfil the inclusion/ exclusion criteria, the Medical Site Investigator obtained patient consent and/ or relative/ carer/ independent clinician assent, and then randomized the patient using the central randomization service that is part of the secure COSSACS website (<http://cossacs.cvsu.co.uk>). The patients were randomized to continue or discontinue pre-existing antihypertensive therapy, and the relevant medication recorded on the drug prescription chart.

Antihypertensive therapy prescription was confirmed with the patient's General Practitioner, as well as reviewing the treatment brought into hospital by the patient. For those patients randomized to the continuation arm, treatment was given when the next dose would normally be due. Photocopies of the patient prescription charts were forwarded to the Trial Co-ordinator to record treatment compliance for each patient. Those patients randomized to the continuation arm of the study who become dysphagic and were subsequently unable to be administered oral medication were considered on an intention-to treat basis in the analysis.

Specific baseline functional assessments performed at randomisation include the Modified Rankin score (Appendix: 1) (also retrospective premorbid) and Barthel Index (Appendix: 1). Specific baseline neurological assessments performed at randomisation include the National Institutes of Health Stroke Scale (Appendix: 1) and the Oxfordshire Community Stroke Project Classification (Appendix: 2). The neurological assessments were repeated 24 hours following randomisation to identify those patients with transient ischaemic attack. All researchers were trained and appropriately certified to undertake the afore mentioned assessments.

2.1.4 At day 14

Repeat assessments were completed at this time point, and included BP measurement, Modified Rankin Score, Barthel Index and the National Institutes of Health Stroke Scale. After this assessment, BP management was at the discretion of the local investigator, though this would follow British Hypertension Society guidelines in most cases(265).

2.1.5 At 6-monthly intervals

The patients' Primary Care Physicians were contacted by telephone at 6-month to identify current treatment and intervening vascular complications. Furthermore, the COSSACS Trial Office recorded mortality, as well as cause of death and prior non-fatal vascular events. The co-ordinating centre also collected data on International Stroke Trial Questionnaire(266;267) (Appendix: 3) and EuroQOL(268-270) (Appendix: 4) at 6 months following stroke. Death was noted from the NHS Register.

2.2 Study Measurements

2.2.1 Primary Efficacy Measures

The primary outcome measure will be the proportion of patients who are dead or dependent in personal activities of daily living (defined by a mRS >3) at 14 days post-stroke.

2.2.2 Secondary Efficacy Measures

2.2.2.1 Early Secondary Efficacy Measures

The following secondary outcome measures will be assessed at 14 (+2) days:

- Neurological deterioration as defined by an increase in NIHSS score >4(271)
- Functional status as determined by the Barthel Index.
- BP changes between admission and day 14 assessed by casual BP monitor methods.
- Discharge destination (home with/ without person, residential or nursing home, hospital, death).
- Serious adverse and adverse events.

2.2.2.2 Late Secondary Efficacy Measures

The following secondary outcome measures will be assessed at 180 (+5) days:

- Death and dependency in personal activities of daily living (mRS>3).
- Fatal and non-fatal stroke recurrence.
- Health-related quality of life assessed by the International Stroke Trial Questionnaire and EuroQOL
- Discharge destination (home with/ without person, residential or nursing home, hospital, death).

All study measurements will be performed by appropriately trained research nursing staff at the participating centres. In particular, staff will be reviewed annually throughout the study in the application of the National Institutes of Health Stroke Scale, Modified Rankin Score, and Quality of Life measures, using training and assessment packages already available.

2.2.3 Safety Measures

A serious adverse event form should be completed for all serious adverse events occurring within the first 14 days. The form should be faxed to the coordinating centre within one working day as well as the data being inputted onto the secure COSSACS website. A serious adverse event is defined as an adverse event that results in death, is life threatening (i.e. the patient was at immediate risk of death from the adverse event as it occurred), or required in-patient hospitalisation or prolongation of existing hospitalisation. Adverse events within the first 14 days will also be collected and input onto the secure COSSACS website as well as being forwarded at monthly intervals to the coordinating centre. An adverse event is defined as any unintended and unfavourable sign, symptom or disease temporally associated with the use of the study therapy, whether or not causally related to the product. For all serious adverse and adverse events, the centre co-investigator is required to assess the causal relationship to the study therapy according to the following classification:

- (1) Probable – time relationship exists and no other possible causative factor exists;
- (2) Possible – time relationship exists and other possible causative factor may exist;
- (3) Unlikely – time relationship non-existent or doubtful and/ or other factor certain or probable to have been causative.

2.3 The Data and Safety Monitoring Committee

It will monitor serious adverse and adverse event reports throughout the trial. This independent committee will conduct safety reviews at predetermined intervals, and, if appropriate, recommend to the Steering Committee to suspend or amend the study protocol.

2.4 Data Management

All data will be inputted directly onto the secure COSSACS website

(<http://cossacs.cvsu.co.uk>) at randomisation, and follow-up.

At study entry, the following data will be recorded: inclusion/ exclusion criteria, randomisation details, baseline information (to include demographics, risk factors, stroke classification, and baseline neurological and functional assessments), and BP measurements. At two weeks post-stroke, data with respect to BP measurements, treatment schedule, and adverse events will be recorded. At 14 days and 6 months, the following data will be recorded: BP measurements; current treatment (including antihypertensive therapy); neurological, functional and quality of life outcomes; adverse events; and place of residence.

The maintenance of an accurate, up-to-date, and complete study database will be the responsibility of the study coordinator. The study coordinator will also generate data queries to be returned to the co-investigators.

2.5 Statistical Considerations

The primary analysis will be on an intention-to-treat analysis. All major analyses involve the comparison of the proportions of subjects with events, and differences in proportions between continuation and discontinuation groups will be presented with 95% confidence intervals. BP changes and adverse event data will be assessed with descriptive statistics.

Logistic regression analysis will be used to assess the effect of continuation versus discontinuation of antihypertensive therapy on death and dependency corrected for baseline prognostic factors, including: age, sex, stroke type and subtype, and admission BP.

2.5.1 Sample Size Calculation

Assuming an overall rate of 60% death and dependency at 14 days post-stroke(272), a study patient population of 2900 would have an 90% power at the 5% significance level to detect a relative reduction of 10% (absolute risk reduction of 6%) in death and dependency between continuation and discontinuation groups at 2 weeks. A total of 8400 patients will need to be screened to enable this population size to be recruited, allowing for patients on treatment (40%) and patient dropout (15%). The degree of risk reduction sought is in keeping with the IMAGES Trial (5.5% absolute risk reduction).

2.6 Patient Data Protection

Patient number and initials will identify all patient data computerheld at the Coordinating Centre only. These data will be stored and analysed in accordance with national data legislation.

2.7 Ethics

2.7.1 Good Clinical Practice

The study is performed in accordance with the principles stated in the Declaration of Helsinki. The conduct of the study accorded to the principles of Good Clinical Research Practice. The study has a valid multi-centre research ethics committee

approval (MREC: 02/4/051). It is also in accordance with the European research ethical requirement (EudraCT: 8000/13247).

2.7.2 Patient Information and Consent

Consent will be obtained according to the requirements of the Multi-centre and Local Research Ethics Committee.

The patient will receive full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. A copy of the Patient Information Sheet and the signed Consent Form will be provided to the patient. The patients will be notified that they will be free to discontinue their participation in the study at any time.

Due to the nature of stroke, communication problems are common. As approved by the Multi-centre and Local Research Ethics Committee, the witnessed agreement of an immediate relative or guardian will be sought and the Relative's Assent Form will be completed. In such cases, patient consent will be sought following sufficient recovery, and the Patient Confirmation of Consent Form will be completed.

2.7.3 Study Monitoring

The Coordinating Centre will be responsible for individual site monitoring. Trial coordinator will contact and visit each co-investigator's site regularly. These contacts will confirm that facilities were acceptable, that the investigational team was adhering to the protocol, that data were being accurately recorded, and will provide information and support to the co-investigator. The trial coordinator will

also ensure that drug accountability was being carried out. Source data verification (in accordance with patient confidentiality) will also be performed.

2.7.4 Sponsorship

The study was sponsored by University Hospitals of Leicester NHS Trust.

2.7.5 Funding

The study was funded by The Health Foundation. The sub-studies were funded by The Stroke Association, UK.

2.7.6 Medicines and Healthcare products Regulatory agency (MHRA)

COSSACS is being regulated by MHRA. MHRA is a government agency which is responsible in ensuring that medicines are acceptably safe.

3 HAEMODYNAMIC PREDICTORS OF EARLY OUTCOME FOLLOWING ACUTE STROKE IN TREATED HYPERTENSIVE PATIENTS

3.1 Background and aims

From the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study and work by Kleiger et al, it is clearly established that abnormal autonomic regulation, as measured by heart rate variability (HRV) and cardiac baroreceptor sensitivity (BRS), are independent predictors of death after myocardial infarction(180;181). In all of the other observational studies of patients after myocardial infarction, a depressed HRV measured from a 24-h period as well as from shorter duration recordings has been consistently associated with an increased risk of cardiac and overall mortality(181-185). This finding has been extended to patients with hypertension(187) and diabetes(188;189).

The Finapres is an automated device that measures beat-to-beat BP non-invasively. It has now been widely validated against intra-arterial measurements and has been shown to accurately demonstrate BP trends(273). The influence of HRV, BRS, beat-to-beat BP, beat-to-beat BP variability and 24 hour BP on stroke outcome has been examined in various observational studies. An elevated beat-to-beat MAP (mean Arterial Pressure) and a higher beat-to-beat MAP variability measured within 72 hours post-ictus is associated with increased risk of death/dependency(274) on day-30. Similarly, in 219 stroke patients, a higher 24 h systolic BP (> 160 mmHg) was associated with hazards ratio of 2.41 (95% CI: 1.24, 4.67) for death, compared to the reference group (SBP 140 to 159 mmHg) for over a 2.5 year follow-up(74). The TAIST group demonstrated that poor 6-month death and dependency (mRS >2) in 1484 acute ischaemic strokes (48 hours post-ictus) was related to high SBP (adjusted OR 1.11; 95% CI (1.03, 1.21)), PP (adjusted OR 1.14; 95% CI (1.02, 1.26)), and MAP (adjusted OR 1.15; 95% CI (1.02–1.31))(109).

Acute stroke patients (72-hours post-ictus) with impaired BRS values ($\leq 5\text{ms/mmHg}$) had a significantly poorer prognosis (28% versus 8% mortality rate during 4-year follow-up period), though there were no differences in age, stroke severity, stroke type, or casual or 24-hour BP parameters between the 2 groups(262).

In over 2000 subjects with essential hypertension (mean age 51 ± 12), after adjustment for age, sex, and diabetes, for every 10 mm Hg increase in 24-hour MAP, the risk of cerebrovascular events increased by 42% (95% CI 19% to 69%) and 24-hour MAP was an independent predictor of fatal cerebrovascular events(275).

All of the above observational studies examined the relationship between acute haemodynamic parameters (either casual or 24-hour) and long-term (≥ 30 days) outcome. However, the predictive value of such parameters for early (2 weeks) outcome in previously treated hypertensive stroke patients is unknown.

The aim of the study was to examine relationship between acute stroke haemodynamic parameters and early (2-week) death and dependency in previously treated hypertensive acute stroke patients.

3.2 Methods

3.2.1 Subjects

One hundred and six patients with a clinical diagnosis of acute stroke and treated hypertension were recruited from COSSACS (Continue or Stop post-Stroke

Antihypertensive Collaborative Study). From patients fulfilling the inclusion/exclusion criteria 3.2.3 and 3.2.4), informed patient consent and/ or relative/ carer/ independent clinician assent was obtained, and then the patient was randomised using the central randomisation service that is part of the secure COSSACS website. The patients were randomised to continue or discontinue pre-existing antihypertensive therapy, as described earlier(276).

Each subject was assessed at one of three different sites (Bournemouth, Exeter and Leicester). Specific baseline functional assessments at randomisation included the Modified Rankin score and Barthel Index. Baseline neurological assessments included the National Institutes of Health Stroke Scale (NIHSS) and the Oxfordshire Community Stroke Project (OCSP) Classification(277) (see Appendix: 1 and Appendix: 2). All patients were haemodynamically stable.

All patients had a CT or MRI. With the use of neuroimaging, patients were subdivided into cortical, sub-cortical, both cortical and sub-cortical and normal neuro-imaging or established changes.

3.2.2 Ethics

The study was supported by the local ethics committee (MREC: 02/4/051, LREC : 6837 M), and all participants (or their carers where appropriate) gave written informed consent (see Appendix: 6).

3.2.3 Inclusion criteria

Similar to COSSACS (see section 2.1.1.3).

3.2.4 Exclusion criteria

In addition to COSSACS (see section 2.1.1.4)

Atrial fibrillation

Diseases known to be associated with autonomic dysfunction or impaired cardiac

BRS (acute myocardial infarction, unstable angina, left ventricular failure).

Ectopics >2%

3.2.5 Pre-randomisation

Assessment similar to COSSACS (see section 2.1.2). A total of three centres participated, Leicester being the coordinating centre (contributed 80% of the patient recruitment) and Exeter and Bournemouth (recruited 10% each).

3.2.6 At randomisation

Additional measurements were undertaken on patients participating in the Relationship of Cardiac BRS and Large Artery Function to Prognosis Following Acute Stroke Sub-study at the following time points:

3.2.7 Within 24 hours

Patients enrolled in the sub-study were studied in a quiet dedicated research room within 24 hours of stroke onset. Patients were asked to avoid caffeinated products for 4 hours, and cigarettes and alcohol for 24 hours before the study period. They were also asked to micturate immediately prior to resting supine on a bed or couch. Patients initially underwent a 5-minute period of continuous non-invasive beat-to-beat BP recording using the FinapresTM device (Finapres 2300, Ohmeda, USA, Figure 1:11), applied to the hemiparetic hand. Three electrocardiographic (ECG)

electrodes were positioned on the chest to obtain an ECG signal (model Cardiorater CR7, Cardiac Recorders Limited), and an elasticated waistband was placed around the patient's abdomen to record the rate and depth of respiration. After a period of >15 minutes rest and achievement of satisfactory stable BP (mean 2-minute BP levels not varying by >10 mm Hg over ≥ 10 minutes), ECG and respiratory rate, recordings were performed for 3 sequential periods of 5 minutes whilst ensuring that the patient remained awake, onto a magnetic DAT tape for later offline analysis. During study test the Finapres was connected via an appropriately sized adjustable finger cuff to the middle finger of the hemiparetic arm, and maintained at heart level throughout. If sustained appropriate signals were not achieved with the Finapres on the middle finger, the ring finger, index finger or any alternative was then tried. If this failed, measurements were then made in the non-hemiparetic hand. However, if the finger site was 'cold', then the finger was warmed up (soaked in warm water) and covered to reduce heat loss (this was the case in 3 patients). During the recording, light was kept dimmed, there was no direct communication with the patient and any other external stimuli were minimized as described below. The arterial pressure waveform together with the analogue ECG signal and respiratory signals were converted to a digital signal using a dedicated PC fitted with an analogue to digital converter board at 500 Hz and saved as a file for off-line analysis (See section 3.4 and Figure 3:1). This was performed using software specially written for the department by Professor R Panerai in the Department of Medical Physics at Leicester University.

Figure 3:1 Equipment used to acquire cardiac BRS data



3.3 Outcome

Early outcome was assessed using the modified Rankin score (graded 0 to 6, 0 as asymptomatic and 6 as death) at 2 week post-ictus.

3.4 Data Analysis

3.4.1 Cardiac BRS

Three 5 min continuous recording of pulse interval (PI) from a three-lead surface ECG and finger arterial BP using a Finapres device was conducted. Offline analysis of the beat-to-beat BP and PI recordings were performed using departmental software.

Power spectral analysis of the re-sampled tracings was performed by means of Fast-Fourier transformation with 256 samples, as described previously(278) , and estimates of cardiac BRS were obtained by calculation of the square root of the ratio of the powers of PI to SBP in the LF (low-frequency) band (0.05 to 0.15 Hz; cardiac BRS LF). Normalized LF and HF (high frequency: 0.15 to 0.40 Hz) powers for PI were calculated and the LF/HF ratio was used as an index of sympathovagal balance.

Cardiac BRS was also calculated using time domain method with help of departmental software. This resulted in up-BRS (three or more consecutive beats during which SBP is increased by at least 1 mmHg per beat, while RR interval progressively prolongs) , down-BRS (three or more consecutive beats during which SBP is decreased by at least 1 mmHg per beat, while RR interval progressively shortens) and all-BRS sequences.

3.4.2 Casual BP

Two sets of three successive casual oscillometric brachial BP in the non-hemiparetic limb were measured using a monitor validated by the British Hypertension Society (UA-767; A&D Company Ltd, Tokyo, Japan). The mean of the six recordings was used in the analysis. Pulse Pressure (PP) was derived as difference between SBP and DBP. Mean Arterial Pressure (MAP) was calculated as DBP plus one-third of PP.

3.4.3 BP Variability (BPV)

BPV was calculated with the use of the standard deviations of the beat-to-beat recordings (time-domain) and from square root power of beat-to-beat BP (frequency-domain). The mean of the results from the 3 periods was used in the final analysis.

3.4.4 PI variability

PI was calculated with the use of the standard deviations of the beat-to-beat recordings (time-domain) and from square root power of beat-to-beat PI (frequency-domain). The mean of the results from the 3 periods was used in the final analysis.

3.5 Statistical Analysis

All normally distributed continuous variables are described as mean (SD), skewed continuous variables as median with inter quartile range (IQR). Student 't' test is used to compare variables between two independent groups when data were normally distributed. Mann-Whitney U test was used for data that were nonparametric and not normally distributed. When baseline parameters were skewed, logarithm transformation was used to obtain approximate normal distributions. For continuous outcome

comparing relationship of cardiac BRS, PI variability, BP variability and 2-week death/dependency, general linear regression analysis was used.

All baseline variables were divided into nine subgroups.

It is known that age, gender, ethnicity, stroke severity, stroke type, beat-to-beat BP and variability, cardiovascular risk factors affect outcome. We separated all variables in such a way that each sub-group represented clinically relevant variables as follows:

- age, baseline NIHSS and mRS
- Beat-to-beat SBP (FinSBP), DBP (FinDBP), MAP (FinMAP) and SBP LF/HF ratio (low frequency to high frequency ratio)
- beat-to-beat SBP variability (FinSBPv), DBP variability (FinDBPv), MAP variability (FinMAPv) and square root power of SBP
- gender, ethnicity, new (Angiotensin Converting Enzyme inhibitor - ACE, Angiotensin Receptor Blocker - ARB, Calcium Channel Blocker - CCB) vs old antihypertensive (Beta blocker - BB and or diuretic) medications
- Past history of stroke, ischaemic heart disease (IHD), admission plasma glucose and cholesterol
- OSCP classification, laterality of stroke, cortical vs non-cortical stroke
- PI mean (pulse interval), PI SD (PI variability), square root power PI, and PI LF/HF ratio
- Frequency domain: BRS alpha, BRS LF and BRS HF
- Time domain: up BRS, down BRS and all BRS sequences

Each variable group was used in a single variable linear model where age and baseline NIHSS were forced into the model. The variables in each of the above groups were

examined for a linear relationship. If a linear relationship was found then only one variable was entered into the univariate analysis. The variable with significant values ($p < 0.05$) from each group was tested in the final model. Thus, the final relationship of baseline variables and 2-week outcome was tested.

The analysis was carried out using SPSS version 12.0 for Windows. 5% level was considered significant.

3.6 Results

Of 106 subjects, twelve were excluded from final analysis due to poor quality of data. The demographic characteristics are described in Table 3:1 and Table 3:2.

Ninety-four patients were studied (51 men, 43 women, mean age 72.4 (12.5) years, range 45 to 104 years) with a mean casual BP of $152 \pm 22 / 81 \pm 13$ mmHg and mean arterial BP (MAP) of 104 (15) mmHg, with a mean Barthel Index of 12 (6), mean mRS of 3 (1) and median NIHSS of 5 (IQR 3 to 9).

OCSF classification(277) (see Appendix: 2) subdivided stroke patients into TACS (13%), PACS (38%), LACS (35%) and POCS (14%). Only 79 patients could be classified according to TOAST classification(279) (see Appendix: 5). Other baseline variables are stated in Table 3:1.

There were a total of 2 deaths at 2-weeks. The median mRS at 2-week was 2(IQR 1, 4). Outcome at 2-week showed a strong correlation with age ($r = 0.38$, $p < 0.001$). In age adjusted models baseline measurements such as mRS and NIHSS showed strong relationships with outcome ($r = 0.61$, $p < 0.001$) and ($r = 0.63$, $p < 0.001$) respectively.

The relationship of each variable group with 2-week outcome in regression analysis is shown in Table 3:3.

Baseline variables	Values *
Age, yrs	72.4 (12.5)
Sex (male), n (%)	51 (54)
Time from stroke onset to randomisation, hours	22 (9.45)
Time from last anti hypertensive treatment, hours	20 (11.35)
Smoking, n (%)	14 (15)
Stroke severity & disability	
NIHSS (median (IQR))	5 (3, 9)
Barthel index	12 (6)
mRS (median (IQR))	4 (2, 4)
OCSF, n (%)	TACS: 12 (13)
	PACS: 36 (38)
	LACS: 33 (35)
	POCS: 13 (14)
Type of stroke (from CT or MRI)	
Cortical, n (%)	30 (32)
Sub-cortical, n (%)	36 (38)
Both, n (%)	7 (8)
Normal or old changes, n (%)	21 (22)
TOAST classification (n=79)	
Large vessel disease, n (%)	4 (5)
Cardioembolic, n (%)	14 (18)
Lacunar, n (%)	17 (22)
Unclassified, n (%)	39 (49)
Haemorrhage, n (%)	5 (6)
Pre-existing diseases	
History of stroke, n (%)	20 (21)
Diagnosed diabetes mellitus, n (%)	8 (9)
History of Ischaemic Heart Disease, n (%)	21 (22)

Table 3:1 (A) Demographic details of patients

*Values as mean (SD) or values as stated, OCSF: Oxfordshire Community Stroke Project(277), TOAST: Trial of Org 10172 in Acute Stroke Treatment(279)

Antihypertensive use	Values *
'Old' (Beta blocker and/diuretic), n (%)	30 (32)
'New' (ACE inhibitor, Angiotensin receptor blocker, Calcium channel blocker, Alpha blocker), n (%)	25 (27)
Both, n (%)	39 (41)
Casual BP parameters	
SBP, mmHg	152 (22)
DBP, mmHg	81 (13)
PP, mmHg	72 (16)
MAP, mmHg	104 (15)
Beat-to-beat BP parameters	
SBP, mmHg	146 (22)
DBP, mmHg	72 (15)
PP, mmHg	74 (20)
MAP, mmHg	96 (16)
Cardiac alpha BRS, ms/mmHg (median, IQR)	4.57 (3.20, 6.82)
Heart rate variability, ms (median, IQR)	30.17 (23.12, 46.95)

Table 3:2 (B) Demographic details of patients

*Values as mean (SD), values as stated

SBP: systolic BP, DBP: diastolic BP, PP: pulse pressure, MAP: mean arterial pressure

Model	Variable	Coefficient	95% Confidence Interval		P
1	Age	0.031	0.010	0.052	0.004
	NIHSS	0.148	0.067	0.230	0.001
	mRS	0.367	0.103	0.630	0.007
2	FinMAP	-0.020	-0.037	-0.004	0.016
	FinSBP	-0.012	-0.025	0.002	0.085
	FinDBP	-0.005	-0.025	0.015	0.618
3	FinMAPv	-1.031	-2.189	0.126	0.080
	FinSBPv	1.017	0.124	1.910	0.026
	FinDBPv	-1.295	-2.248	-0.342	0.008
	Square root powerSBP	0.759	-0.234	1.752	0.132
4	Ethnicity	0.115	-0.788	1.018	0.800
	Gender	0.325	-0.236	0.885	0.253
	New vs Old antihypertensives	-0.358	-0.999	0.284	0.271
5	History of stroke	-0.438	-1.081	0.205	0.179
	History of IHD	-0.196	-0.822	0.430	0.535
	Admission glucose	0.082	-0.064	0.227	0.270
	Admission cholesterol	0.149	-0.104	0.402	0.245
6	OCSF classification	0.034	-0.361	0.428	0.866
	Hemisphere laterality	0.373	-0.142	0.889	0.154
	Cortical	0.626	0.029	1.224	0.040
	Cortical & subcortical	1.595	0.627	2.563	0.002
	Normal neuro-imaging or old changes	0.248	-0.392	0.887	0.443
7	PI mean	-0.001	-0.003	0.001	0.448
	PI variability	-0.020	-0.565	0.524	0.941
	PI LF/HF	-0.045	-0.350	0.261	0.773
	Square root power PI	0.121	-0.358	0.600	0.618
8	BRS alpha	-0.119	-0.513	0.276	0.552
9	All BRS sequence	-0.024	-0.407	0.360	0.903
	Up BRS sequence	0.036	-0.348	0.420	0.852
	Down BRS sequence	-0.064	-0.426	0.298	0.726
Final	Cortical vs subcortical	0.400	-0.205	1.005	0.192
	Normal neuro-imaging or old changes	0.003	-0.655	0.661	0.993
	Cortical and subcortical	1.422	0.399	2.444	0.007
	Age	0.029	0.008	0.050	0.007
	FinMAP	-0.018	-0.035	-0.001	0.043
	NIHSS	0.222	0.163	0.281	<0.0001

Table 3:3 Relationship of baseline variables and 2-week outcome in regression analysis

FinMAP:beat-to-beat MAP, FinSBP: beat-to-beat SBP, FinDBP:beat-to-beat DBP, FinMAPv: beat-to-beat MAP variability, FinSBPv: beat-to-beat SBP variability, FinDBPv: beat-to-beat DBP variability, IHD: ischaemic heart disease, PI: pulse interval, LF/HF: low to high frequency ratio, NIHSS: National Institutes of Health Stroke Scale

	Δ Increase in a risk factor	Model A	Model B
Risk factors			
Age, years	5 years	0.26 (0.13, 0.40)***	0.07 (-0.04, 0.18)
mRS baseline	1 unit	0.79 (0.60, 0.98)***	0.38 (0.13, 0.63)**
NIHSS baseline	1 unit	0.25 (0.19, 0.31)***	0.14 (0.06, 0.22)**
Beat-to-beat MAP, mmHg	10 mm Hg	-0.30 (-0.54, -0.07)*	-0.27 (-0.45, -0.10)**
Type of stroke			
Cortical vs. sub-cortical		1.19 (0.41, 1.97)**	0.58 (0.01, 1.15)*
Cortical and sub-cortical vs. sub-cortical		2.53 (1.23, 3.83)***	1.46 (0.53, 2.38)**

Table 3:4 Change in mRS at 2 weeks for a Δ increase in a risk factor, holding other risk factors fixed

Model A – univariate model

Model B – adjusted for age, baseline mRS, baseline NIHSS, beat-to-beat MAP, type of stroke and treatment group

* - $p < 0.05$; ** - $p < 0.01$; *** - $p < 0.001$.

When multivariate linear model was adjusted for age and baseline NIHSS, lower beat-to-beat MAP and combination of cortical and sub-cortical stroke were associated with poor outcome. With every 10 mmHg decrease in beat-to-beat MAP there was 0.27 (95% CI -0.45, -0.01) increase in mRS at 2 weeks and that cortical and cortical/sub-cortical type of stroke showed 1.4 (95% CI 0.53, 2.38) increase in 2 weeks mRS compared to sub-cortical stroke (Table 3:4).

From the multivariate regression model age, stroke type, stroke severity and beat-to-beat MAP levels were significant independent predictors of early (2-week) outcome.

3.7 Discussion

This study evaluated the predictive role of cardiac BRS, beat-to-beat BP, beat-to-beat BPV, and PI variability on early (2-week) death/dependency. It is discussed in detail in chapter 6.

3.7.1 BP and outcome

The present study, demonstrated an adverse early (2-week) outcome with lower beat-to-beat MAP independent of age, stroke severity and dependency. Though the relationship of BP during the acute phase of stroke and outcome has been extensively studied, the prognostic influence of acute stroke BP is still a matter of controversy. Indeed, there may be a related U-shaped relationship between BP and outcome as demonstrated in the International Stroke trial (IST)(60). The IST has a methodological issue with regards to a single brachial BP measurement on admission. It is known that there is a natural reduction in BP in the first week following stroke(62;63) that could further comprise cerebral blood flow. Thus, lower beat-to-beat MAP could affect viable penumbra adversely. In contrast, a higher death/dependency with a high beat-to-beat MAP observed in our previous study could be related to difference in the study population (only 60% of the cohort was hypertensive prior to the stroke) (274). In addition, dichotomised outcome (dead/dependent vs independent) in our previous study differed from continuous outcome described in the current study. It is known that dichotomising leads to several problems. Firstly, much information (third of the data) is lost. Secondly,

dichotomisation may also increase the risk of a positive result being a false positive (280). This may account for the contrasting results between our studies.

An increased beat-to-beat SBP variability in the present study was associated with 2-week outcome ($r=1.02$, 95% CI 0.12 to 1.91, $p=0.03$) in model 3, however, the significance disappeared in the final model (Table 3:3). This finding is comparable to our previous study (281).

3.7.2 Pre-existing antihypertensive therapy

All patients were on pre-existing antihypertensive therapy, which clearly may influence brachial and beat-to-beat BP at randomisation. Approximately half of the patients in the present study could have continued their pre-existing antihypertensive, but ethically it was not possible to analyse the effects of 'continue' vs 'discontinue' therapy at randomisation as main COSSACS is still ongoing. The differential prognostic effects of different classes of antihypertensive therapy in Anglo-Scandinavian Cardiac Outcome Trial (ASCOT)(31) could not be examined in the current study due to small size and lack of power. Prior use of the ACE inhibitors in the present study may have effects on autonomic function, beat-to-beat BPV and arterial stiffness by blockade of the central actions of angiotensin II on medullary receptors, which may increase cardiac BRS and reduce beat-to-beat BPV (282). This may explain lack of relationship between baseline cardiac BRS, beat-to-beat BPV and 2-week outcome.

3.7.3 Cardiac BRS and outcome

Cardiac BRS and PI variability were not associated with early outcome in this study. The prognostic values of these parameters is well established (180;181;262),

but the current study was not sufficiently powered to examine their effects in treated hypertensive patients. Li et al (16) reported uncontrolled hypertension in 90% of first-ever stroke, it is possible that high pre-stroke BP could have set cardiac BRS at a lower level, suggesting potential cause for failure of cardiac BRS to predict early outcome in the present study. In addition the pre-stroke BP of the study cohort was not known.

Robinson et al(262) showed a worse prognosis (28% vs 8% long term mortality) in stroke patients with cardiac BRS < 5 ms/mmHg (measured within 72-hours post-ictus). Their outcome (death/dependency) was compared with a dichotomised variable (cardiac BRS < 5 and > 5 mm/Hg). In contrast the present study examined relationship of cardiac BRS with 2-week death/dependency as a continuous outcome, which may explain some of the differences.

3.8 Limitations and future prospects

They are discussed in detail in chapter 6.

3.9 Conclusions

Beat-to-beat MAP and stroke subtype significantly predict early outcome (2-week) in acute stroke treated hypertensive patients, independent of age, stroke severity, and casual BP parameters.

Cardiac BRS and HRV were not predictive of 2-week death/dependency.

**4 CENTRAL ARTERIAL PRESSURE PREDICTS
EARLY OUTCOME FOLLOWING ACUTE STROKE
IN TREATED HYPERTENSIVE PATIENTS**

4.1 Background

In recent years, there has been a revival of interest in using the non-invasive methods of evaluating circulatory function as an alternative to brachial BP measurement to predict cardiovascular risk. Safar(283) and Nichols(226;283) have extensively contributed to the clinical application of these concepts of arterial stiffness in relation of clinical practice.

Increased arterial stiffness is responsible for the increase in SBP and relative decrease in DBP with age, thus increasing pulse pressure (PP)(226). PP is a major determinant of small-artery disease, particularly of cerebral arterioles in stroke-prone spontaneously hypertensive rats(284). Although PP has been associated with stroke(285-287) and increased cardiovascular risk(224) in some longitudinal studies, its predictive value remains controversial(216;288-291). The possible explanation for this is that brachial PP, measured in these studies, may not reflect aortic (central) PP, which influences the extra and intra-cerebral circulation.

Arterial stiffness is a well accepted predictor of cardiovascular mortality. In essential hypertensive patients, pulse wave velocity (PWV), the velocity of the pressure wave as it travels down the arterial tree, has been found to be an independent and highly predictive measure of cardiovascular risk. In addition to hypertension(292;293) it is also predictive of outcome in other groups including end-stage renal disease(239), diabetes(294), ageing(240;295) as well as the general population(243). PWV also independently predicts stroke risk(293) in hypertensive subjects. Increased arterial stiffness may increase the risk of stroke through various mechanisms, including increased central PP, and increased carotid wall thickness leading to the development

of carotid stenosis. In the acute stage of stroke, increased aortic PWV was found to be associated with impaired cardiovascular autonomic function as assessed by cardiac baroreceptor sensitivity (BRS), thus suggesting that arterial wall stiffness of the vessels involved in the baroreflex arc may account for the reduced cardiac BRS observed in acute stroke patients(264). An impaired cardiac BRS is associated with long-term death and disability(262). However, the relationship between arterial stiffness and outcome per se in acute stroke is not known.

Although, PWV is the 'gold standard' for arterial stiffness, in recent years, central augmentation index (AIx)(296-299) has been proposed as a surrogate marker. A strong positive correlation between AIx and PWV has been observed in the offsprings of patients with familial hypertension(300). However, this relationship was not seen in diabetic patients(238) questioning the validity and clinical utility of AIx(301;302).

Central AIx and PP, either directly measured by carotid tonometry(233;234) or estimated using a transfer function from radial artery tonometry(236;244) are both independent predictors of all cause mortality in end-stage renal disease(233;234), in a population based longitudinal study (Strong Heart Study)(237) and in the hypertensive patients of the CAFÉ study(244). All these studies have shown the predictive value of arterial stiffness parameters (brachial PP, central PP, aortic PWV and AIX) for long-term outcome. However, their value as a short-term predictor of outcome has not been studied, particularly in stroke patients. Therefore in the present study we aimed to examine the relationship between a surrogate measure of central BP and central PWV with early (2-week) death/dependency.

4.2 Subjects and Methods

4.2.1 Subjects

One hundred and six treated hypertensive patients with a clinical diagnosis of acute stroke were recruited from the ongoing Continue or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS). This is a multi-centre, prospective, randomized, open, blinded-endpoint (PROBE) study to assess whether continuing or discontinuing existing antihypertensive therapy within the first 48 hours following acute ischaemic or haemorrhagic stroke onset influences short- (2 weeks) and long-term (6 months) outcome in terms of death and disability. In addition to the standard COSSACS inclusion/ exclusion criteria (see section 2.1.1.3 and 2.1.1.4) (276), patients with atrial fibrillation, diseases known to be associated with autonomic dysfunction (acute myocardial infarction, unstable angina, left ventricular failure) and ectopy rate of >2% were excluded. Subjects were randomised using the central randomisation service that is part of the secure COSSACS website (<http://cossacs.cvsu.co.uk>) to continue or discontinue pre-existing antihypertensive therapy. All patients were recruited from the University Hospitals of Leicester NHS Trust.

4.2.2 Methods

Each subject was assessed by one observer (N S) who was blinded to COSSACS treatment group. Specific baseline functional assessments undertaken at randomisation included the Modified Rankin score and Barthel Index (see section Appendix: 1). Baseline neurological assessments included the National Institutes of Health Stroke Scale (NIHSS) and the Oxfordshire Community Stroke Project (OCSP) Classification(277) (see Appendix: 1 and Appendix: 2).

All subjects underwent routine neuroimaging (CT or MRI), and were classified by: cortical, sub-cortical, both cortical and sub-cortical, and normal neuro-imaging or old changes.

The study was supported by the local ethics committee (MREC: 02/4/051, LREC: 6837 M), and all participants (or their carers where appropriate) gave written informed consent (see Appendix: 6).

4.2.3 Protocol

Subjects were haemodynamically stable at the time of laboratory assessment, and were studied in a quiet, dedicated research room kept at a constant ambient temperature (21°C) and dimly lit to minimize external stimuli. Patients were asked to avoid caffeinated products for 4 hours, and cigarettes and alcohol for 24 hours before the study period; they were encouraged to micturate before recording. All subjects were studied supine on a couch, with their head supported by 2 pillows and their arm supported at atrial height within 48 hours of symptom onset. Two sets of three casual brachial BP in the non-paretic arm were measured using BP monitor (UA-767; A&D Company Ltd, Tokyo, Japan) , validated to British Hypertension Society standards, with an appropriately sized cuff; the average of 6 readings was taken (Figure 2:1).

4.2.3.1 Applanation tonometry

Applanation tonometry of the radial artery was performed on the non-paretic arm, once an adequately defined waveform was achieved for approximately 20 seconds. This was repeated until three waveforms were achieved. These measures were

performed within 48 hours of stroke. Applanation tonometry of the carotid, femoral and radial arteries was conducted using a high-fidelity micromanometer (SPT-301B; Millar Instruments, Texas, USA) coupled to the SphygmocorTM system (Sphygmocor, PWV Medical, Sydney, Australia) to estimate carotid to femoral pulse wave velocity (PWV_{cf}) and arterial waveform characteristics (AIx- aortic augmentation index) estimated using a transfer function from radial artery tonometry (Figure 1:16, Figure 1:17 and Figure 1:18).

4.2.3.2 Pulse wave analysis (PWA) and pulse wave velocity (PWV) measurement

Arterial wave using applanation tonometry and 3-lead surface ECG were recorded simultaneously. Pulse transit length was estimated by subtracting the sternal notch to carotid applanation point from the sternal notch to femoral and radial applanation point and foot-to-foot methodology was employed to determine pressure contour transit time in relation to the ECG R-wave. Pulse wave data were obtained for the ascending aorta via radial artery applanation and the use of a generalised transfer function incorporated in the Sphygmocor software (version 7.01). The aortic AIx was also derived using the proprietary transformation function with radial data. AIx values were corrected for the heart rate using the in-built facility with the software. PWV recordings with >5% standard deviation of the mean time between R-wave and pulse waveform sequence and PWA recordings with >10% variation in pulse height or diastolic variability were rejected automatically by software and the measurement repeated. Qualifying recordings were performed in triplicate and mean values taken for subsequent analysis.

4.2.3.3 Central BP

Central BP was calculated from radial applanation tonometry, using the inbuilt transfer function.

All applanation tonometry was carried out on the non-paretic limb but if a signal was unattainable, the paretic limb was used for that and all further measurements.

4.2.4 Outcome

Early outcome was assessed using the modified Rankin score [mRS] (graded 0 to 6, 0 as asymptomatic and 6 as death) at 2 week post-ictus.

4.2.5 Statistical Analysis

All normally distributed continuous variables are described as mean (SD), continuous variables, that are not normally distributed, are described as median with inter quartile range. When baseline parameters were skewed, logarithm transformation was used to obtain approximate normal distributions. Baseline glucose and PWVcf were log transformed. Univariate correlation using Pearson and Spearman formula and partial correlation analyses were used to assess the interaction between the variables of interest. Forward stepwise multiple-regression analysis was performed to assess independent predictors of 2-week dependency. Arterial stiffness parameters were adjusted for body mass index (BMI) and corrected for heart rate to avoid bias from the effects of heart rate limiting medications. An examiner blinded to patient's randomisation group assessed 2-week death and dependency.

All baseline variables were divided into eight subgroups:

- Age, NIHSS, mRS
- Casual SBP, casual DBP, casual MAP and casual PP
- Central SBP, central DBP, central PP
- Gender, ethnicity, new vs old antihypertensive medications at baseline
- Past history of stroke, ischaemic heart disease, admission plasma glucose (log transformed) and cholesterol
- OCSF classification, laterality of stroke, cortical vs non-cortical stroke
- PWVcf (log transformed), aortic AIx, AIx corrected at heart rate 75
- Body mass index (BMI in kg/m²), heart rate

Each variable sub-group was used in a single variable linear model where age and baseline NIHSS and mRS were forced in the model. The variables in each of the above groups were examined for a linear relationship. If a linear relationship of these variables was found then only one variable was entered into the linear model as per clinical importance of the variable. The variables with significant values ($p < 0.05$) from each group were tested in the final model. Thus, the final relationship of baseline variables and 2-week outcome was tested.

The analysis was carried out using SPSS version 12.0 for Windows. A 5% level ($p < 0.05$) was considered significant.

4.2.6 Results

A total of 106 patients were recruited to the study. Due to poor data quality or missing data, 12 patients were excluded from final analysis. The 94 patients studied of whom 51(54%) are men, mean age 72.4 (12.5) years, range 45 to 104 years had a mean casual

SBP (SD) of 152 (22), DBP 81(13) mmHg and mean arterial BP (MAP) of 104 (15) mmHg, with a mean Barthel Index of 11 (6), median mRS of 4 (IQR 2, 4) and NIHSS of 5 (IQR 3, 9) at baseline (table:1). Median mRS at 2-week was 2 (1, 4). Eighty-nine percentage of study population belonged to Caucasian group.

The OCSF classification (Appendix: 2) subdivided stroke patients into TACS 12 (13%), PACS 36 (38%), LACS 33 (35%) and POCS 13 (14%) (Table 4:1).

Baseline variables	Values *
Age, yrs	72.4 (12.5)
Sex (male), n (%)	51 (54)
Time from stroke onset to randomisation, hours	22 (9.45)
Time from last anti hypertensive treatment, hours	20 (11.35)
Smoking, n (%)	14 (15)
Ethnicity	
Caucasian, n (%)	84 (89)
Asian, n (%)	8 (9)
Black, n (%)	2 (2)
Stroke severity & disability	
NIHSS (median (IQR))	5 (3, 9)
Barthel index	12 (6)
mRS (median (IQR))	4 (2, 4)
OCSP, n (%)	TACS: 12 (13) PACS: 36 (38) LACS: 33 (35) POCS: 13 (14)
Type of stroke (from CT or MRI)	
Cortical, n (%)	30 (32)
Sub-cortical, n (%)	36 (38)
Both, n (%)	7 (8)
Normal or old changes, n (%)	21 (22)
Pre-existing diseases	
Stroke, n (%)	20 (21)
Diabetes mellitus, n (%)	8 (9)
Ischaemic Heart Disease, n (%)	21 (22)
BMI, kg/m² (median (IQR))	26 (23, 30)
Antihypertensive use	
'Old' (Beta blocker and/or diuretic), n (%)	30 (32)
'New' (ACE inhibitor, Angiotensin receptor blocker, Calcium channel blocker, Alpha blocker), n (%)	25 (27)
Both	39 (41)

Table 4:1 Baseline of patients

* Values as mean (SD) or as stated, IQR: Interquartile range, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale, OCSP: Oxfordshire Community Stroke Project, TACS: total anterior circulation stroke, PACS: partial anterior circulation stroke, LACS: lacunar stroke, POCS: posterior circulation stroke, BMI: body mass index

Baseline BP and arterial stiffness parameters are shown in table:2. Central SBP (139 [22] mmHg) but not DBP (82 [14] mmHg) was lower than casual brachial BP 152/81 (22/13) mmHg (Table 4:2).

	Values *
Casual BP parameters	
SBP, mmHg	152 (22)
DBP, mmHg	81 (13)
PP, mmHg	72 (17)
MAP, mmHg	104 (15)
Arterial stiffness parameters	
Central SBP, mmHg	139 (22)
Central DBP, mmHg	82 (14)
Central PP, mmHg	58 (16)
Central AIx (%)	33 (11)
Central AIx at heart rate 75 (%)	28 (10)
Heart rate, bpm	68 (13)
PWVcf, m/s (median (IQR))	11.5 (8.9, 13.4)

Table 4:2 Casual BP and arterial stiffness parameters

SBP: systolic BP, DBP: diastolic BP, PP: pulse pressure, AIx: augmentation index (augmented pulse height/total pulse height), PWV : Pulse Wave Velocity, cf: carotid_femoral

* values as mean (SD) or as stated

Outcome at 2-weeks was strongly correlated with age ($r = 0.38$, $p < 0.001$), and in an age adjusted model, baseline measurements of mRS and NIHSS showed a strong

relationship with 2-week outcome ($r = 0.61$, $p < 0.001$) and ($r = 0.63$, $p < 0.001$), respectively.

In an univariate correlation, central SBP ($r = -0.308$, $p < 0.007$) but not aortic AIx ($p < 0.5$) or PWVcf ($p < 0.11$) were significantly associated with 2-week dependency. In univariate age, baseline NIHSS and mRS adjusted model, casual brachial SBP did not show an association with 2-week dependency. For every 10 mmHg fall in casual SBP, the 2-week dependency worsened by 0.06 on mRS scale (95% CI -0.21, 0.09, $p = 0.42$). When the effect of 'old' (beta-blockers and/or diuretic) compared with 'new' (ACE inhibitor, angiotensin receptor blocker, calcium channel blocker, alpha blocker) antihypertensives was studied, there was no significant effect on 2-week outcome (coefficient - 0.36, 95% CI - 1.00, 0.29, $p = 0.27$, adjusted for age and baseline NIHSS, mRS).

In the final linear regression model, when adjusted for age and baseline NIHSS/ mRS, a lower central SBP and combination of cortical and sub-cortical stroke were associated with poor outcome. With every 10 mmHg decrease in central SBP there was a 0.19 (95% CI -0.30, -0.07, $p < 0.01$) worsening in mRS at 2 weeks, and the presence of cortical and cortical/sub-cortical stroke on neuroimaging showed a 1.1 (95% CI 0.12, 2.10, $p < 0.05$) increase in 2 weeks mRS compared to sub-cortical stroke (Table 4:3).

Risk factors	Δ Increase in a risk factor	Change in mRS at 2 weeks for a Δ increase in a risk factor, holding other risk factors fixed
Age, years	5 years	0.12 (0.02, 0.22)*
mRS baseline	1 unit	0.50 (0.24, 0.75)†
NIHSS baseline	1 unit	0.10 (0.02, 0.19)*
Central SBP, mmHg	10 mm Hg	-0.19 (-0.30, -0.07)‡
Cortical vs. sub-cortical		0.65 (0.05, 1.25)*
Cortical and sub-cortical vs. sub-cortical		1.11 (0.12, 2.10)*

Table 4:3 Results from a final model, adjusted for age, baseline mRS, baseline NIHSS, type of stroke (“normal”, cortical, cortical and sub-cortical vs. sub-cortical) and central SBP are presented

mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure

- $p < 0.05$; ‡ $p < 0.01$; † $p < 0.001$.

4.3 Discussion

This study evaluates the predictive role of central BP, PWVcf and AIx on early (2-week) death/dependency. It is discussed in detail in chapter 6.

4.3.1 Blood pressure and outcome

It is described in detail in chapter 6.

4.3.2 Cerebral autoregulation

Cerebral autoregulation (CA) is impaired following acute stroke. As a result any changes in BP cause a significant change in cerebral blood flow (CBF). On the background of a cerebral event lower central SBP particularly in the context of impaired CA may result in lower CBF and poor penumbral viability. As such following

stroke there is a fall in BP over the initial few days, which may further compromise CBF in presence of a low central SBP. Poor early outcome in the context of a lower central SBP may represent poor penumbral viability in the present study.

4.3.3 Stroke sub-type

Cortical and sub-cortical compared to sub-cortical stroke predicted early outcome independent of age, stroke severity and BP parameters. This finding was comparable to previous study (277). Stroke represents a wide variety of underlying pathologies. Each stroke sub-type could be affected differentially by sudden changes in haemodynamics. Though there is no conclusive evidence, Bamford et al suggested a large artery disease for cortical strokes and small vessel disease for lacunar strokes (277). Toyoda et al found higher SBP in lacunar and atherothrombotic stroke and higher DBP in lacunar stroke compared with the patients with the other stroke subtypes during first week following stroke (303). Hassan et al and Chen et al suggested endothelial dysfunction in lacunar stroke(304;305) highlighting additional mechanism - 'beyond BP lowering' - in predicting outcome. All these studies were observational and too small. In addition they were not designed to examine the differential responses to haemodynamic manipulation in different stroke sub-type.

4.3.4 Arterial stiffness and outcome

It is important as in addition to BP reduction, blockade of angiotensin II effects of ACE inhibitor on the vascular endothelium may reduce local oxidative stress and improve the bioavailability of nitric oxide leading to a reduction in arterial stiffness (306). Reeves et al showed that pretreatment with statins was associated with lower

odds of poor outcome (OR=0.74, 95% CI 0.52, 1.02) (307). In the present study arterial stiffness (PWVcf and AIx) failed to predict early outcome. Pre-treatment with ACE inhibitor and statin may have affected vascular remodelling and endothelial function, respectively, explaining negative result. However, it was an underpowered study and the negative result could have been by chance.

4.4 Limitations

They are discussed in detail in chapter 6.

4.5 Conclusions

Lower central SBP, in addition to age and stroke severity, predicted early outcome in treated hypertensive stroke patients even when adjusted for stroke type, severity, and other arterial stiffness parameters (central PP, PWVcf, aortic AIx, heart rate corrected aortic AIx and BMI). Cortical and sub-cortical compared to sub-cortical stroke predicted early outcome independent of age, stroke severity and BP parameters. Further large-scale studies are needed to establish whether these initial findings can be confirmed and if class of antihypertensive therapy influences outcome. These findings have potential implications on the management of acute stroke BP.

**5 RELATIONSHIP OF CARDIAC BARORECEPTOR
SENSITIVITY AND ARTERIAL STIFFNESS
FOLLOWING ACUTE STROKE IN TREATED
HYPERTENSIVE PATIENTS**

5.1 Background

An elevated BP immediately post stroke is independently associated with poor short and long term death and dependency(60;74;109). Various haemodynamic parameters like a high casual BP(109), high 24 hour SBP (systolic BP)(74) or high MAP (mean arterial BP) and DBP (diastolic BP) beat to beat variability(274), assessed within less than 72 hours post-ictus, have been associated with a poor short and long term functional outcome. It is likely that the baroreceptor reflex is responsible for the adverse changes in haemodynamic parameters in acute stroke that are related to poor outcome.

The Baroreflex arc plays an important part in short-term BP regulation and is under autonomic regulation. An increase in BP results in activation of baroreceptors via stretch reflex in aortic and carotid arteries. This is transmitted to central vasomotor centres through the afferent loop (vagus and glossopharyngeal nerves) of the Baroreflex arc. The efferent loop consists of sympathetic and parasympathetic system that influences vessel tone and heart rate. A rise in BP results in an increase in pulse interval and vasodilatation, thus restoring BP to normal limits. The regression of the pulse interval against systolic BP represents an index of cardiac baroreceptor sensitivity (BRS)(160). Therefore, cardiac BRS is determined by the mechanical properties of an arterial wall and sympathetic and parasympathetic system.

An impaired cardiac BRS, assessed by power spectral analysis of 10 min continuous BP and PI (pulse interval) data within 72 h of stroke, has been shown to be predictive of cardiovascular death during long-term follow-up, independently of age, BP level, stroke severity or stroke subtype(262). In patients with coronary artery disease, the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study also

found impaired cardiac BRS to be an independent risk factor for subsequent cardiac mortality(180).

The mechanism of impaired cardiac BRS following stroke is not very clear(308), as it is not known if it is a direct result of disturbances in the central neuronal processing or due to abnormality in other cardiovascular parameters. Though the site of stroke appears to affect BRS, studies in hypertensive subjects, the elderly and in subjects with coronary artery disease (groups with an elevated risk of stroke) have demonstrated associations between decreased cardiac BRS and reduced carotid sinus and aortic arch distensibility(309-312). Increased large artery stiffness in subjects with hypertension or diabetes or renal disease, is an independent predictor of cardiovascular risk(239;294;313) and has recently been identified as an independent risk factor for fatal stroke(293). Observational studies have reported higher degrees of aortic stiffness in stroke patients, in comparison with control subjects matched for age, BP level and cardiovascular risk profile(314). A study from our department showed that cardiac BRS and arterial stiffness, when measured within 48 hours post-stroke, compared to well matched controls, were negatively correlated(264). Similar correlation was also observed in a group of patients who were on chronic haemodialysis(315). However, it is not known if this relationship between cardiac BRS and arterial stiffness persists in treated hypertensive subjects immediately following stroke.

The aim of the present study was to examine relationship of cardiac BRS and arterial stiffness in treated hypertensive acute stroke patients and examine the long-term prognostic effects of cardiac BRS and PWVcf.

5.2 Methods

5.2.1 Subjects

Sixty-nine patients admitted to the Acute Stroke Units of University Hospitals Leicester NHS Trust and with neuroradiologically confirmed stroke were studied within 48 h of stroke symptom-onset (if the patient first noticed stroke symptoms on waking, the time of stroke onset was taken as the time of onset of sleep), as participants of the COSSACS (Continue Or Stop post-Stroke Antihypertensives Collaborative Study). Patients were either randomized to continue or stop pre-existing antihypertensive therapy immediately following the first study measurements until day 14 post-stroke. Stroke type according to the OCSP (Oxfordshire Community Stroke Project) classification and stroke severity according to NIHSS (National Institutes of Health Stroke Scale) were recorded (see Appendix: 1 and Appendix: 2). Unconscious patients or those with neurological signs lasting <24 h were excluded, as were those with a concomitant acute coronary syndrome, cardiac failure or cardiac arrhythmia. Subjects were studied at the bedside or in a dedicated cardiovascular research laboratory (ambient room temperature 21⁰ C) in the supine position with external stimuli (background noise and lighting) minimized and at least 2 h following a light meal, having abstained from all caffeinated products, smoking and alcohol for at least 4 h prior to this. All subjects were asked to micturate before the study. The study was approved by the Multi-centre and local Research Ethics Committees (see Appendix: 6), in accordance with the Declaration of Helsinki, and written patient consent or relative assent (where the stroke patient lacked capacity) was obtained (MREC:02/4/051, LREC:6837 M).

5.2.2 Cardiac BRS

A total of three 5 min continuous recordings of pulse interval (PI) from a three-lead surface ECG and finger arterial BP using a Finapres device (Finapres 2300; Ohmeda, Englewood, CO, U.S.A.) were conducted. Measurements were performed on the hemiparetic arm. The mean of three readings was taken for final analysis. Software specially written by the Division of Medical Physics was used in the offline analysis of the beat-to-beat BP and PI recordings. Cardiac BRS was calculated using spectral and sequence analysis. Fast-Fourier transformation (FFT) was used to perform power spectral analysis of the resampled tracings as described previously(278), and estimates of cardiac BRS were obtained by calculation of the square root of the ratio of the powers of PI to SBP(systolic BP) in the LF (low-frequency) band (0.05–0.15 Hz; cardiac BRS LF). Normalized LF and HF (high frequency) powers for PI were calculated and the LF/HF ratio was used as an index of sympathovagal balance.

5.2.3 Blood pressure (BP)

Two sets of three casual oscillometric brachial BP in the non-hemiparetic limb was measured using a monitor (Figure 2:1) validated by the British Hypertension Society (UA-767; A&D Company Ltd, Tokyo, Japan). Total 10 minutes rest was observed between the two sets of BP measurements. The mean of the recordings was used in the analysis.

5.2.4 Arterial stiffness

5.2.4.1 Applanation tonometry

Applanation tonometry of the radial artery was performed on the non-paretic arm, once an adequately defined waveform was achieved for approximately 20 seconds. This was repeated until three waveforms were achieved. These measures were performed within

48 hours of stroke. Applanation tonometry of the carotid, femoral and radial arteries was conducted using a high-fidelity micromanometer (SPT-301B; Millar Instruments, Texas, USA) coupled to the SphygmocorTM system (Sphygmocor, PWV Medical, Sydney, Australia) to estimate arterial waveform characteristics (Figure 1:16, Figure 1:17 and Figure 1:18).

5.2.4.2 Pulse wave analysis (PWA) and pulse wave velocity (PWV) measurement

The arterial wave using applanation tonometry and 3-lead surface ECG were recorded simultaneously. Pulse transit length was estimated by subtracting the sternal notch to carotid applanation point from the sternal notch to femoral and radial applanation point and foot-to-foot methodology was employed to determine carotid femoral and carotid radial PWV (PWV_{cf} and PWV_{cr}, respectively). Pulse wave data were obtained for the ascending aorta via radial artery applanation and the use of a generalised transfer function incorporated in the Sphygmocor software (version 7.01). The aortic AIx was also derived using the proprietary transformation function with radial data. AIx values were corrected for the heart rate using the in-built facility with the software. PWV recordings with >5% standard deviation of the mean time between R-wave and pulse waveform sequence and PWA recordings with >10% variation in pulse height or diastolic variability were rejected automatically by software and the measurement repeated. Acceptable recordings were performed three times and mean values taken for subsequent analysis.

5.2.5 Statistical analysis

All normally distributed continuous variables are described as mean (SD), continuous variables, that are not normally distributed, are described as median with inter quartile

range. When baseline parameters were skewed, logarithm transformation was used to obtain approximate normal distributions. Baseline PWVcf, sequence BRS, spectral BRS, BRS LF to HF were log transformed. Bivariate correlation using Pearson and Spearman formula and partial correlation analyses were used to assess the interaction between the variables of interest. Arterial stiffness parameters were adjusted for body mass index (BMI) and corrected for heart rate to avoid bias from the effects of heart rate limiting medications. PWVcf was taken as a surrogate marker of arterial stiffness(257). All significant bivariate correlations between cardiac BRS and PWVcf were adjusted for age, baseline NIHSS and mRS.

The relationship of cardiac BRS with cardiovascular risk factors was studied using a QR (quantile regression) method for multivariate analysis.

Binary logistic regression analysis was performed to examine relationship of baseline cardiac BRS, PWVcf, and other arterial stiffness parameters with 6-month IST Questionnaire data. Kaplan-Meier survival curve was used to demonstrate survival over 3.3 years. Statistical significance was taken at the 5% level. Statistical analyses were performed using SPSS 12.0.1(SPSS, Chicago, IL, USA).

5.3 Results

A total of 69 patients from COSSACS were recruited to the study, of whom thirty-six (52%) were men, mean age 72 (13) years. They were randomized to the study within a mean of 22 (9.3) hours from stroke onset. Thirteen percent of study population belonged to an ethnic minority group (Asian 8, Black 1).

Stroke sub-type by OSCP classification(277) showed seven total anterior circulation, 25 partial anterior circulation, 36 lacunar and 11 posterior circulation strokes. The baseline characteristics are shown in Table 5:1.

Baseline median sequence, alpha BRS and PWVcf were 5.32 (3.3, 7.9), 4.52 (3.0, 7.6) and 11.5 (8.9, 13.4), respectively (Table 5:2).

On bivariate Spearman correlation age ($r = 0.50$, $p < 0.0001$) was significantly correlated to PWVcf. The sequence ($r = -0.35$, $p = 0.003$) and spectral BRS ($r = -0.24$, $p = 0.049$) were negatively correlated to PWVcf (Table 5:3 and Figure 5:2 and Figure 5:3). When adjusted for age, baseline NIHSS and mRS, the significant correlation between BRS and PWVcf was nullified (Table 5:4).

The mean follow-up of 2.08 (0.8) years is shown in figure 5.4

Baseline variables	Values *
Age, yrs	72 (13)
Sex (male), n (%)	36 (52)
Time from stroke onset to randomisation, hours	22 (9.30)
Time from last anti hypertensive treatment, hours (median (IQR))	23 (9, 29)
Smoking, n (%)	11 (16)
Ethnicity	
Caucasian, n (%)	60 (87)
Asian, n (%)	8 (12)
Black, n (%)	1 (1)
Stroke severity & disability	
NIHSS (median (IQR))	5 (5, 21)
Barthel index	12 (6)
mRS	3 (2)
OCSP, n (%)	TACS: 7 (10) PACS: 25 (36) LACS: 26 (38) POCS: 11 (16)
Type of stroke (from CT or MRI)	
Cortical, n (%)	22 (32)
Sub-cortical, n (%)	29 (42)
Both, n (%)	4 (6)
Normal or old changes, n (%)	14 (20)
Pre-existing diseases	
Stroke, n (%)	13 (19)
Diabetes mellitus, n (%)	4 (6)
Ischaemic Heart Disease, n (%)	17 (25)
BMI, kg/m²	26 (5)
Antihypertensive use	
'Old' (Beta blocker and/or diuretic), n (%)	22 (32)
'New' (ACE inhibitor, Angiotensin receptor blocker, Calcium channel blocker, Alpha blocker), n (%)	16 (23)
Both	31 (45)

Table 5:1 Baseline characteristics

IQR: Interquartile range, NIHSS: National Institutes of Health Stroke Scale, OCSP Oxfordshire Community Stroke Project, BMI: Body Mass Index

	Value*
SBP, mmHg	152 (22)
DBP, mmHg	81 (14)
MAP, mmHg	104 (15)
PP, mmHg	72 (17)
Sequence BRS, ms/mmHg, (median (IQR))	5.32 (3.3, 7.9)
Alpha BRS, ms/mmHg, (median (IQR))	4.52 (3.0, 7.6)
BRS LF, ms/mmHg, (median (IQR))	1.35 (0.99, 1.76)
BRS LF/HF, ms/mmHg	0.21 (0.65)
PWVcf, m/s, (median (IQR))	11.5 (8.9, 13.4)
Aix at heart rate 75	28.5 (9.6)
Heart rate, beats/min	68 (13)

Table 5:2 Baseline haemodynamic parameters

* values as mean (SD) unless stated otherwise, SBP: systolic BP, DBP: diastolic BP, MAP: mean arterial BP, PP: pulse pressure, BRS: baroreceptor sensitivity, LF: low frequency, HF: high frequency, PWVcf: pulse wave velocity, Aix: augmentation index

variable	Correlation Coefficient With PWVcf	p
Age, years	0.50	0.000
Sequence BRS, ms/mmHg	-0.35	0.003
Alpha BRS, ms/mmHg	-0.24	0.049
BRS LF, ms/mmHg	-0.12	0.339
BRS LF/HF	-0.23	0.057

Table 5:3 Spearmans Correlation with PWVcf

PWVcf: carotid femoral pulse wave velocity, BRS:baroreceptor sensitivity, HF:high frequency, LF:low frequency

Age, baseline NIHSS & mRS		
adjusted variables	Correlation with PWVcf	p
Sequence BRS, ms/mmHg	-.13	0.31
Alpha BRS, ms/mmHg	-.06	0.63
BRS LF, ms/mmHg	-.12	0.33
BRS LF/HF	-.17	0.18

Table 5:4 Age, NIHSS and mRS adjusted Spearman correlation with PWVcf

NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale, PWVcf: carotid femoral pulse wave velocity, BRS:baroreceptor sensitivity, HF:high frequency, LF:low frequency

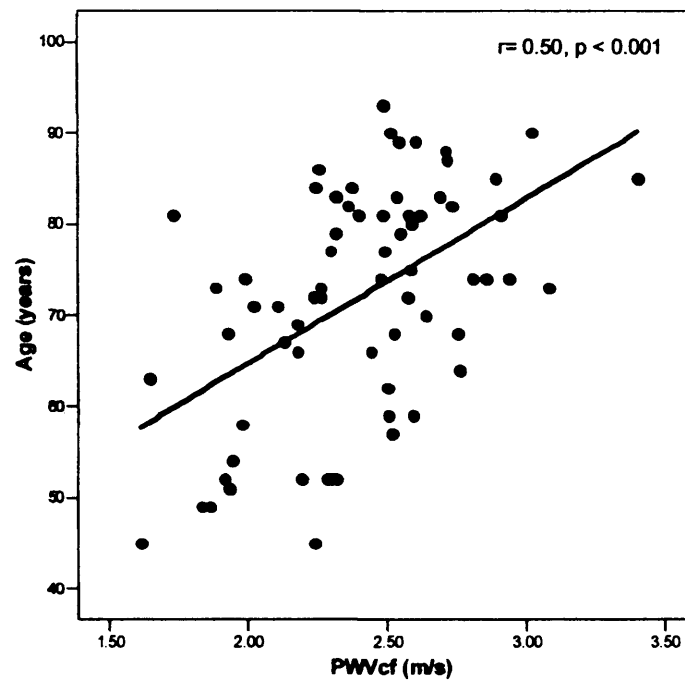


Figure 5:1 Age and PWVcf correlation (PWVcf is log transformed)

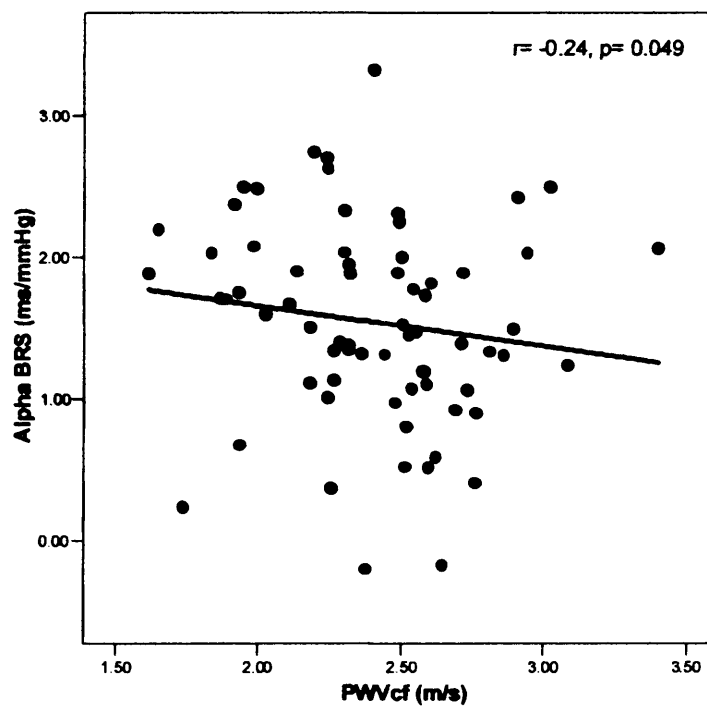


Figure 5:2 Alpha BRS and PWVcf (both alpha BRS & PWVcf are log transformed)

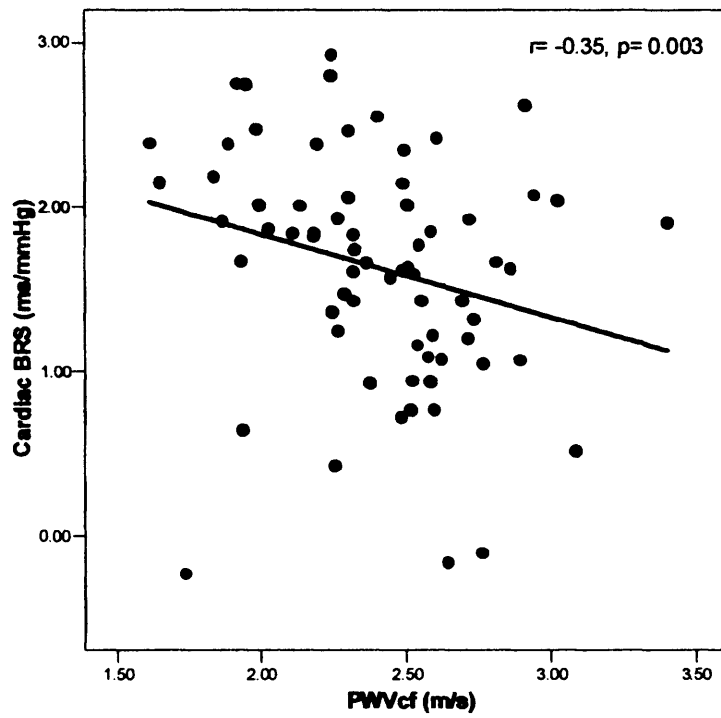


Figure 5:3 Cardiac BRS(sequence) & PWVcf (both cardiac BRS & PWVcf are log transformed)

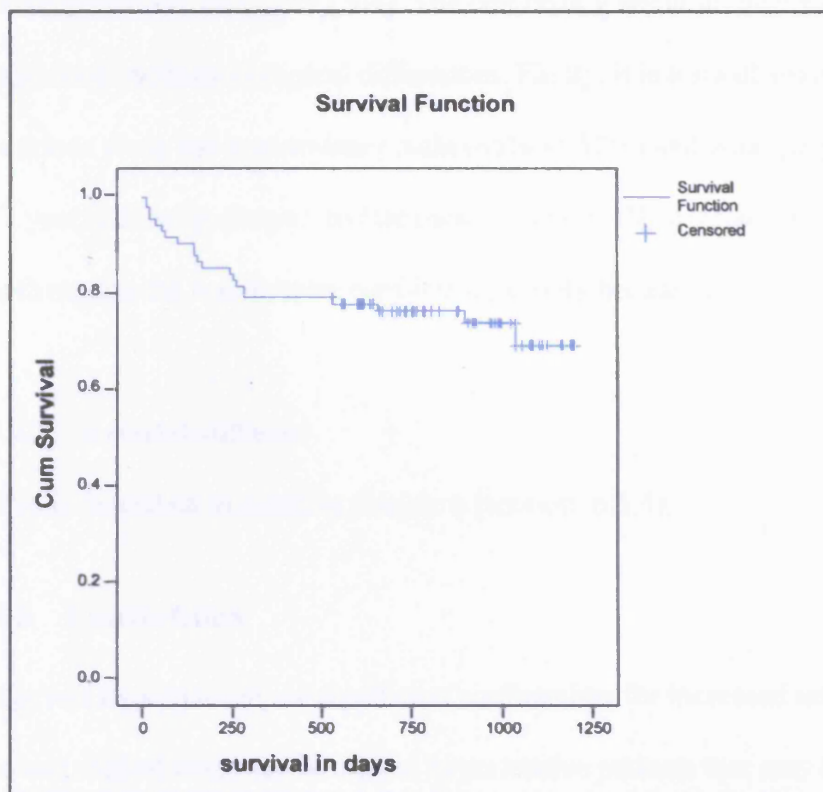


Figure 5:4 Kaplan- Meier Survival curve

5.4 Discussion

This study shows that arterial stiffness assessed by PWVcf is not associated with cardiac BRS in a sub-group of COSSACS.

5.4.1 Cardiac BRS

Arterial stiffness of aortic arch and carotid artery may reduce baroreceptor stretch in response to changes in BP that may result in, at least in part, the reduced cardiac BRS in ischaemic stroke. In subjects with high risk of stroke reduced cardiac BRS is shown to be related to reduced aortic arch distensibility (309-312), however, all these studies were too small to draw a conclusion. Eveson et al confirmed a negative relationship in a group of 31 subjects, half of them were on pre-existing

antihypertensive treatment (264). The contrasting result in the present study may be explained by methodological differences. Firstly, it is a small study. Secondly, previous study has predominant male (65% vs 52%) and younger population (66 vs 72 years). Finally, despite similar mean values of BP, cardiac BRS and PWVcf in both studies the results were conflicting, simply because of lack of power.

5.4.2 Arterial stiffness

This is described in detail in chapter 6 (section :6.1.4).

5.5 Limitations

Age and hypertension are significant confounders for increased arterial stiffness. The cohort studied consisted of treated hypertensive patients that may have caused lack of relationship between cardiac BRS and PWVcf . Overall the sample size is small, this result may therefore need to be confirmed in larger patient populations.

5.6 Conclusions

Arterial stiffness of the afferent loop involved in the baroreflex arc may account for, at least in part, the reduced cardiac BRS observed in acute stroke patients previously treated with antihypertensives, though age is a strong confounder and nullifies the relationship of cardiac BRS and PWVcf following acute stroke. Neither cardiac BRS nor arterial stiffness predict long-term mortality. These findings have potential implications on the assessment of arterial stiffness parameters as current methods of arterial stiffness assessment does not include assessment of sclerotic component of the arterial wall. In future, it would be worth introducing measurement of intima-media thickness along with non-invasive arterial stiffness measurements.

6 DISCUSSION AND SUMMARY

6.1 Summary

- 1) In this thesis I have studied the relationship of baseline cardiac BRS and PWV with 2-week death and dependency in previously treated hypertensives following acute stroke (chapters 3 and 4). I have also explored the correlation between baseline cardiac BRS and PWV and their effects on 6-month prognosis including quality of life and mortality (chapter 5).
- 2) The main findings of this thesis are that 2-week death and dependency in previously treated hypertensive subjects following acute stroke were strongly correlated with age ($r = 0.38$, $p < 0.001$). In an univariate correlation, central SBP ($r = -0.308$, $p < 0.007$) and beat-to-beat MAP ($r = -0.225$, $p < 0.029$) but not cardiac BRS ($p < 0.2$), aortic AIx ($p < 0.5$) or PWVcf ($p < 0.11$) were significantly associated with 2-week dependency.
- 3) At baseline, cardiac BRS values, both spectral and sequence were inversely correlated with PWVcf but age was a significant confounder nullifying this relationship in an age-adjusted correlation.
- 4) Following adjustment for age, baseline NIHSS and mRS, increased 2-week dependency was associated with lower central SBP ($p = 0.001$), cortical, compared to sub-cortical, stroke type ($p = 0.035$) and lower beat-to-beat MAP ($p = 0.043$).

6.1.1 Cerebrovascular autoregulation

Importantly, cerebrovascular autoregulation (CA) is impaired following acute stroke and cerebral blood flow (CBF) is therefore very sensitive to changes in systemic BP levels. This may be particularly important for sudden changes in systemic BP levels that occur over periods of seconds as it has been shown that dynamic CA is more impaired than static CA post-stroke(316). In the context of a cerebral event, lower beat-to-beat MAP and lower central SBP particularly in the context of disordered CA may result in lower CBF and poor penumbral viability. Following stroke there is a fall in BP over the initial few days(59), which may further compromise CBF in presence of a low beat-to-beat MAP and central SBP.

6.1.2 BP and outcome

Though the relationship of BP during the acute phase of stroke and outcome has been extensively studied, the prognostic influence of acute stroke BP is still a matter of controversy. It is thought that acutely elevated BP might be a protective mechanism in maintaining cerebral perfusion pressure and promoting CBF to the ischaemic penumbra, but the effects of post-stroke hypertension on neurological outcome give conflicting results(73). Indeed, there may be a related U-shaped relationship between BP and outcome as demonstrated in the International Stroke trial(60). In contrast to our previous results(274) showing increased odds ratio (OR) of a 30-day death/dependency in higher beat-to-beat MAP (OR 1.38, CI 1.1 to 1.8, $p < 0.02$), the present study showed a worse death/ dependency with lower beat-to-beat MAP and lower central SBP readings in the acute phase. However, in our previous study, the 24-hour $SBP \leq 140$ mmHg cohort also showed a worse outcome than 140 – 160 mmHg group (non-significant). Furthermore there are studies showing poor short-term outcome with

lower BP following acute stroke (76;93;94). There is also a recognised discrepancy between central (present study) and peripheral (previous study) BP levels, particularly in older subjects.

6.1.3 Pre-existing antihypertensive therapy

The present study (chapters 3 and 4) was also of patients on pre-existing antihypertensive therapy, which clearly may influence central and peripheral SBP at randomisation. However, our small study did not demonstrate an effect of ‘new’ (ACE inhibitor, Angiotensin receptor blocker, Calcium channel blocker, Alpha blocker) versus ‘old’ (Beta blocker and/or diuretic) antihypertensive treatment. Furthermore, analysing whether treatment was continued or not was not possible as the main COSSACS trial is ongoing and trial steering committee did not wish to prejudice the results of the main trial. However, it is recognised that different antihypertensive classes have differential effects on central BP(31;244). Indeed, the CAFÉ study suggests that better cardiovascular outcomes in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) may be related to lower central BP in calcium channel blocker based treatment compared to betablocker (BB) based treatment, despite a similar reduction in brachial BP (31;244). In contrast to the CAFÉ study, the Second Australian National Blood Pressure Trial (ANBP2) suggests that in the older subjects (mean age 72 ± 5) differences between central and peripheral BP are much less than in young subjects and this approximate equivalence of central and peripheral BP persists on treatment in older subjects(317). Following stroke there is a spontaneous fall in BP over initial few days, which is greater if the initial values are higher (59), continuation of antihypertensive following stroke may reduce BP further. In addition to already low BP, lower beat-to-beat MAP and central SBP compromise CBF and cerebral

autoregulation. It contributes to death/dependency at 2-week as found in our study (chapters 3 and 4).

Studies in the general population(216) and in subjects with hypertension(288;291) have suggested an association of a high casual PP with cardiac events and an association of a high MAP with cerebrovascular events. In the Systolic Hypertension in the Elderly Program (SHEP), MAP and PP were both independent determinants of stroke risk; however, stroke risk increased more with MAP (by 20% for every 10 mm Hg) than with PP (by 11% for every 10 mm Hg)(24). This can be explained by vulnerability of small end arteries of brain to adverse effects of higher BP. In contrast to this, our study failed to demonstrate any unfavourable effects of casual BP parameters on outcome. This could be due to the different effects of aortic stiffness on peripheral and central BP.

6.1.4 Arterial stiffness

Though previous studies revealed PWVcf as an independent predictor of all cause mortality in hypertensive(239;292;313), end-stage renal disease(239) and elderly population(240), PWV is also identified as a robust and important indicator of vascular disease in cardiovascular disease patients(318). Our small study failed to demonstrate a relationship of PWVcf with 2-week dependency. Similarly, the correlation of central pulse pressure and composite outcome reported in a three-year follow-up of hypertensive subjects in CAFÉ study(244) could not be demonstrated in our study. There are number of possible explanations for the failure of the present study to demonstrate a relationship between measures of arterial stiffness and outcome. Firstly, the CAFÉ study was of a predominantly male (59%) and young (mean age 62 ± 8

years) cohort. Secondly, AIx was not corrected for heart rate. Thirdly, numbers were small in our study and follow-up intentionally short, though a sample size of 76 for multiple regression analysis and continuous variable as outcome as in our study has an 80% power at the 5% significance level when number of regressor is 1.

There are atherosclerosis and sclerosis component of arterial stiffness. Currently, most diagnostic techniques to detect atherosclerosis focus on the atheromatous component, which is represented by morphological changes of the arterial wall as assessed by plaque deposition or thickening of the arterial wall in the aorta and carotid arteries(319;320). The sclerotic component, or the physical information provided by the assessment of arterial stiffness, is not as often evaluated. Although these two components are inter-related, studies examining the association between arterial physiological changes and morphological changes have given conflicting results, confirming(320) or denying(248) a close association. The lack of relationship between cardiac BRS and PWVcf in chapter 5 may represent the difficulty assessing the atherosclerosis and sclerosis components of arterial wall. Furthermore, arterial stiffness is affected by endothelial dysfunction that has no influence on cardiac BRS.

The study population between our previous study was different consisting of 55% lacunar strokes compared to 38% in the present study. Lacunar strokes may affect sclerotic rather than atherosclerosis component of arterial stiffness, hence the contrasting result in present study. Arterial stiffness may, in part, affect afferent loop of baroreceptor reflex arc, which may cause autonomic dysfunction and poor outcome.

6.1.5 Cardiac BRS

The ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study and Kleiger et al, clearly demonstrated that abnormal autonomic regulation, as measured by heart rate variability (HRV) and cardiac baroreceptor sensitivity (BRS), are independent predictors of death after myocardial infarction(180;181). Heart rate dynamics and impaired cardiac BRS following acute ischaemic stroke also predict long-term mortality(196;262). Chapter 3 failed to establish effect of cardiac BRS on 2-week death/dependency. This could be due to smaller number in the present study. In addition, the study group in chapter 3 had a mild stroke (median NIHSS – 5) and it was on pre-existing antihypertensive therapy. The class of pre-existing antihypertensive therapy ('new' versus 'old'), may have an additional effects via vascular remodeling or abnormal endothelial function, that may account for discrepancy in the result.

6.1.6 Stroke sub-type

Chapter 4 highlighted poor 2-week outcome in cortical and sub-cortical stroke compared to sub-cortical stroke. The potential justification is discussed in chapter 4.

6.2 Implications

Chapters 3, 4 and 5 shed light on the link between cardiac BRS and central arterial stiffness. It elucidates prognostic relevance of central SBP and beat-to-beat MAP in the acute stroke phase to early (2-week) outcome that, to my knowledge, has never been examined earlier. From the results of this work, the central SBP derived from the radial artery using a generalised transfer function appears to show potential and

requires evaluation in a larger study for short-term (days) and long-term prognosis (months to years). However, this study is not free from limitations.

6.3 Limitations

The study was underpowered to detect any effect of haemodynamic parameters following acute stroke on early outcome

Chapter 3, 4 and 5 studied patients on pre-existing antihypertensive therapy, which clearly may influence central and peripheral SBP at randomisation.

Subjects in the study had mild stroke as per inclusion criteria. Less severe stroke at randomisation may affect 2-week outcome.

As the main COSSACS trial is ongoing, analysing by treatment group (whether treatment was continued or not) was not possible.

Due to a small number of subjects, effects of different classes of antihypertensives on 2-week outcome was difficult assess.

The chapter 5 did not compare stroke subjects with controls that may have some influence on lack of relationship in cardiac BRS and PWVcf when age-adjusted.

6.4 Prospects for further work

It is not established that improvement in central SBP and beat-to-beat MAP in acute stroke improves short-term (weeks) or long-term (months to years) outcome. Further large-scale cohort studies similar to International Stroke Trial(60) are needed to establish optimum central SBP and beat-to-beat BP in acute stroke for good short-term (weeks) and long-term (months to years) outcome. Once these most favorable parameters are established, there is potential to develop strategy to modify central SBP in acute stroke.

Use of pre-existing antihypertensives may affect arterial stiffness as it is known that ACE inhibitors may reduce arterial stiffness independently of blood pressure reduction by effects on endothelial function and, and via vascular remodelling(321). The non-lipid lowering effects of statins are of recent interest. Statins may modify vascular endothelial function via upregulation of endothelial nitric oxide synthase, and thereby improving arterial stiffness. However effects of antihypertensives and statins on short-term arterial stiffness and cardiac BRS have not been studied yet.

Although caution should be applied in interpreting these multiple inter-relationships in a relatively small study, blood pressure modification may appear to improve several prognostically-important parameters.

These findings have potential implications on the management of acute stroke BP. In future, it would be worth introducing measurement of cardiac intima-media thickness along with non-invasive arterial stiffness measurements.

6.5 Conclusions

In conclusion, lower central SBP, and beat-to-beat MAP in addition to age and stroke severity, predicted early outcome in treated hypertensive stroke patients even when adjusted for stroke type, severity, and other arterial stiffness parameters (central PP, PWVcf, aortic AIx, heart rate corrected aortic AIx and BMI).

Arterial stiffness of the afferent loop involved in the baroreflex arc may account for, at least in part, the reduced cardiac BRS observed in acute stroke patients previously treated with antihypertensives, though age is a strong confounder and nullifies the relationship of cardiac BRS and PWVcf following acute stroke.

7 APPENDICES

Appendix: 1 Stroke severity and functional assessment tools

1. National Institutes of Health Stroke Severity Scale

Level of consciousness:

- 0 = Alert, keenly responsive
- 1 = Drowsy, but rousable by minor stimulation to obey, answer, or respond
- 2 = Stuporous, require repeated stimulation to attend, lethargic or obtunded, requiring strong or painful stimulation to make movements
- 3 = Coma, respond only with reflex motor or autonomic effects, or unresponsive

Level of consciousness questions:

Ask patient the month and his/her age. Score for the first answer.

- 0 = Answers both correctly
- 1 = Answers one correctly
- 2 = Both incorrect

Level of consciousness commands:

Ask patient to open/close non-paretic hand and eyes. Score if he/she makes unequivocal attempt.

- 0 = Obeys both correctly
- 1 = Obeys one correctly
- 2 = Incorrect

Best gaze:

- 0 = Normal
- 1 = Partial gaze palsy; abnormal but not forced deviation
- 2 = Forced deviation/total gaze paresis

Best visual:

Confrontation testing using finger movements, including double simultaneous stimulation. Use visual threat if consciousness or comprehension limit testing, Scoring '1' for any asymmetry demonstrated.

- 0 = No visual loss
- 1 = Partial hemianopia
- 2 = Complete hemianopia, to within 5 degrees of fixation
- 3 = Bilateral hemianopia (blind including cortical blindness)

Facial palsy:

- 0 = Normal
- 1 = Minor
- 2 = Partial
- 3 = Complete

Best motor - arm:

Arms held for 10 seconds at 90 degrees if sitting, 45 degrees if lying. Grade weaker arm. Place arms in position if comprehension reduced.

- 0 = No drift after 10 seconds
- 1 = Drift after brief hold
- 2 = Can not resist gravity, but some effort made
- 3 = No effort against gravity
- 4 = No movement

Best motor - leg:

While lying, patient to hold weaker leg raised at 30 degrees for 5 seconds. Place leg in position if comprehension reduced.

- 0 = No drift after 5 seconds
- 1 = Drift within 5 seconds
- 2 = Can not resist gravity, falling to bed but some effort made
- 3 = No effort against gravity
- 4 = No movement

Limb ataxia:

Finger-nose and heel-to-shin tests performed; ataxia is only scored if out of proportion to weakness. If total paralysis score as absent.

- 0 = Absent
- 1 = Present in leg or arm
- 2 = Present in leg and arm

Sensory:

Tested with pin; only hemisensory loss scored. If comprehension or consciousness reduced, only score if obvious evidence.

- 0 = Normal
- 1 = Partial loss, subjectively different but still felt
- 2 = Dense loss, unaware of being touched

Best language:

Assessed from responses during evaluation.

- 0 = No aphasia
- 1 = Mild to moderate aphasia; nominal errors, paraphrasias, etc.
- 2 = Mute

Dysarthria:

- 0 = Normal articulation
- 1 = Mild to moderate dysarthria, slurring some words
- 2 = Near unintelligible or worse

Neglect and inattention:

0 = No neglect

1 = Partial neglect, visual, tactile, or auditory

2 = Complete neglect, affecting more than one modality.

2. Modified Rankin Scale.

- 0 No symptoms at all
- 1 Minor symptoms. No significant disability, despite symptoms; able to carry out all usual duties and activities.
Symptoms that do not interfere with lifestyle
- 2 Minor handicap. Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.
Symptoms that do lead to some restriction in lifestyle, but do not interfere with patients' capacity to look after themselves
- 3 Moderate handicap. Moderate disability; requiring some help, but able to walk without assistance.
Symptoms that appreciably restrict the patients' lifestyle, or prevent totally independent existence, or both
- 4 Moderately severe handicap. Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
Symptoms that clearly prevent independent existence, though patient does not need constant attention
- 5 Severe handicap. Severe disability; bedridden, incontinent and requiring constant nursing care and attention
Totally dependent, patient requiring constant attention day and night

3. Barthel Index.

TASK	DESCRIPTION	SCORE
Feeding	Independent	2
	Food needs to be cut	1
	Dependent	0
Moving bed to chair including sitting up	Independent	3
	With minimal help	2
	Able to sit but maximum assistance to transfer	1
	Unable	0
Personal toilet: wash face, comb hair, shave, clean teeth	Independent	1
	Needs help	0
Getting on and off toilet, handling wipe, flush.	Independent	2
	Needs help	1
	Unable	0
Bathing self	Independent	1
	Needs Help	0
Walking on a level surface (or propel wheelchair if unable to walk).	Independent for 50 yards	3
	With help for 50 yards	2
	Wheelchair for 50 yards	1
	Unable	0
Ascend and descend stairs	Independent	2
	With help	1
	Unable	0
Dressing: including tying shoes, fastening buttons	Independent	2
	With help	1
	Dependent	0
Controlling bowels	No accidents	2
	Occasional accidents	1
	Incontinent	0
Controlling bladder	No accidents	2
	Occasional accidents	1
	Incontinent	0

Appendix: 2 Oxfordshire Community Stroke Project classification (OCSP)

Stroke is classified into four sub-groups:

TACS – total anterior circulation stroke

PACS – partial anterior circulation stroke

LACS – lacunar stroke

POCS – posterior circulation stroke

Classification depends on 3 main features:

- Unilateral motor or sensory involvement (face/arm/leg)
- Visual involvement - hemianopia or quadrantanopia or visual neglect
- Higher cerebral dysfunction (dysphasia, dyscalculia, visuospatial disorder/inattention/neglect).

FEATURES	CLASSIFICATION
All 3 present	TACS
2 out of 3 present	PACS
Drowsy + unilateral weakness (visual + higher cerebral involvement assumed)	TACS
Motor/Sensory/sensori-motor involvement affecting ≥ 2 out of arm/face/ leg	LACS
Isolated speech or visual involvement	PACS
Motor or sensory involvement affecting only one area (face or arm or leg)	PACS
Cerebellar syndrome or brainstem involvement	POCS

Appendix: 3 The International Stroke Trial Questionnaire

1. Is the patient alive?

YES/ NO

2. Does the patient require help from another person for everyday activities?

YES/ NO

3. Does the patient feel that they have made a complete recovery from their stroke?

YES/ NO

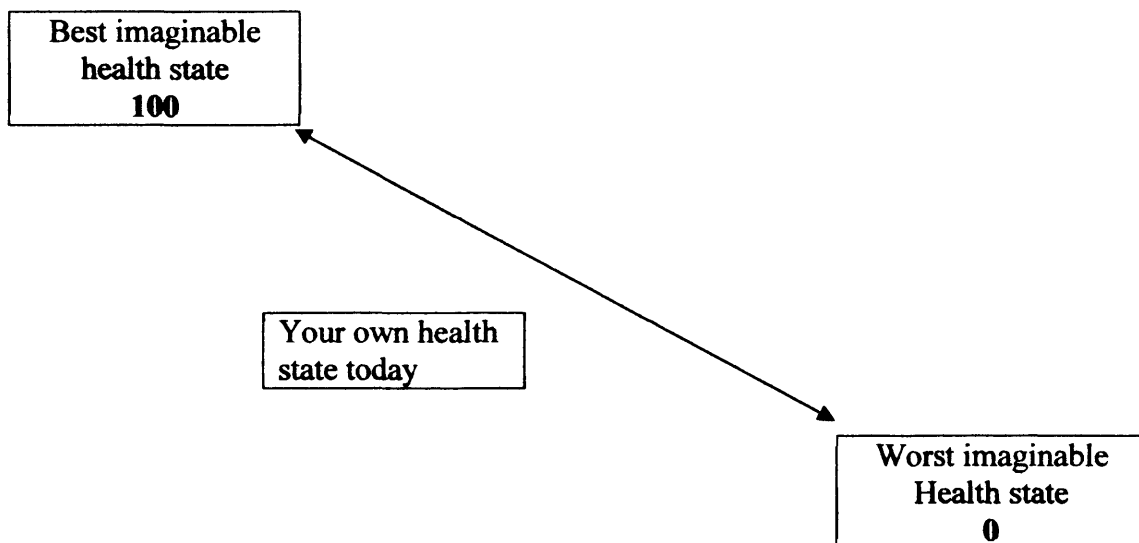
Appendix: 4 The EuroQOL Questionnaire

1. Please indicate which statements best describe your own health state today:
(Please Circle)

Health state			
Walking about	No problems	Some problems	Confined to bed
Self care (e.g. washing and dressing)	No problems	Some problems	Unable
Usual activities (e.g. work, study, family or leisure activities)	No problems	Some problems	Unable
Pain or discomfort	None	Moderate	Extreme
Anxiety/ depression	None	Moderate	Extreme

2. To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad is your health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.



Appendix: 5 TOAST classification of ischaemic stroke

TOAST stroke subtype classification	Clinical features	Neuroimaging	Supporting Features	Other
Large artery atherosclerosis	Cortical impairment (eg. dysphasia, neglect) or Cerebellar or brainstem signs	Significant stenosis or occlusion of major brain artery Cortical/cerebellar infarct or subcortical infarct >1.5cm May be similar to above	Carotid artery stenosis >50% History of same-territory TIA Peripheral vascular disease History of TIA in a different territory or history of a systemic occlusive vascular event	No evidence of cardioembolic cause
Cardioembolism	May be similar to above		Identifiable high or medium risk source of cardioembolus History of hypertension, diabetes	No evidence of large artery atherosclerosis as cause
Small vessel occlusion (lacunae)	Lacunar syndrome (motor/sensory/sensori-motor involvement affecting ≥ 2 out of arm/face/ leg, ataxic hemiparesis)	Subcortical or brainstem infarction <1.5cm	History of hypertension, diabetes	No evidence of large artery atherosclerosis or cardioembolic cause
Other determined aetiology	Clinical features of acute ischaemic stroke	CT/MRI consistent with acute ischaemic stroke	Diagnostic evidence of a rare cause, eg vasculopathy, haematological disorder, procoagulable state	No evidence of large artery atherosclerosis or cardioembolic cause
Undetermined aetiology	Clinical features of acute ischaemic stroke	CT/MRI consistent with acute ischaemic stroke	Lack of diagnostic evidence, or diagnostic evidence for >1 subtype	No likely cause identified, or more than one possible cause (eg atrial fibrillation and ipsilateral carotid stenosis > 50%)

Appendix: 6 COSSACS Sub-study ethics, data and consent forms

1. MREC approval letter



Trent Multi-centre Research Ethics Committee

Chairman: Dr Robert Bing
Administrator: Jill Marshall

Derwent Shared Services
Laurie House
Colyear Street
Derby
DE1 1LJ

Your Ref:

30 May 2003

Telephone: 01332 868905
Fax: 01332 868930

Email: Jill.Marshall@derwentsharedservices.nhs.uk

Dr Thompson Robinson
Senior Lecturer in Medicine for the Elderly/
Hon Consultant Physician in Cerebro-vascular Medicine
Leicester Warwick Medical School
University Hospitals of Leicester NHS Trust
Gwendolen Road
Leicester LE5 4PW

Dear Dr Robinson

MREC/02/4/051 - please quote this number on all correspondence
Continue or Stop post-stroke Antihypertensives Collaborative Study (COSSACS)

The Trent MREC has reviewed the proposed Protocol amendment 1 'Relationship of Cardiac Baroreceptor Sensitivity and Large Artery Function to Prognosis Following Acute Stroke Sub-Study' to the above application.

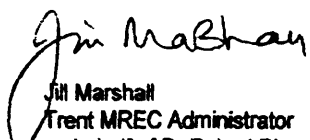
The members of the Committee present agreed that there is no ethical objection to the proposed amendment to the study. I am, therefore, happy to give you our approval on the understanding that you will follow the protocol and conditions of approval, as agreed.

Documents approved for this amendment:

Protocol Amendment 1 Version 1 dated 9 May 2003
Patient Information Sheet, Protocol Amendment 1 Version 1, dated 9 May 2003
Patient consent Form, Protocol Amendment 1 Version 1, dated 9 May 2003
Relative Information Sheet, Protocol Amendment 1 Version 1, dated 9 May 2003
Relative Assent Form, Protocol Amendment 1 Version 1, dated 9 May 2003
Patient Confirmation Information Sheet, Protocol Amendment 1 Version 1, dated 9 May 2003
Patient Confirmation Consent form, Protocol Amendment 1 Version 1, dated 9 May 2003

A copy of this amendment should be sent to all the LRECs involved in the review of this study for information. If the issues contained in the amendment are local issues as defined in the DoH Guidelines, then the LRECs' approval is required.

Yours sincerely


Jill Marshall
Trent MREC Administrator
on behalf of Dr Robert Bing, Chairman

MREC/02/4/051

The Central Office for Research Ethics Committees is responsible for the operational management of Multi-centre Research Ethics Committees

2. DATA form

COSSACS BRS SUB-STUDY	PATIENT NUMBER						
LABORATORY 1 DATA FORM (<24 HOURS)	DATE (DD/MM/YY)						

Time Since:
(if within last
48hrs)

Caffeine
Cigarettes
Alcohol

Casual Blood Pressure

Reading	SBP	DBP	Reading	SBP	DBP	Reading	SBP	DBP
1			4			Average		
2			5					
3			6					

Beat-To-Beat Blood Pressure, HR and RR

Recording	Start Time	End Time	File Name
1			
2			
3			

Analysis

	Beats	PI Mean	PI SD	SBP Mean	SBP SD	MAP Mean	MAP SD	DBP Mean	DBP SD
1									
2									
3									
Average									

	All BRS Sequence		Up BRS Sequence		Down BRS Sequence		Non-BRS Sequence	
	Number	Mean	Number	Mean	Number	Mean	BP Up /PI Down	BP Down /PI Up
1								
2								
3								
Average								

	BRS Alpha	BRS HF	BRS LF	SBP LF/ HF	PI LF/ HF
1					
2					
3					
Average					

Pulse Wave Analysis and Velocity

Right Carotid to Suprasternal Notch (mm)		Right Femoral to Suprasternal Notch (mm)	
Right Radial to Suprasternal Notch (mm)		Left Radial to Suprasternal Notch (mm)	
Right Arm Span (cm)		Left Arm Span (cm)	

Derived Blood Pressure, ascending aortic and carotid

	Aortic from radial		Aortic from carotid		Carotid		PP amp brachial/PP/carotid/PP
	SBP	DBP	SBP	DBP	SBP	DBP	
1							
2							
3							
Average							

	HR	RAAIX	CAAIX	CDAIX	RATR	CATR	PWV cf	PWV cr
1								
2								
3								
Average								

Radial tonometry performed on non-stroke side. RAAIX: aortic augmentation index from radial (AIX – augmented pulse height/total pulse height in %), CAAIX: aortic AIX from carotid, CDAIX: carotid AIX, RATR: aortic time to reflected wave derived from radial (Tr in ms), CATR: aortic Tr derived from carotid.

COSSACS BRS SUB-STUDY	PATIENT NUMBER						
LABORATORY 2 DATA FORM (14 ± 2 DAYS)	DATE (DD/MM/YY)						

Time Since: (if within last 48hrs)	Caffeine Cigarettes Alcohol	

Casual Blood Pressure

Reading	SBP	DBP	Reading	SBP	DBP	Reading	SBP	DBP
1			4			Average		
2			5					
3			6					

Beat-To-Beat Blood Pressure, HR and RR

Recording	Start Time	End Time	File Name
1			
2			
3			

Analysis

	Beats	PI Mean	PI SD	SBP Mean	SBP SD	MAP Mean	MAP SD	DBP Mean	DBP SD
1									
2									
3									
Average									

	All BRS Sequence		Up BRS Sequence		Down BRS Sequence		Non-BRS Sequence	
	Number	Mean	Number	Mean	Number	Mean	BP Up /PI Down	BP Down /PI Up
1								
2								
3								
Average								

	BRS Alpha	BRS HF	BRS LF	SBP LF/ HF	PI LF/ HF
1					
2					
3					
Average					

Pulse Wave Analysis and Velocity

Right Carotid to Suprasternal Notch (mm)		Right Femoral to Suprasternal Notch (mm)	
Right Radial to Suprasternal Notch (mm)		Left Radial to Suprasternal Notch (mm)	
Right Arm Span (cm)		Left Arm Span (cm)	

Derived Blood Pressure, ascending aortic and carotid

	Aortic from radial		Aortic from carotid		Carotid		PP amp brachialPP/carotidP P
	SBP	DBP	SBP	DBP	SBP	DBP	
1							
2							
3							
Average							

	HR	RAAIX	CAAIX	CDAIX	RATR	CATR	PWV cf	PWV cr
1								
2								
3								
Average								

Radial tonometry performed on non-stroke side. RAAIX: aortic augmentation index from radial (AIX – augmented pulse height/total pulse height in %), CAAIX: aortic AIX from carotid, CDAIX: carotid AIX, RATR: aortic time to reflected wave derived from radial (Tr in ms), CATR: aortic Tr derived from carotid.

COSSACS BRS SUB-STUDY	PATIENT NUMBER							
ADDITIONAL INFORMATION	DATE (DD/MM/YY)							

Ethnicity

Caucasian
Asian
Other (state)

Black
Oriental

Date

D	D	M	M	Y	Y

Result

(please tick as appropriate)

Side	Normal	Plaque	Stenosis				Occluded
			<30%	30-49%	50-69%	>70%	
Right	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Left	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. CONSENT FORMS

(Hospital/ Institution/ GP Practice Headed Paper)

PATIENT INFORMATION LEAFLET

Centre Number:

Patient Number:

COSSACS: Relationship of Cardiac BRS and Large Artery Function to Prognosis Following Acute Stroke Sub-study

You have already been invited and agreed to participation in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS). As you will remember, this study will compare the effects of continuing or stopping the treatment for high blood pressure that you were already taking at the time of your admission to hospital for the first two weeks after your stroke.

You are now being invited to take part in a small supplementary research study, which will involve four additional 60-minute measurement periods of your blood pressure and blood vessels during the COSSAC Study. You should know that you may continue in the main COSSAC Study without any obligation to participate in this small supplementary research study.

However, before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

1. What is the purpose of the study?

Stroke is a common condition, and is associated with an increased risk of heart problems (such as angina, heart attack or rhythm problems), as well as an increased risk of future stroke. Areas of specialized cells (baroreceptors) in the carotid artery in the neck and in the heart are important in the control of blood pressure and heart rate. Baroreceptor function may be impaired following stroke, and may explain the increased risk of heart problems. These changes may also be related to hardening or stiffening of the blood vessels. This study will assess the relation between baroreceptor function, blood vessel stiffness and future heart problems and stroke, and whether this is altered by any blood pressure treatments that are taken immediately after stroke.

2. Why have I been chosen?

You have been chosen to join in this study, because you have already agreed to participate in the COSSAC Study. Altogether, 500 patients throughout the United Kingdom will be asked to join in this additional study.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any

time, or a decision not to take part, will not affect the standard of care you receive.

4. What will happen to me if I take part?

If you agree to join this study, you will have a study test on coming into hospital, at 3 and 7 days, and at two weeks following the stroke, in addition to the study tests already involved in COSSACS. On each occasion, you will be asked to lie quietly on your bed whilst a small cuff is attached to the fingers of one hand to measure your blood pressure, 3 stickers to your chest to monitor your heart rate, and a band around your waist to measure your breathing pattern. After the readings have stabilised over a period of 15 minutes, recordings will then be made for three 5-minute periods. Assessment of blood vessel stiffness will then be made using a sensitive pressure probe mounted in a pen. Light pressure will be placed over the artery in the wrist and three 20-second recordings will be made. The procedure will then be repeated at the artery in the neck and in the groin, though there will be no need to remove undergarments.

5. What treatments will be used?

No specific treatments are given as part of this small study.

6. What are the possible disadvantages and risks of taking part?

The blood pressure cuff applies only a gentle pressure to your fingers to enable a blood pressure recording to be made every heart beat. This may cause a slight tingling in your fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care.

7. What are the possible benefits of taking part?

You should not expect to receive any benefit from taking part in this study.

8. What if something goes wrong?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

9. Will my taking part in this study be kept confidential?

The blood pressure and blood vessel stiffness data recorded during the study will be stored on computer, and transferred to the coordinating centre at Leicester University for subsequent analysis. However, you will not be identified by name, and only your doctor will know that the information is related to you. Any information collected during the study will be treated with the usual degree of confidentiality under the data protection act. Your identity will not be revealed in any publication or presentation of the results from this study. With your permission, your own doctor (GP) will be notified of your participation in the study.

10. Who is organizing and funding the research?

This research is coordinated by Professor Potter and Dr Robinson from the Leicester Warwick Medical School. The research is supported by the Stroke Association.

11. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (Dr, Telephone Number), or you may contact the hospital complaints department.

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.

(Hospital/ Institution/ GP Practice Headed Paper)
CONSENT FORM

Centre Number:
Patient Number:

**COSSACS: Relationship of Cardiac BRS and Large Artery
Function to Prognosis Following Acute Stroke Sub-study**

Researcher Name: **Dr**

I confirm that I have read and understand the information sheet dated 9th May 2005 (Protocol Amendment 1, Version 2) for the above study, and have had the opportunity to ask questions.

Please Initial

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.

I understand that my GP will be informed about my participation in this study, and I understand that by signing this consent form that I am granting permission for this.

I agree to take part in the above study.

Patient Name

Date

Signature

Witness Name

Date

Signature

Researcher

Date

Signature

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

Centre Number:

Patient Number:

**COSSACS: Relationship of Cardiac BRS and Large Artery
Function to Prognosis Following Acute Stroke Sub-study**

You or your relative has already been invited and agreed to their participation in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS). As you will remember, this study will compare the effects of continuing or stopping the treatment for high blood pressure that your relative was already taking at the time of their admission to hospital for the first two weeks after their stroke.

You are now being invited to confirm that you know of no reason why your relative would object to participation in a small supplementary research study, which will involve four additional 60-minute measurement periods of their blood pressure and blood vessels during the COSSAC Study. You should know that your relative may continue in the main COSSAC Study without any obligation to participate in this small supplementary research study.

However, before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your relative to take part. Thank you for reading this.

1. What is the purpose of the study?

Stroke is a common condition, and is associated with an increased risk of heart problems (such as angina, heart attack or rhythm problems), as well as an increased risk of future stroke. Areas of specialized cells (baroreceptors) in the carotid artery in the neck and in the heart are important in the control of blood pressure and heart rate. Baroreceptor function may be impaired following stroke, and may explain the increased risk of heart problems. These changes may also be related to hardening or stiffening of the blood vessels. This study will assess the relation between baroreceptor function, blood vessel stiffness and future heart problems and stroke, and whether this is altered by any blood pressure treatments that are taken immediately after stroke.

2. Why has your relative been chosen?

Your relative has been chosen to join in this study, because you or your relative have already agreed to their participation in the COSSAC Study. Altogether, 500 patients throughout the United Kingdom will be asked to join in this additional study.

3. Does your relative have to take part?

It is up to you to decide whether or not your relative should take part. If you do decide to their participation you will be given this information sheet to keep and be asked to sign a consent form. If you decide to their participation you or your relative are still free to withdraw at any time and

without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your relative receives.

4. What will happen to your relative if they take part?

If you agree to your relative joining this study, they will have a study test on coming into hospital, at 3 and 7 days, and at two weeks following the stroke, in addition to the study tests already involved in COSSACS. On each occasion, your relative will be asked to lie quietly on their bed whilst a small cuff is attached to the fingers of one hand to measure their blood pressure, 3 stickers to their chest to monitor their heart rate, and a band around their waist to measure their breathing pattern. After the readings have stabilised over a period of 15 minutes, recordings will then be made for three 5-minute periods. Assessment of blood vessel stiffness will then be made using a sensitive pressure probe mounted in a pen. Light pressure will be placed over the artery in the wrist and three 20-second recordings will be made. The procedure will then be repeated at the artery in the neck and in the groin, though there will be no need to remove undergarments.

5. What treatments will be used?

No specific treatments are given as part of this small study.

6. What are the possible disadvantages and risks of taking part?

The blood pressure cuff applies only a gentle pressure to the fingers to enable a blood pressure recording to be made every heart beat. This may cause a slight tingling in the fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care.

7. What are the possible benefits of taking part?

Your relative should not expect to receive any benefit from taking part in this study.

8. What if something goes wrong?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or you and your relative treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you and your relative.

9. Will your relative's taking part in this study be kept confidential?

The blood pressure and blood vessel stiffness data recorded during the study will be stored on computer, and transferred to the coordinating centre at Leicester University for subsequent analysis. However, your relative will not be identified by name, and only your relative's doctor will know that the information is related to them. Any information collected during the study will be treated with the usual degree of confidentiality under the data protection act. Your relative's identity will not be revealed in any publication or presentation of the results from this study. With your

permission, your relative's own doctor (GP) will be notified of their participation in the study.

10. Who is organizing and funding the research?

This research is coordinated by Professor Potter and Dr Robinson from the Leicester Warwick Medical School. The research is supported by the Stroke Association.

11. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (Dr, Telephone Number), or you may contact the hospital complaints department.

Once again, thank you for taking the time to read this information sheet and for considering your relative's participation in this study.

(Hospital/ Institution/ GP Practice Headed Paper)

RELATIVE ASSENT FORM

Centre Number:

Patient Number:

**COSSACS: Relationship of Cardiac BRS and Large Artery
Function to Prognosis Following Acute Stroke Sub-study**

Researcher Name: Dr

I confirm that I have read and understand the information sheet dated 9th May 2005 (Protocol Amendment 1, Version 2) for the above study, and have had the opportunity to ask questions.

Please Initial

I understand that my relative's participation is voluntary and that I am free to withdraw them at any time, without giving reason, without their medical care or legal rights being affected.

I understand that my relative's GP will be informed about their participation in this study, and I understand that by signing this consent form that I am granting permission for this.

I know of no reason why my relative would have refused to take part in research.

I agree to my relative taking part in the above study.

Patient Name

Relative Name
(Relationship)

Date

Signature

Researcher

Date

Signature

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

(Hospital/ Institution/ GP Practice Headed Paper)
PATIENT CONFIRMATION INFORMATION LEAFLET

Centre Number:

Patient Number:

**COSSACS: Relationship of Cardiac BRS and Large Artery
Function to Prognosis Following Acute Stroke Sub-study**

While you were unwell, your relative agreed to your participation in a research study. Now your condition has improved, you are being invited to decide for yourself whether you wish to join.

However, before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

1. What is the purpose of the study?

Stroke is a common condition, and is associated with an increased risk of heart problems (such as angina, heart attack or rhythm problems), as well as an increased risk of future stroke. Areas of specialized cells (baroreceptors) in the carotid artery in the neck and in the heart are important in the control of blood pressure and heart rate. Baroreceptor function may be impaired following stroke, and may explain the increased risk of heart problems. These changes may also be related to hardening or stiffening of the blood vessels. This study will assess the relation between baroreceptor function, blood vessel stiffness and future heart problems and stroke, and whether this is altered by any blood pressure treatments that are taken immediately after stroke.

2. Why have I been chosen?

You have been chosen to join in this study, because you have already agreed to participate in the COSSAC Study. Altogether, 500 patients throughout the United Kingdom will be asked to join in this additional study.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

4. What will happen to me if I take part?

If you agree to join this study, you will have a study test on coming into hospital, at 3 and 7 days, and at two weeks following the stroke, in addition to the study tests already involved in COSSACS. On each occasion, you will be asked to lie quietly on your bed whilst a small cuff is attached to the fingers of one hand to measure your blood pressure, 3 stickers to your chest to monitor your heart rate, and a band around your waist to measure your

breathing pattern. After the readings have stabilised over a period of 15 minutes, recordings will then be made for three 5-minute periods. Assessment of blood vessel stiffness will then be made using a sensitive pressure probe mounted in a pen. Light pressure will be placed over the artery in the wrist and three 20-second recordings will be made. The procedure will then be repeated at the artery in the neck and in the groin, though there will be no need to remove undergarments.

5. What treatments will be used?

No specific treatments are given as part of this small study.

6. What are the possible disadvantages and risks of taking part?

The blood pressure cuff applies only a gentle pressure to your fingers to enable a blood pressure recording to be made every heart beat. This may cause a slight tingling in your fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care.

7. What are the possible benefits of taking part?

You should not expect to receive any benefit from taking part in this study.

8. What if something goes wrong?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

9. Will my taking part in this study be kept confidential?

The blood pressure and blood vessel stiffness data recorded during the study will be stored on computer, and transferred to the coordinating centre at Leicester University for subsequent analysis. However, you will not be identified by name, and only your doctor will know that the information is related to you. Any information collected during the study will be treated with the usual degree of confidentiality under the data protection act. Your identity will not be revealed in any publication or presentation of the results from this study. With your permission, your own doctor (GP) will be notified of your participation in the study.

10. Who is organizing and funding the research?

This research is coordinated by Professor Potter and Dr Robinson from the Leicester Warwick Medical School. The research is supported by the Stroke Association.

11. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (Dr, Telephone Number), or you may contact the hospital complaints department.

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.

(Hospital/ Institution/ GP Practice Headed Paper)

PATIENT CONFIRMATION CONSENT FORM

Centre Number:

Patient Number:

**COSSACS: Relationship of Cardiac BRS and Large Artery
Function to Prognosis Following Acute Stroke Sub-study**

Researcher Name: **Dr**

I confirm that I have read and understand the information sheet dated 9th May 2005 (Protocol Amendment 1, Version 2) for the above study, and have had the opportunity to ask questions.

Please Initial

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.

I understand that my GP will be informed about my participation in this study, and I understand that by signing this consent form that I am granting permission for this.

I agree to take part in the above study.

Patient Name

Date

Signature

Witness Name

Date

Signature

Researcher

Date

Signature

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

Appendix: 7 Publications arising from this thesis

Papers

- D J Eveson, T G Robinson, N S **Shah**, R B Panerai, S K Paul, J F Potter. Abnormalities In Cardiac Baroreceptor Sensitivity In Acute Ischaemic Stroke Patients Are Related To Aortic Stiffness. Clin Sci [Lond]:108(5): 441–447, 2005
- Eames PJV, Mistri AK, **Shah N**, Robinson TG. Acute stroke hypertension: current and future management. Expert Review of Cardiovascular Therapy 3(3), 405–412, 2005.

Abstracts

- N **Shah**, J Chernova, R Panerai, J Potter, T Robinson. Reduced Cardiac Baroreceptor Sensitivity is not related to increased arterial stiffness following acute stroke in treated hypertensive patients. Cerebrovasc dis; (25); S2; 47; 2008
- N **Shah**, P Johnson, T Black, N Taub, R Panerai, J Potter, T Robinson. Age does not predict early outcome following acute stroke in treated hypertensive patients. Age & Ageing; Vol 37 (1); i54, 2008
- N **Shah**, P Johnson, T Black, J Chernova, N Taub, R Panerai, J Potter, T Robinson. Central arterial pressure predicts early outcome following acute Stroke in treated hypertensive patients. Stroke (38);510, 2007
- N **Shah**, N Taub, T Black, P Johnson, R Panerai, J Potter, T Robinson. Acute haemodynamic predictors of early outcome following acute stroke in treated hypertensive patients. J Human Hypertension, (20); S 23, 2006
- D.J.Eveson, N.S.**Shah**, T.G.Robinson, J.F.Potter. Central arterial stiffness is highly correlated with cerebrovascular risk factors and blood pressure in the acute stroke phase. Cerebrovascular diseases: (21); supp 4, 93, 2006

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