A FEASIBILITY AND SAFETY STUDY OF IMMEDIATE BLOOD PRESSURE MANIPULATION IN ACUTE POST-STROKE PATIENTS

Doctor of Medicine Thesis

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LIST OF ABBREVIATIONS

ACCESS	Acute Candesartan Cilexitil Evaluation of Stroke Study
ACE	Angiotensin-Converting Enzyme
AIS	Acute Ischaemic Stroke
ARB	Angiotensin Receptor Blocker
ASA	American Stroke Association
BD	Bis in die (twice daily)
BEST	Betablockers Evaluation in Stroke Trial
BI	Barthel Index
BP	Blood Pressure
BPV	Blood Pressure Variability
BRHS	British Regional Heart Study
BRS	Baro Receptor Sensitivity
CAST	Chinese Acute Stroke Trial
CBF	Cerebral Blood Flow
CCBs	Calcium Channel Blockers
CEA	Carotid End-Arterectomy
CHD	Coronary Heart Disease
CHHIPS	Controlling Hypertension and Hypotension Immediately Post-Stroke
CI	Confidence Interval
COSSACS	Continue Or Stop post-Stroke Antihypervensives Collaborative Study
CONSORT	Consolidated Standards of Reporting Trial
CRP	C-Reactive Protein
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DCLHb	Diaspirin Cross-Linked Haemoglobin
DW-MRI	Diffusion Weighted Magnetic Resonance Imaging
ECASS2	Second European-Australasian Acute Stroke Study
ECST	European Carotid Surgery Trial
EEG	Electro Encephalo Gram
EMBASE	Excerpta Medica DataBASE
EPO	Erythropoietin
ESR	Erythrocyte Sedimenation Rate
EUSI	European Stroke Initiative
FDA	Food and Drug Administration

GCS	Glasgow Coma Scale
GIST-UK	Glucose Insulin Stroke Trial-UK
GTN	Glyceryl Tri-Nitrate
HOPE	Heart Outcomes Prevention and Evaluation
HR	Hazard Ratio
HTA	Health Technology Assessment programme
ICD	International Classification of Diseases
ICH	Intra Cerebral Haemorrhage
IMAGES	Intravenous MAgnesium in Stroke Study
INTERACT	INTEnsive blood pressure Reduction in ACute haemorrhage Trial
IQR	Inter Quartile Range
IST	International Stroke Trial
LACS	LACunar Stroke Syndrome
MAP	Mean Arterial Pressure
MEDLINE	National Library of Medicine Database
MCA	Middle Cerebral Artery
MHz	Mega Hertz
mg	milligrammes
mmHg	millimetres of mercury
mmol/l	millimoles per litre
μmol/l	micromoles per litre
MONICA	MONItoring of trends and determinants in CArdiovascular disease
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NA	Noradrenaline
NaCl	Normal Saline (0.9% sodium chloride)
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NE	Nor Epinephrine
NIHSS	National Institutes of Health Stroke Scale
NHS	National Health Service
NINDS	National Institutes of Neurological Disorders and Stroke
NMDA	N-Methyl D-Aspartate
OCSP	Oxfordshire Community Stroke Project Classification
OR	Odds Ratio
OXVASC	OXford VAScular Study

PACI	Partial Anterior Circulation Infarct
PE	Phenyl Ephrine
PET	Positron Emission Tomography
PICH	Primary Intra Cerebral Haemorrhage
PEG	Percutaneous Endoscopic Gastrostomy
POCI	POsterior Circulation Infarct
PP	Pulse Pressure
PROGRESS	Perindopril pROtection aGainst REcurrent Stroke Study
R&D	Research & Development
RCT	Randomised Controlled Trial
RR(R)	Relative Risk (Reduction)
rt-PA	Recombinant Tissue-Plasminogen Activator
SAE	Serious Adverse Event
SAH	Sub Arachnoid Haemorrhage
SBP	Systolic Blood Pressure
SD	Standard Deviation
SPECT	Single Photon Emission Computed Tomography
TACI	Total Anterior Circulation Infarct
TCD	Trans Cranial Doppler
TIA	Transient Ischaemic Attack
TOAST	Trials of ORG 10172 in Acute Stroke Treatment
UK	United Kingdom
US	United States
WHO	World Health Organisation

STUDY DECLARATION

The CHHIPS Trial Steering Committee conceived the idea of the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) Study, and acquired funding from the National Health Service Research & Development Health Technology Assessment (NHS R&D HTA) Programme. Members included: Professor John Potter (Co-Principal Investigator), Professor Of Ageing and Stroke Medicine, University of East Anglia; Professor Thompson Robinson (Co-Principal Investigator), Professor of Stroke Medicine, Leicester Warwick Medical School; Professor Hugh Markus (Chairman), Professor of Neurology, St Georges Hospital Medical School, London; Professor Christopher Bulpitt, Professor of Geriatric Medicine, Imperial College School of Medicine; Dr Avril Drummond, Lecturer in Occupational Therapy, Queens Medical Centre, Nottingham; Professor Gary Ford, Professor of Pharmacology of Old Age, University of Newcastle-Upon-Tyne; Professor Carol Jagger, Professor of Epidemiology, University of Leicester; and Dr Joanne Knight, Associate Director of Research and Development, Stroke Association.

I was the overall Trial Coordinator, with responsibility for the day-to-day management of the study, trial reporting, site monitoring, data cleaning and liaison with the funding body, and relevant ethical and regulatory bodies. I was also the main researcher carrying out recruitment and retention in Leicester.

Data collection was carried out at the various sites participating in the CHHIPS Study by local researchers, including: Aintree – Elalaine Bacabac, John Jones; Bournemouth – Dr Toby Black, Anna Orpen; Exeter – Dr Paul Johnson; Leicester – Dr Nainal Shah, Dr Penny Eames; Newcastle – Dr Anand Dixit, John Davis; Wansbeck – Sue Elliott.

ETHICAL DECLARATION

This study (within the confines of the Controlling Hypertension and Hypotension Immediately Post-Stroke study) was 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. Consent was obtained according to the requirements of the multi-centre and local research ethics committees. Regulatory approval was obtained from the Medicines and Healthcare products Regulatory Authority and the Research & Development Departments of participating sites. Management of all personal data was in compliance with the Data Protection Act 1998. Changes were made to the study to ensure compliance with the European Clinical Trials Directive (Directive 2001/20/EC), including appointing a Sponsor, the NHS R&D HTA.

ACKNOWLEDGEMENTS

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I would like to acknowledge the funding provided by the National Health Service Research & Development Health Technology Programme, for the CHHIPS study and my post as Trial Coordinator.

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Suzanne Stevens, Statistician, Department of Cardiovascular Sciences carried out the statistical analysis for Chapter 6, and Julia Chernova, Statistician, Trent RDSU, Leicester carried out the statistical analysis for Chapters 4 and 5.

This work is a tribute to the patients who, despite having suffered a life-changing stroke, understand the benefits of research in clarifying the prevailing uncertainties in clinical medicine and consent to participation, for the greater good, and at no great benefit to themselves.

Last, but not the least, I cannot neglect to mention my wife, Hayley, and our two children, Krishn and Jessica, who have endured my absences during the conduct of this study, with little complaint.

ABSTRACT

A feasibility and safety study of immediate blood pressure manipulation in acute post-stroke patients

Amit K Mistri

This thesis examines the feasibility and safety of blood pressure (BP) lowering using labetalol or lisinopril, in acute ischaemic or haemorrhagic stroke within the confines of a randomised double-blind placebo-controlled trial.

A systematic review of pressor therapy in acute stroke identified pilot studies which have reported no harmful effects, and no randomised controlled trials. While pressor therapy was not investigated in this study, centres with established rapid admission protocols, availability of urgent computerized tomography and intensive monitoring facilities will be needed for such a study.

Elevated BP following acute stroke is associated with adverse prognosis. Whether BP lowering in this situation is beneficial or harmful is unknown. Active intervention in this study significantly reduced SBP during the first 24 hours and at two weeks, but not DBP, compared to placebo. No significant difference in short-term outcome (death and dependency at 2 weeks), or adverse events (including early neurological deterioration) was seen.

Sublingual lisinopril for dysphagic patients was as effective and well-tolerated as oral lisinopril. This is a novel method of administering anti-hypertensives in acute stroke, which could be administered at first contact with healthcare providers, and does not require intensive monitoring as with intravenous agents like labetalol.

Recruitment to the study was poor, primarily due to inadequate number of centres, fewer patients conforming to eligibility criteria than initially estimated, and delays in hospital admission. Analysis of screening data showed that only a small minority of patients with acute stroke were randomised to one of two stroke-BP studies (<9%). This will limit the applicability of results to the clinical scenario.

A definitive trial of BP lowering in acute stroke with adequate sample size is needed to confirm the safety results of the current study, and to establish the impact on clinically relevant outcomes.

1 INTRODUCTION

1.1 STROKE

1.1.1 Definition

Stroke is a clinical syndrome typically defined as a sudden onset focal neurological deficit, presumed to be of vascular origin (i.e. excluding other potential causes for that presentation), resulting from focal brain dysfunction, with symptoms lasting more than 24 hours[1]. The underlying pathology of stroke can be cerebral ischaemia (acute ischaemic stroke – AIS), primary intracerebral haemorrhage (PICH) or subarachnoid haemorrhage (SAH). However, the pathogenesis of SAH is quite different from the other sub-types, and the management is generally considered distinct from that of AIS or PICH. This thesis will not include this stroke type, and the term "stroke" hence refers to AIS and PICH only. Even among patients with AIS, subtypes exist[2], thus stroke is not a single disease entity, but a heterogeneous condition with varying pathogenesis, each subtype being associated with different risk factors and requiring an individualised management strategy.

Depending on the duration from symptom onset, stroke can be classified as: acute (<2 weeks); or chronic (>2 weeks). The cut-off points are based on the observation that the initial physiological instability including blood pressure (BP) elevation following stroke settles down after about 2 weeks[3].

If the symptoms last for less than 24 hours, the syndrome is termed a 'transient ischaemic attack' (TIA)[1]. This cut-off point is historical, and diffusion-weighted magnetic resonance imaging (DW-MRI) has revealed that 49% (35-67%) of those with clinical TIA's have underlying brain abnormalities[4]. In one study of patients with a TIA, 56% (5 out of 9 patients) of those who had a relevant DW-MRI abnormality at presentation demonstrated a subsequent infarct in the corresponding region. Conversely, among the five patients with no DW-MRI abnormality at presentation who had follow up imaging, none had a subsequent infarct[5]. It has been suggested that the clinical diagnosis of a TIA should be restricted to a much shorter time interval, to agree with the findings of brain imaging[6,7] and the fact that ischaemic abnormalities on DW-MRI are more frequent with longer duration of symptoms[5]. Whilst most TIA's resolve within 60 minutes, the vast majority (85%) of the remainder have persistent symptoms beyond 24 hours[8,9]. Clinical differentiation between a TIA and a stroke is not possible until either the first 24 hours have elapsed or all neurological deficits have resolved.

1.1.2 Impact of Stroke

Stroke is the third leading cause of mortality (see Figure 1.1 and Figure 1.2 below) in the Western world, after coronary heart disease (CHD) and cancer[10], accounting for ~11% of all deaths in England and Wales over the past decade[11]. It is also the commonest cause of long-term disability[10] affecting quality of life, particularly for older people. Each year 110,000 people in England and Wales have their first stroke, 30,000 people go on to have further strokes and 20,000 people have a transient ischaemic attack (TIA). However, it is not restricted to the elderly, with 25% of strokes occurring in those under 65 years of age[12]. At any one time there are 25-35 patients with stroke as their primary diagnosis in the average UK general hospital[13]. There are close to a million stroke survivors in England, with around half being dependent on others for everyday activities[11]. A substantial proportion of health and social care resources are devoted to the immediate and continuing care of people who have had a stroke. In the United Kingdom (UK), with an estimated annual cost of £7 billion, and a new stroke occurring every five minutes, the burden to society is substantial[12]. Underlining the significant burden to society from stroke is the fact that direct healthcare costs are 1.5 times that for CHD.

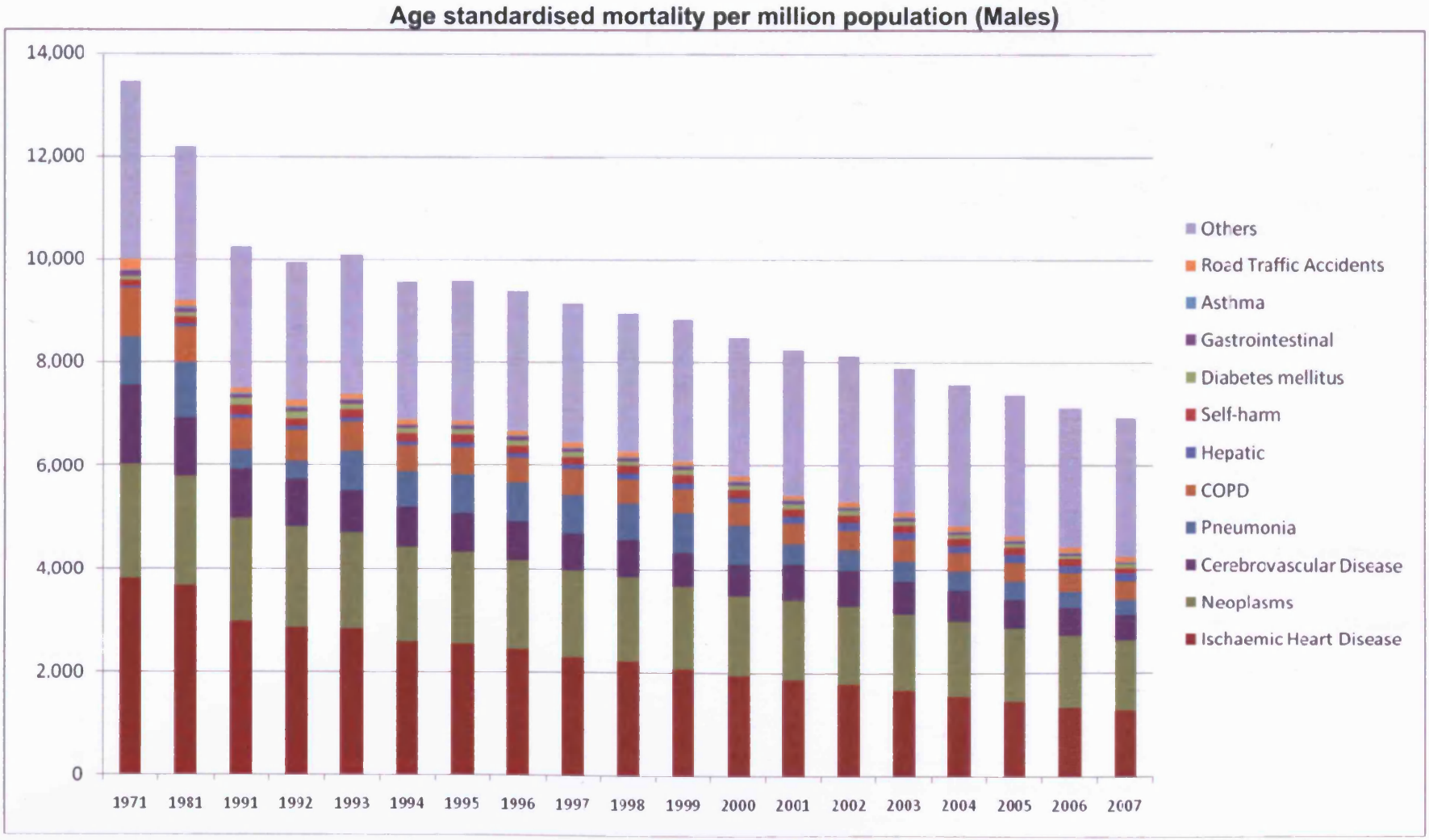

Figure 1.1: Causes of mortality in England and Wales (a) Males
Data from Office of National Statistics – Accessed 16th December 2008

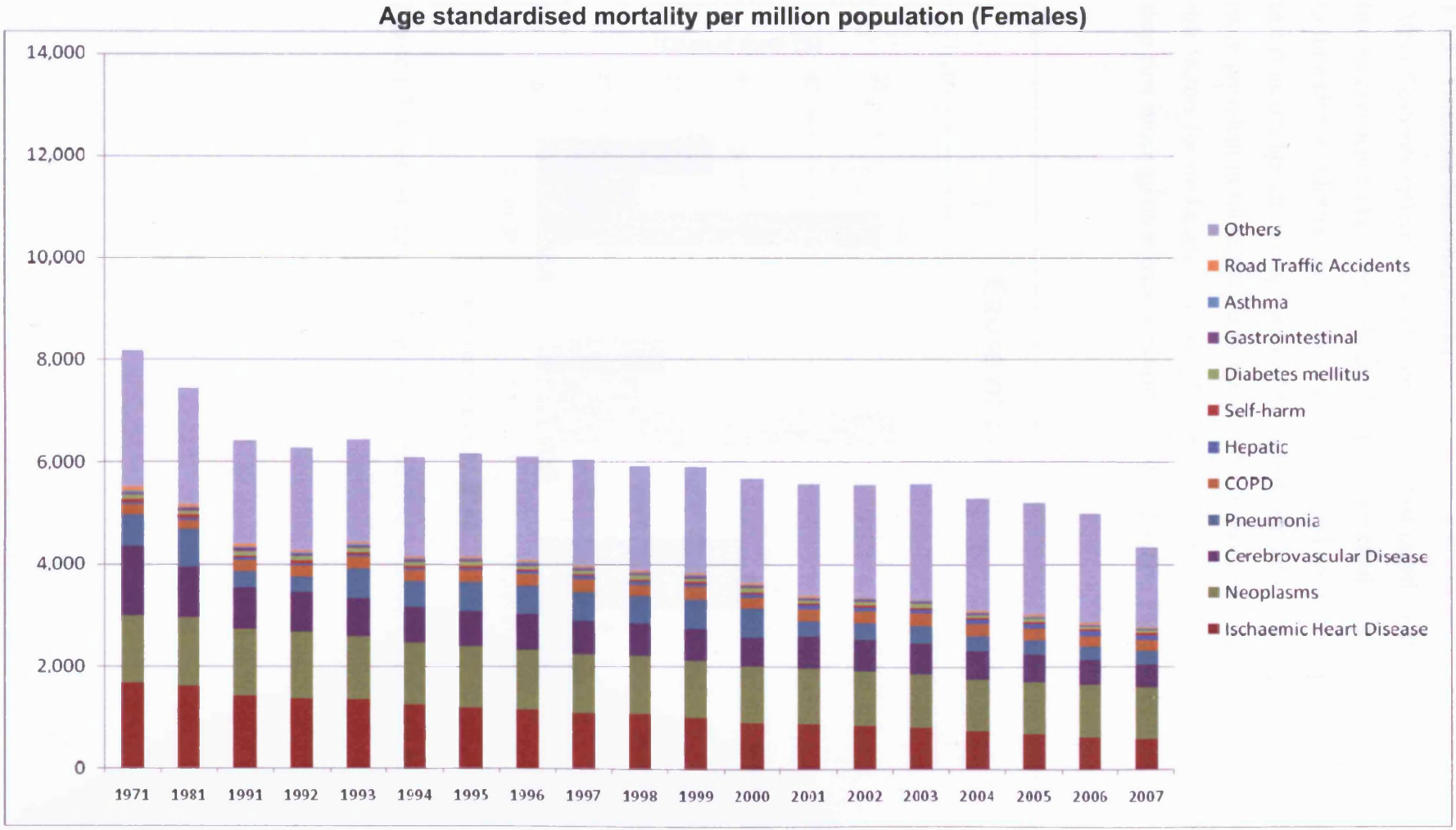

Figure 1.2: Causes of mortality in England and Wales (b) Females
Data from Office of National Statistics – Accessed 16th December 2008

1.1.3 Outcome following Stroke

70% of patients suffering a stroke survive the first month, and amongst the survivors, 65% can live independently at one year whilst 35% are significantly disabled, and around 5% are admitted to long-term residential care[11]. Following a first ischaemic stroke, the majority of deaths in the initial month are due to the direct effects of the stroke (~50%), but deaths from CHD become more prevalent in those that survive 6 months or more, not unduly surprising given the similar risk factors for stroke and CHD (see Figure 1.3)[14]. About a third of patients who have suffered their first stroke go on to have a recurrence within 5 years.

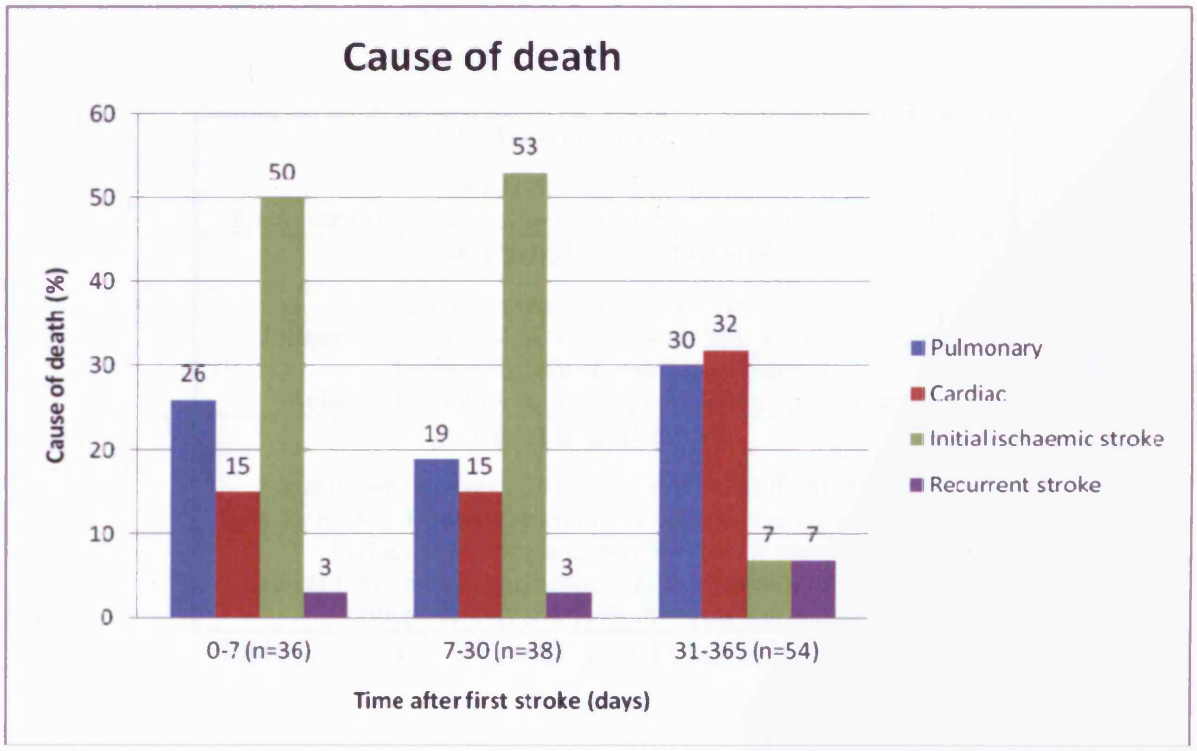

Figure 1.3: Cause-specific mortality at selected time intervals following a first ischaemic stroke[14]

1.2 THE EPIDEMIOLOGY OF STROKE

1.2.1 Limitations

Studies investigating the epidemiology of stroke are difficult to conduct, and do not lend themselves to comparison due to various reasons including: inadequate case-ascertainment; inclusion of limited age groups; differing study designs; changing definition of stroke over time; lack of information on stroke subtypes; lack of clarity of population at risk; short duration of study; and non-standardized presentation of rates by age, group, and sex. Sudlow and Warlow suggested standardised criteria for comparable studies of stroke incidence (see Table 1.1)[15].

STANDARD DEFINITIONS
WHO definition of stroke; First-ever-in-a-lifetime stroke data available (even if unpublished)
STANDARD METHODS
Complete, community-based ascertainment; Prospective study design, ideally with "hot pursuit" of cases; Large well defined stable population; Reliable method for estimating population denominator.
STANDARD DATA
Separate whole years of data available (even if unpublished); Data for men and women separately available (even if unpublished); Include ages up to and over 85 years if possible; Standard mid-decade age bands available (even if unpublished); Data preferably available in 5-year age bands.

Table 1.1: Criteria for comparable studies of stroke incidence[15]

Study Site	Data collection	Duration (years)	Population	Age range (years)	Total strokes	Incidence/ 1000 years	Hospital admission rate	CT/MRI or autopsy rate	Delay to scan after onset
Oxfordshire UK (OCSP)	1984	4	105,476	--	675	--	60	--	--
Dijon France	1987	5	135,711	--	909	--	90	--	--
Oyabe Japan	1987-1991	4	170,312	≥25	701	4.1 (3.8-4.4)	41	--	--
Umbria Italy	1988	3	49,218	--	375	--	85	--	--
Rochester Minnesota	1988	5	65,933	--	496	--	85	--	--
Valle d'Aosta Italy	1989	1	114,325	--	255	--	81	--	--
Perth Australia	1989	1	138,708	--	250	--	80	--	--
Frederiksberg Denmark	1989-1990	1	85,611	all	262	3.1 (2.7-3.4)	--	74	--
Espook Finland	1989-1991	2	134,804	≥25	594	2.2 (2.0-2.4)	86	62	--
Soderham Sweden	1990	2	29,624	--	220	--	90-95	--	--
Auckland New Zealand	1991-1992	1	945,369	≥15	1305	1.4 (1.3-1.5)	73	41	30
Warsaw Poland	1991	2	183,199	--	462	--	87	--	--
Novosibirsk Russia	1992	1	158,234	all	366	2.3 (2.1-2.5)	60	46	28
Belluno Italy	1992-1993	1	211,389	all	474	2.2 (2.0-2.4)	92	90	30
Arcadia Greece	1993-1995	2	80,774	≥18	555	3.4 (3.1-3.7)	90	82	7
L'Aquila Italy	1994	1	297,838	all	819	2.8 (2.6-2.9)	92	89	7
Inherred Norway	1994-1996	2	69,295	≥15	432	3.1 (2.8-3.4)	87	88	21
Erlangen Germany	1994-1998	2	101,450	all	354	1.3 (1.2-1.4)	95	96	3-14
Perth Australia	1995-1996	1	136,095	all	213	1.6 (1.4-1.8)	88	78	--
South London UK	1995-1996	2	234,533	all	612	1.3 (1.2-1.4)	84	88	30
Melbourne Australia	1996-1997	1	133,816	all	276	2.1 (1.8-2.3)	--	91	28
Martinique Fr W Indies	1998-1999	1	381,364	all	580	1.6 (1.5-1.8)	94	93	30
Uzhgorod W Ukraine	1999-2000	1	125,482	all	352	2.8 (2.5-3.1)	66	41	--
Oxfordshire UK (OXVASC)	2002-2004	1	91,106	all	262	0.4 (0.3-0.5)	--	--	--

Table 1.2: Studies reporting stroke incidence, confirming to guidelines proposed by Sudlow and Warlow (adapted from Sudlow et al[15], Feigin et al[16], and Rothwell et al[17])

Study Site	Data collection	Age Range (years)	No of stroke patients	Observed crude rate/1000 population		
				Male	Female	Total
Auckland New Zealand	1991-1992	≥15	7491	10.7	9.7	10.2
Rochester Minnesota	1990-1993	≥55	352	5.0 (4.2-5.8)	4.3 (3.7-4.9)	--
Cordillera Bolivia	1994	all	16	2.5	1.0	1.7 (0.9-2.5)
Four regions USA	1989-1990	≥65	246	6.8	3.2	4.7
Yorkshire UK	1991	≥55	415	5.0 (4.3-5.8)	4.4 (3.9-5.1)	4.7 (4.3-5.2)
Newcastle UK	1993	≥45	116	--	--	4.7 (4.6-5.9)
Kitara Papua New Guinea	1990	20-96	0	0	0	0
Taiwan China	1994	≥35	71	6.37	5.53	5.95
L'Aquila Italy	1992	≥65	80	9.6 (6.9-12.3)	5.5 (3.6-7.3)	7.3 (5.7-8.8)

Table 1.3: Studies reporting stroke prevalence, confirming to guidelines proposed by Sudlow and Warlow (adapted from Sudlow et al[15] and Feigin et al[16])

1.2.2 Stroke Incidence

Two recent systematic reviews have estimated the age standardised incidence of stroke to be 3-5 per 1000 patient years (1996)[15]and 4.2-11.7 per 1000 patient years (2003), the second only including those aged 55 years or more[16] (see Table 1.2 above). Where studies included reliable data on stroke subtype, the age-standardised incidence of AIS was 3.4 to 5.2 per 1000 person-years, and for PICH was 0.3 to 1.2 per 1000 person-years. Age-specific incidence of stroke increases progressively with each decade of life, ranging from 0.1-0.3 per 1000 patient years (age<45) to 12-20 per 1000 patient years (age 78-84), the highest rates reported in studies from Japan, Russia and Ukraine.

Socioeconomic gradient

Despite adjustment for conventional risk factors, a significant socioeconomic gradient in the incidence of stroke has been documented in several studies, with higher incidence in the lower socioeconomic classes[18,19,20,21,22,23]. There is a stronger gradient in ischaemic (as opposed to haemorrhagic) stroke[18,19]. The socioeconomic disparity has persisted over time, despite overall fall in mortality[24].

1.2.3 Stroke Prevalence

The age-standardised prevalence of stroke is 46.1-73.3 per 1000, with higher rates in men (58.8-92.6 per 1000) than women (32.2-61.2 per 1000)[16]. The highest prevalence was reported in L'Aquila, Italy and Newcastle, UK, with no significant differences among the other centres. Two studies from New Zealand and Yorkshire UK reported the proportion of total strokes with associated disability or impairment as 55% and 77% respectively (see Table 1.3 above). Though the WHO-MONICA study reported significant geographical variation[25], this was not confirmed in the more recent review by Feigin et al[16]. Across England, a significant variation has been reported[26], with a "north-south gradient", incidence being lower in the south, after adjustment for individual risk factors[22]. Similarly stroke prevalence is higher in the south eastern states of the United States ("stroke belt"), partly explained by the higher prevalence of risk factors in this region, including hypertension and cigarette smoking[27].

1.2.4 Stroke Case-Fatality

One month case fatality for all strokes (including SAH) was 22.9% in a review of 13 studies (AIS – 16%, PICH – 42%, SAH – 32%)[16]. There was little geographical variation, though rates in Japan were lower (17%) and rates from Belluno, Italy were high (33%). Annual mortality rates specific for age and sex increased progressively with age.

The variation in age-standardised mortality across Western Europe is summarised in Figure 1.4 (next page). Age-standardised mortality is the highest in Portugal. The UK fares poorly with rates being second highest amongst women and third highest amongst men (see Figure 1.4). Mortality among men is much higher across the board, compared to women.

Coding of diagnosis may play a part in explaining some of the variation in stroke-related mortality, though variation in care for stroke patients, both acute and longer-term rehabilitation, is the likely underlying cause. The reason for gender differences in terms of outcome remains unclear.

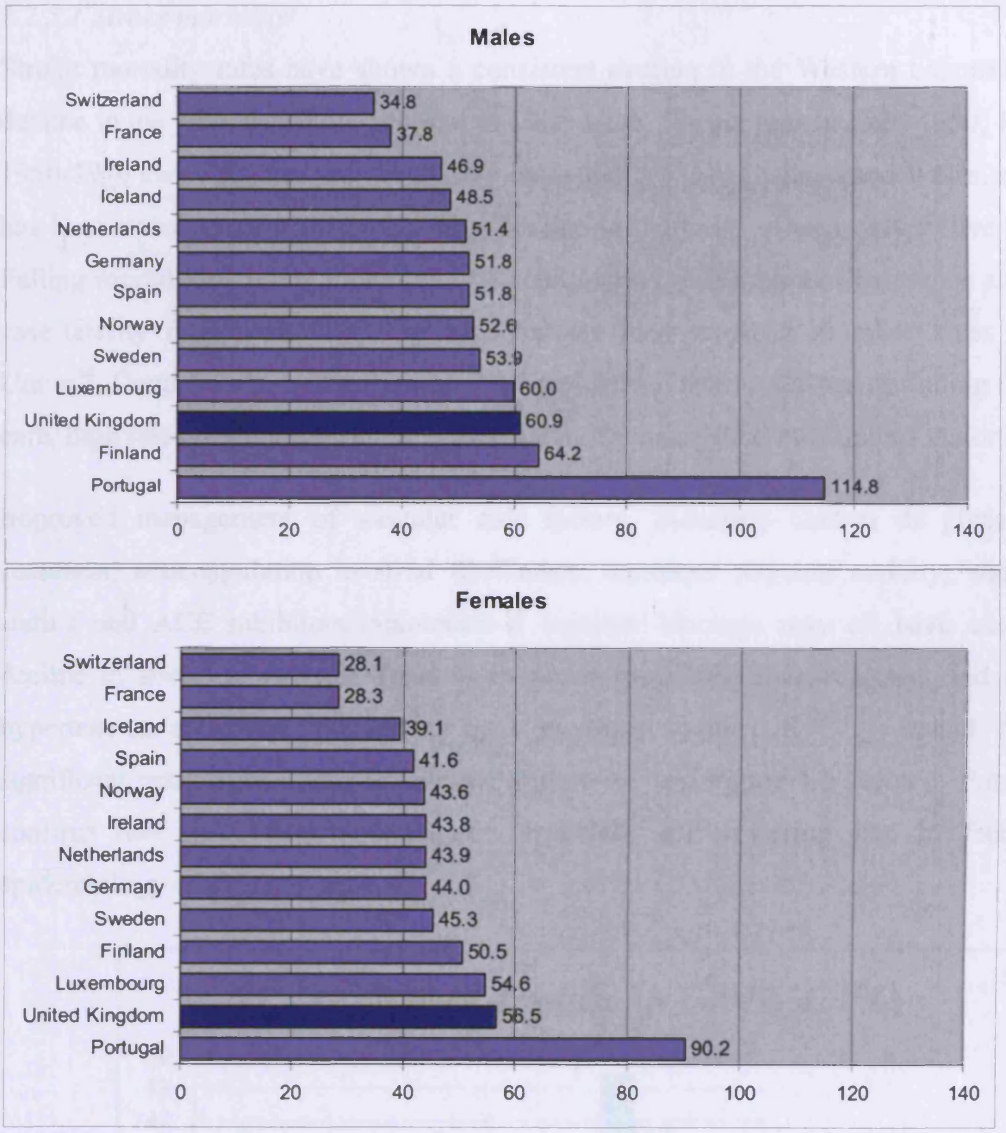

Figure 1.4: Age standardised death rate due to cerebrovascular diseases (ICD-10 code: I60-I69) for Western European Countries in 2004.
European health for all database (HFA-DB). World Health Organization Regional Office for Europe. Updated: November 2007 (Accessed 15th Jan 08 - data.euro.who.int/hfadb/)

1.2.5 Time Trends

1.2.5.1 Stroke mortality

Stroke mortality rates have shown a consistent decline in the Western countries. The rate of decline in the USA was 0.5% per year in 1900-1920, 1% per year in 1920-1950, 1.5% per year in 1950-1970 and 4-5% per year from 1974 onwards[28,29,30]. In England and Wales, a similar decline has been noted since 1900[31,32,33]. This decline in mortality is seen irrespective of age and sex. Falling mortality is likely to be due to a combination of decrease in incidence and a decrease in case-fatality rates. However, stroke mortality has increased in other areas (former Soviet Union[34], Central and Eastern Europe[35]), where socioeconomic factors, including decline in health care, high rates of smoking and increased alcohol consumption may have a major influence.

Improved management of vascular risk factors, including control of glycaemia, smoking cessation, anticoagulation in atrial fibrillation, increased physical activity, widespread use of statins and ACE inhibitors/angiotensin-II receptor blockers may all have contributed to the decline in stroke mortality. There is evidence suggesting that treatment and control rates of hypertension and other risk factors have increased in the UK[36,37,17], though there remains a significant margin for improvement (see Figure 1.5 and Figure 1.6 below). Future studies may confirm that risk factor modification especially BP lowering has in fact modified the epidemiology of stroke disease.

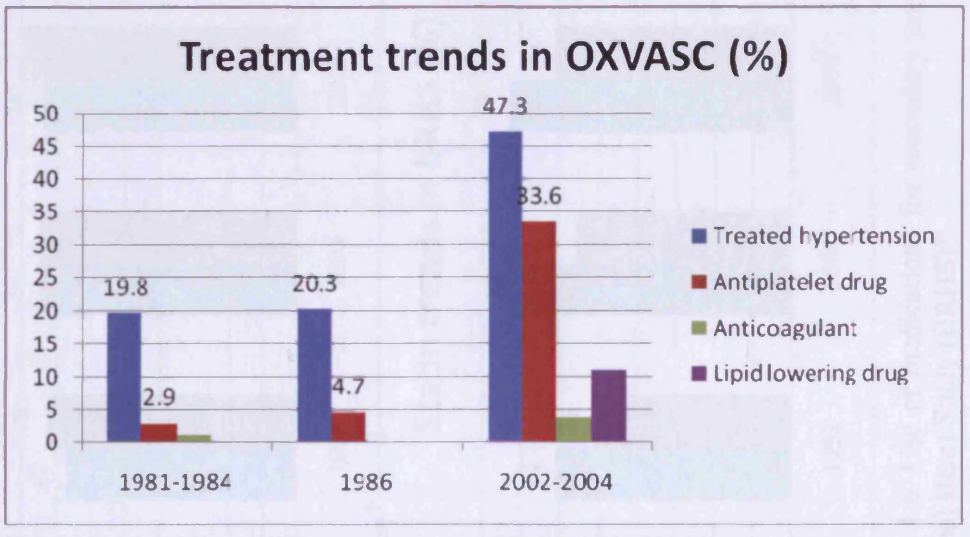

Figure 1.5. Longitudinal prevalence (%) of medications in patients with incident stroke - Oxford Vascular Study[37]

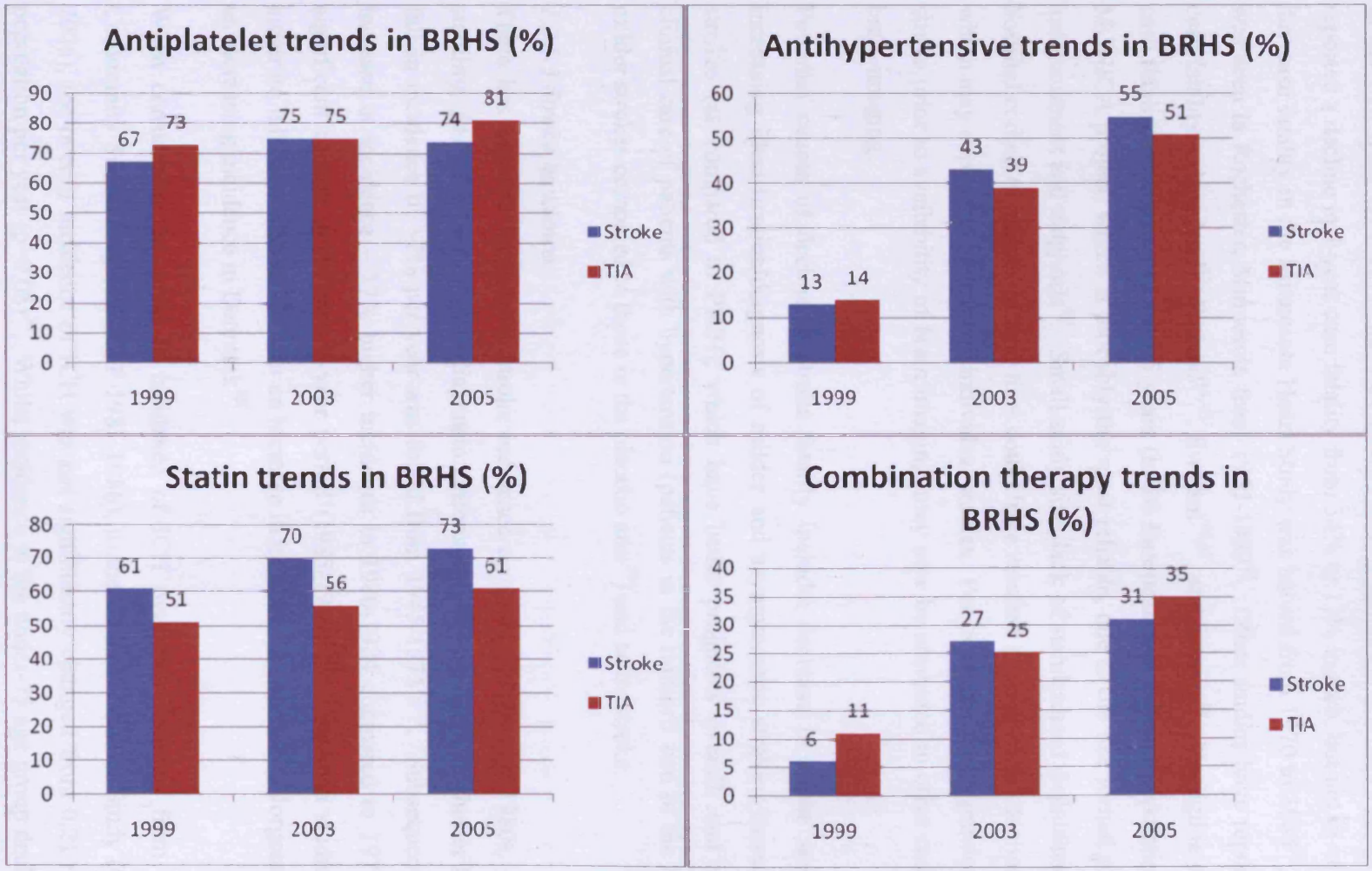

Figure 1.6. Use of medications for secondary prevention of cerebrovascular disease in patients with stroke and TIA – British Regional Heart Study (BRHS)[38]

1.2.5.2 Stroke case-fatality

In the UK, from 1955-1971, the case fatality fell by about 30%[39]. The Framingham study also reported a decline in 1-year case fatality from 34% to 13% in men, but not in women[40]. The 28-day case fatality in the Minnesota Heart Study was halved from 1970 to 1985[41], but no decrease was seen in Rochester, Minnesota from 1955-1989[42]. Other studies have reported reduction in case fatality – Auckland[43], Finland[44,45], Sweden[46,47], and Estonia[48]. Negligible changes in stroke case fatality were reported over 5 years (in 16 European and 2 Asian populations) in the WHO MONICA project, which is probably the most reliable, due to the use formal protocols for case ascertainment and diagnosis[49]. Small study size, lack of standardised definitions and changes in hospital coding of diagnoses over time could have resulted in an artificial decline in case fatality, which may explain the results of individual studies. For example, deaths previously attributed to stroke prior to availability of brain imaging, may now be attributed to other causes identified on brain imaging.

Potential causes of decline in stroke fatality include: decrease in stroke severity over time; increasing identification/diagnosis of milder and asymptomatic strokes; increase in ischaemic strokes (as compared to PICH), which have better prognosis overall; and improvements in clinical care of patients with hypertension (patients in the ramipril arm of the HOPE study had milder strokes compared to those in the placebo arm[50]) and acute stroke.

1.2.5.3 Stroke incidence

There has been an increase in stroke incidence up to the 1970s and 1980s, with subsequent stability. Standard methods and diagnostic criteria have been used in Rochester Minnesota, and a fall in incidence of ~2% per year was found from 1945-1975[42,51]. Subsequently there was an increase in incidence – 17% higher incidence in 1980-1984 compared to 1975-1979, with no significant change in the next 5-year period (1985-1989)[42,52]. Swedish studies have reported either no fall in incidence[53,46,47], or an increase in incidence in women[54]. Jorgensen et al reported an increasing incidence in Denmark[55].

When considering the trend in incidence of ICH over two decades, from the Oxfordshire Community Stroke Project (OCSP 1981-1986), to the Oxford Vascular Study (OXVASC 2001-2006), the overall incidence of ICH was not significantly changed from 0.21 to 0.16 per 1000 population per year (p=0.08)[56]. Whilst incidence in the under-75 age group declined from 0.1 to 0.06 per 1000 population per year (p=0.03), the incidence in the growing older population

remained unchanged (1.55 to 1.44 per 1000 population per year, p=0.72). Also there was a fall in the incidence of intracerebral haemorrhage associated with pre-morbid hypertension (BP≥160/100 mmHg, RR 0·37, 95% CI 0·20-0·69, p=0·002), and an increase in the incidence of antithrombotic-associated ICH (RR 7·4, 95% CI 1·7-32, p=0·007).

Possible causes of bias in studies reporting decline in stroke mortality include: changes in diagnostic practice with increasing identification of milder strokes following the advent of neuroimaging; improvements in medical note keeping resulting in better diagnostic coding may have contributed to an apparent increase in stroke incidence; increasing clinical and research interest in stroke; and changing socioeconomic conditions.

Possible causes for decreasing stroke incidence include: treatment of high BP (the National Health Survey for England reported an increased rate of awareness, treatment and control of hypertension, from 1994 to 1998[36]); reduced exposure to risk factors associated with high BP; overall reduction in dietary salt; reduced exposure to other risk factors, including cigarette consumption, physical activity and diet; and atmospheric pollution[57,58]; and the competing risk of CHD - Haberman et al suggested that stroke prone individuals may be dying of CHD-related events before reaching an age where a stroke is likely to occur[59].

In summary, the existing data on stroke lacks standardisation in study design and data collection to enable comparison across different regions, thus denying us a comprehensive understanding of the epidemiology. It remains unclear whether the documented trends in stroke incidence and prevalence are a reflection of true trends or artefacts e.g. due to changes in definition or documentation of strokes. The reliable datasets suggest falling stroke-related mortality in the West, with increase in Eastern Europe, reduction in case fatality, decreasing stroke incidence until the 1970s followed by stabilisation or even an increase.

1.3 PROGNOSTIC FACTORS IN EARLY ACUTE STROKE

Epidemiological studies have identified factors associated with poor prognosis following stroke. This information is useful when communicating likely outcome to stroke patients and their relatives. In addition, it may be possible to identify factors that are amenable to intervention, thus potentially improving outlook following stroke. While stroke subtypes (ischaemic and primary haemorrhagic) share some prognostic factors, their relevance is different, and these subtypes are considered separately below.

1.3.1 Acute Ischaemic Stroke

1.3.1.1 Mortality

Age

Age is an independent risk factor for mortality following acute ischaemic stroke[60,61,62,63,64]. In the German Stroke Database, age was an independent predictor of mortality at 100 days (OR 1.08, 95% CI 1.06-1.10)[60]. Data from 152 consecutive patients in a French centre and the Randomized Trial of Tirilazad Mesylate in Acute Stroke trial revealed that age was an independent predictor of death or dependence at 3 months[61,62]. Other studies have reported a higher chance of a positive functional outcome in younger stroke survivors[63], and a trend towards increased mortality in elderly patients (age≥80 years), compared to younger counterparts[64].

Gender

Data with regards to the impact of gender on mortality following stroke have been conflicting. While some studies have shown that women had higher case-fatality rates[25] and a higher death rate for the first year following a stroke[65], compared to men, the Framingham study reported the converse[66].

Ethnicity

Studies have reported an increased mortality rates following stroke in certain ethnic groups e.g. higher mortality following stroke amongst blacks (2.5 times that of Caucasians)[67], African-Americans[68], and Maoris of New Zealand[43]. However, the North Manhattan study did not report significant variation[69]. Proposed reasons for ethnic variation include variation in risk factors and lifestyle choices.

Initial Stroke Severity

Various markers of increased stroke severity have been associated with worse outcome e.g. higher NIHSS score[60,61,62,63,70], reduced consciousness[71], infarct size on brain scan[72] and stroke syndrome (major hemispheric or basilar[73,74], total anterior circulation strokes[75]). Thus initial stroke severity is an important predictor of outcome.

Pyrexia

Admission pyrexia occurs in almost half of patients admitted with acute stroke[76]. It has been associated with large infarct volume[77], high case-fatality and poor functional outcome (after adjustment of initial severity)[78]. In the Copenhagen Stroke Study, a 1°C increase in temperature was associated with a 30% increase in 5-year mortality[79]. A meta-analysis of human studies concluded that there was an increased risk of mortality in pyrexial patients as opposed to apyrexial (OR 1.19, 95% CI 0.99 to 1.43)[80]. Body temperature is also related to early neurological deterioration[81].

Diabetes and hyperglycaemia

Hyperglycaemia is common, seen in 40% of patients following an acute stroke[82]. Higher admission glucose levels following acute ischaemic stroke have been associated with worse functional outcome, increase mortality, higher odds of symptomatic ICH (OR 1.75, 95% CI 1.11-2.78, per 100 mg/dL increase in admission glucose, p=0.02)[83], and higher rates of ICH following thrombolysis[84,85,86,87,88,89], as well as increased mortality[90,91,82]. Hyperglycaemia independently increased the risk for death at 30 days (HR 1.87, p<0.01), 1 year (HR 1.75, p<0.01), and 6 years after stroke (HR 1.41, p<0.01)[82]. Hyperglycaemia has also been associated with poor prognosis after stroke independent of size or severity[92]. In those with type 2 diabetes, a 1% decrease in HbA1c was associated with a 21% reduction in deaths related to diabetes, 14% decrease in deaths related to MI, and a 14% decrease in microvascular complications[93]. The increased vascular risk has been attributed to promotion of atherosclerosis, and the occurrence of atherogenic conditions including hypertension (seen in up to 60% of people with Type 2 diabetes[94]), obesity and dyslipidaemia, and predisposition to brain injury and/or ICH[83]. Similarly a diagnosis of pre-stroke diabetes is associated with increased mortality[62,60].

Cardiac disease

Atrial fibrillation and congestive cardiac failure are both associated with increased stroke severity and case-fatality rates[95,96,97]. Congestive cardiac failure is also an independent predictor of death 5 years after stroke[98]. Dilated cardiomyopathy predisposes to left ventricular thrombus formation and consequent increased risk of embolic stroke.

Biochemical Derangements

Raised CRP is associated with an increased risk of death following stroke[99,100]. Similarly raised CRP at discharge is associated with subsequent risk of ischaemic stroke at 1 year[99]. This is in keeping with an increased risk of ischaemic stroke seen in the Framingham study, after adjusting for other risk factors[101]. Other non-specific inflammatory markers may also have prognostic value e.g. raised ESR, raised leucocyte count and raised fibrinogen. Renal dysfunction (elevated urate level[102], reduced creatinine clearance and raised creatinine[103]) has also been associated with an increased risk of death following a stroke.

1.3.1.2 Early Deterioration

Early deterioration following stroke has previously been classified into three categories: early neurological deterioration (progressive neurological deficits); cerebral oedema; and medical complications[104]. Early neurological deterioration occurs in 19-58% of patients, and is associated with increased morbidity and mortality[104,105,106,107,108]. The significant variability results from differences in definition, time to hospital admission and the patterns of stroke seen. It is unclear what degree of overlap exists between the three categories.

In the Lausanne Stroke Registry, neurological worsening was significantly less frequent in patients with small-artery disease versus other TOAST subtypes[107]. Age <65 years, hypertension, lesion outside the superficial anterior circulation, absence of TIA, and reduced consciousness in patients with small artery disease, and involvement of the posterior circulation and reduced level of consciousness in patients with large-artery atherosclerosis, were independently associated with neurological worsening[107]. In a study of Japanese patients, early CT findings in total anterior circulation infarcts (TACI), large-artery atherosclerosis in TACI and posterior circulation infarcts, and stroke severity in lacunar infarcts predicted deterioration[108]. From the German Stroke Database, internal carotid artery occlusion, middle cerebral artery

occlusion, territorial or brainstem infarction, and diabetes mellitus were identified as independent predictors of early neurological worsening[109]. Overall, larger lesions with significant vascular pathology, severe clinical deficits, and posterior circulation strokes tend to have more neurological deterioration.

1.3.1.3 Recurrence

Recurrent stroke is a major cause of morbidity and mortality following an ischaemic stroke. Prospective studies have estimated the risk of recurrence at 1.7-4% (30 day), 6-13% (1st year), and 5-8% (next 2-5 years), amounting to an overall 5-year risk of 19-42%[62,110,111,112,113]. Factors associated with an increased risk of recurrent stroke included: older age; clinical stroke syndrome; history of TIA; history of hypertension or diabetes; elevated or lowered BP; elevated glucose; history of cardiac disease; abnormal findings on CT brain; and dementia after stroke[114].

Early stroke recurrence was more frequent following ischaemic stroke associated with large vessel atherosclerosis[110], with some bias due to early endarterectomy-related stroke. Recurrence rates were lower following cardioembolic strokes[115,116], which may be due to a higher rate of anticoagulation. Other significant predictors included: atrial fibrillation (RR 4.0); alcohol consumption (RR 6.8, 2 to 4 drinks versus none); and hypercholesterolaemia (RR 0.15)[115]. The association of hypercholesterolaemia with reduced early recurrence is consistent with existing literature e.g. FASTER study[117], where simvastatin use was not associated with reduced stroke recurrence at 90 days, and a meta-analysis of the short term effects of statins after acute coronary syndromes, where early statin therapy did not reduce the recurrence of death, myocardial infarction or stroke, at 1 and 4 months[118]. The most important predictor of late recurrence is age, while other predictors (including control of vascular risk factors) are poorly understood, with conflicting reports from published studies[114].

1.3.2 Intracerebral Haemorrhage

1.3.2.1 Mortality

Predictors of death following an intracerebral haemorrhage included: large volume of haematoma[119,120,121]; haematoma growth[122]; impaired consciousness/lowered GCS[121,123]; intraventricular haemorrhage[120,121,123]; increased PP; older age; and infratentorial location[123]. Early seizure activity has not been associated with worse outcome[124].

1.3.2.2 Recurrence

A systematic review of 10 studies (mean follow up: 3.4 years) reported a stroke recurrence rate following ICH of 4.3% per patient-year, the risk of recurrent ICH being greater than that for recurrent ischaemic stroke (ICH 2.3% versus ischaemic stroke 1.1% per patient-year)[125]. Those with primary lobar ICH had a higher recurrent ICH rate (4.4% per patient-year), compared to those with a deep ICH (2.1% per patient-year). The Toronto study reported a reverse trend with higher ischaemic stroke rate (3 % per year) than ICH (2.4% per year)[126]. Lobar ICH is felt to have distinct pathophysiology i.e. amyloid angiopathy, with a possibly genetic component to recurrent ICH in this group[127].

1.4 CURRENT THERAPY FOR ACUTE STROKE

1.4.1 Established Interventions

1.4.1.1 Antithrombotic therapy

Aspirin

Early aspirin treatment is associated with significant benefit and is a cheap and easily applicable intervention in acute stroke care. However in absolute terms, the benefit is small, with 13 more patients alive and independent, 7 less recurrent ischaemic strokes, and 9 less patients dead for every 1000 patients treated with antiplatelet agents (Cochrane Analysis, n=41,399)[128]. Inadvertent treatment with aspirin of patients with PICH was not associated with clear evidence of harm. Early aspirin therapy is therefore routinely indicated in the management of AIS, with the two largest trials using a daily dose of 160mg[129] and 300mg[130]. Clinical judgement must prevail in balancing the small benefit in terms of prevention of recurrent ischaemic events with the increased risk of ICH, and decisions must be made on an individual basis e.g. in those with uncontrolled hypertension or history of previous ICH.

A Cochrane Review (11 trials, 42600 patients) concluded that there was a significant increase in ICH associated with the early use of aspirin in acute ischaemic stroke (OR 1.33, 95% CI 1.10 to 1.62; P = 0.004)[128]. In absolute terms, 2 more patients would have a symptomatic intracranial haemorrhage for every 1000 patients treated with aspirin. In addition, a two year consecutive case-control study of patients with ICH in Melbourne, only aspirin doses greater than 1225 mg/day were associated with significantly increased risk (OR 3.05, 95% CI 1.02 to 9.14, p=0.047[131]. In summary, the risk of ICH attributable to low-dose aspirin is low, and outweighed

by the benefits (net reduction of overall stroke recurrence), and low dose aspirin use in acute stroke should be encouraged for early and long-term secondary prevention.

Influence of BP on the effects of Aspirin

The two major antiplatelet studies in acute stroke incorporated subgroup analysis by SBP categories[129,130]. There was no difference in the benefits of aspirin when the Chinese Acute Stroke Trial (CAST) population was grouped by quintiles of SBP[129], and when the International Stroke Trial (IST) population were divided in two SBP subgroups (≤180 and >180 mmHg)[130]. Uncontrolled BP is generally considered a contraindication for aspirin[132], and in view of the marginal benefits, aspirin could be delayed in this situation.

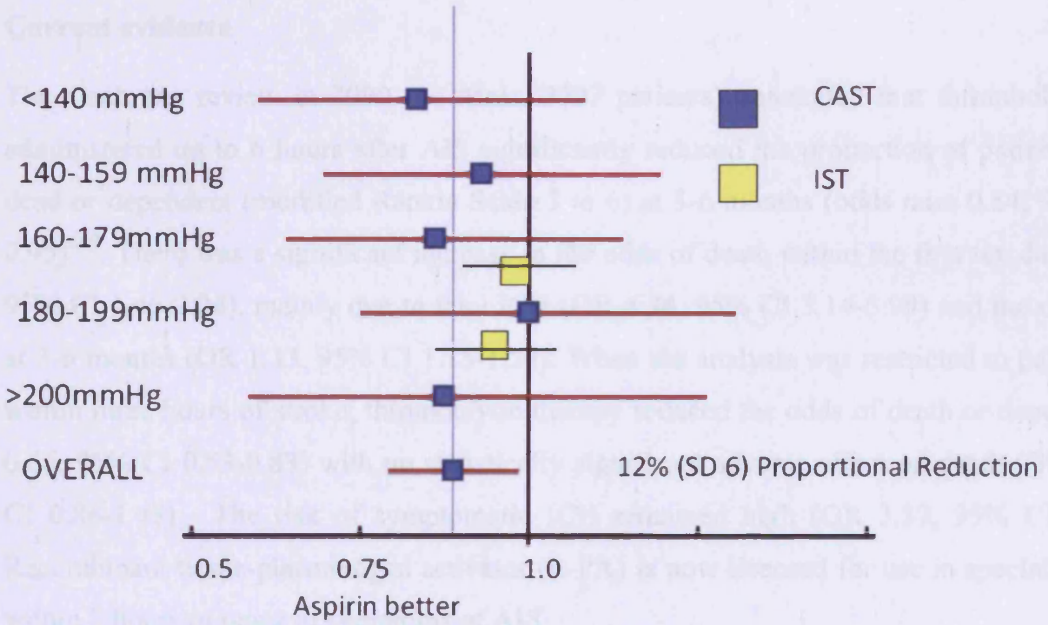

Figure 1.7. Interaction of BP with effects of aspirin[129,130]

Other antiplatelet agents

Other oral antiplatelet agents including dipyridamole, ticlopidine and clopidogrel have not been studied in the setting of acute stroke[133]. The two trials investigating combination platelet therapy in non-acute stroke have not shown any significant overall benefit[134,135]. Though pilot studies suggest possible benefit from early combination therapy[136], this has not been the subject of a randomised controlled trial as yet.

Anticoagulants

No net short or long-term benefit with early use of anticoagulants has been demonstrated (Cochrane Review)[137]. The benefit of 9 fewer recurrent ischaemic strokes was balanced by an increase of 9 symptomatic intracranial haemorrhages, per 1000 patients treated. Early anticoagulant use has not been demonstrated to reduce the rate of early neurological deterioration or stroke recurrence[138]. Therefore early use of anticoagulants within the first 2 weeks of stroke onset is not advised. Though intravenous unfractionated heparin has been used previously in those with progressive stroke, a recent study using historical controls did not demonstrate any benefits with the use of intravenous heparin[139].

1.4.1.2 Intravenous thrombolysis

Current evidence

The Cochrane review in 2000 (18 trials, 5727 patients) concluded that thrombolytic therapy, administered up to 6 hours after AIS significantly reduced the proportion of patients who were dead or dependent (modified Rankin Scale 3 to 6) at 3-6 months (odds ratio 0.84, 95% CI 0.75-0.95)[140]. There was a significant increase in the odds of death within the first ten days (OR 1.81, 95% CI 1.46-2.24), mainly due to fatal ICH (OR 4.34, 95% CI 3.14-5.99) and the odds of death at 3-6 months (OR 1.33, 95% CI 1.15-1.53). When the analysis was restricted to patients treated within three hours of stroke, thrombolytic therapy reduced the odds of death or dependency (OR 0.66, 95% CI 0.53-0.83) with no statistically significant adverse effect on death (OR 1.13, 95% CI 0.86-1.48). The risk of symptomatic ICH remained high (OR 3.37, 95% CI 2.68-4.22). Recombinant tissue-plasminogen activator (rt-PA) is now licensed for use in specialised centres, within 3 hours of onset of symptoms of AIS.

BP as a prognostic variable for symptomatic ICH post-thrombolysis

Experience from thrombolysis trials in cardiology indicated that the risk of intracerebral haemorrhage post-thrombolysis was higher in older people[141], those with higher BP[141,142], and those with a previous history of cerebrovascular disease[143]. Five stroke-thrombolysis publications have reported a significant association between BP and ICH:

1. the NINDS reported a significantly increased risk of intracerebral haematoma in patients with DBP>100 mmHg (18% versus 1% of those with lower DBP values) on univariate analysis, but not on multivariate analysis[144];

2. the Australian Streptokinase Study reported an OR of 1.03 (95% CI 1.01-1.05, p=0.006) for major haemorrhage (bleed with mass effect, extending outside infarct zone, or separate from it, or intraventricular blood), with baseline SBP as a continuous variable, and an ICH rate of 25% for those with baseline SBP>165 mmHg[145];

3. a secondary analysis of the Second European-Australasian Acute Stroke Study (ECASS2) study reported a significantly increased risk of severe haemorrhagic transformation with higher baseline SBP as a continuous variable (OR 1.02, 95% CI 1.00-1.03, p=0.02)[146];

4. an analysis of community-based thrombolysis in Helsinki reported an association between peak SBP during infusion and haemorrhagic change of borderline significance (OR 1.04, p=0.06) – on the contrary, higher baseline DBP was associated with better outcome[88]; and

5. the Multicentre rt-PA Acute Stroke Survey reported a significant difference in pre-treatment SBP and DBP between patients with and without ICH following thrombolysis - mean (SD): 171 (31)/90 (16) vs. 164 (28)/87 (17) mmHg (p<0.05 for both), on univariate, but not multivariate analysis[89].

Most of the other trials have excluded patients with significant hypertension (>180/100 mmHg), treated patients with elevated BP in the first 24 hours, and had a low absolute occurrence of ICH, thus limiting definitive conclusion about the association between BP and ICH (CLOTBUST[147], Cleveland Experience[86], STARS[148], ECASS[149], ATLANTIS[150], ECASS II[151]). Nonetheless, indirect evidence suggests that the risk of symptomatic ICH is likely to be greater with uncontrolled hypertension.

While there have been no randomised controlled trials studying the effect of anti-hypertensive therapy on outcome in the setting of acute stroke-thrombolysis, two thrombolysis studies have reported worse outcomes in those treated with anti-hypertensives[152,88]. These were observational analyses and definitive confirmation from randomised controlled trials is needed.

Other prognostic variables for symptomatic ICH post-thrombolysis

Other variables that have been associated with symptomatic ICH following thrombolysis include: increasing age[85,86,153,146,154]; increasing stroke severity[146,89,85,154,155,156,157]; higher blood glucose[86,88,89]; congestive cardiac failure[146]; pre-treatment with aspirin[156]; deviation from BP monitoring protocol[158]; changes on CT brain scan (early ischaemic change[159,160,151,153];

hyperdense MCA sign[85]; and oedema or mass effect on baseline CT[154]), and moderate-severe leukaraiosis[161].

Thrombolysis in the UK

The uptake of thrombolysis for acute ischaemic stroke in the UK has been disappointing (0.2% of patients – National Sentinel Audit of Stroke 2006), mainly because of the short time window where this therapy is applicable. This compares with a figure of nearly 10% of patients in the best centres[12]. In view of this dismal rate, the Department of Health commissioned the National Audit Office report, and subsequently published the National Stroke Strategy to secure improvements to stroke services and guide high quality health and social services. In addition, a national Stroke Research Network has been setup to support clinical stroke research and remove barriers to its conduct, by enhancing research infrastructure and increasing collaborative working between clinicians, academics and research funders.

1.4.1.3 Carotid Endarterectomy

Early carotid endarterectomy is likely to be beneficial in patients with significant carotid artery stenosis (ECST>70% = NASCET>50%) and a history of recent ipsilateral ischaemic stroke (see Table 1.4 below)[162]. However peri-operative risks are dependent on operator, overall comorbidity and severity of index stroke, with an overall relative risk of 2.5 for disabling stroke or death in the first 30 days[163,164]. Per-operative complication rate <6% has been recommended as an audit criterion to ensure benefit from this procedure[162].

	Severity of stenosis		relative risk of disabling stroke or death (95% CI)	NNT (95% CI)
	ECST	NASCET		
Severe	≥ 80%	≥ 70%	↓ 48% (27 - 73)	15 (10 - 31)
Moderate	70 - 79%	50 - 69%	↓ 27% (15 – 44)	21 (11 - 125)
Mild	<70%	<50%	↑ 20% (0 – 44)	45 (22 - infinity)

Table 1.4. Relative risk reduction of disabling stroke or death following carotid endarterectomy (by severity of carotid artery stenosis)[165] – ↓ decrease; ↑ increase.

Influence of BP on the effects of endarterectomy

While post-operative hypertension is usually associated with pre-operative hypertension, 21% of normotensive patients have elevated BP also[166]. Hypertension (SBP>180 mmHg) has been associated with significantly increased operative risk of stroke and death[165](Figure **1.8**), and post-operative complications, including neck haematoma and hyperperfusion syndrome[166]. Careful BP monitoring and aggressive treatment of elevated BP is advised by the American Stroke Association guidelines, particularly in those with early symptoms of hyperperfusion syndrome (Grade C recommendation)[166]. Persistent uncontrolled post-operative hypertension has been associated with an increased risk of ICH in one study[167]. However, the lack of placebo controlled RCTs investigating the benefits of anti-hypertensive therapy in this group of patients means that Grade A recommendations are unlikely to be available.

Hypertension	Yes	No
Morrow et al (1987)	4/65	0/24
Goldstein et al (1994)	21/186	38/511
Riles et al (1994)	44/1183	22/1116
ECST	41/108	81/1321
TOTAL	110/1842	141/2972

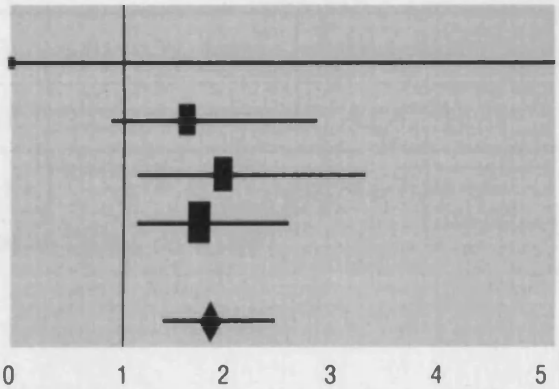

Figure 1.8. Odds of stroke or death associated with the presence of hypertension (SBP>180 mmHg) - ECST European Carotid Surgery Trial[165]

Other prognostic variables following carotid endarterectomy

A retrospective cohort study identified 5 independent predictors of risk-adjusted odds of complications: stroke as indication for surgery (vs. TIA); active coronary artery disease; and contralateral stenosis >50% increased risk, while use of local anaesthesia and patch closure decreased risk[168] (see Figure 1.9 below).

Prognostic variables	Death and stroke			Stroke alone		
	OR	95% CI	p	OR	95% CI	p
Stroke as indication for surgery	2.84	1.55-5.20	.0008	2.78	1.46-5.28	.002
Active CAD	3.58	1.53-8.36	.003	4.00	1.70-9.37	.002
Contralateral stenosis>50%	2.32	1.33-4.02	.003	2.28	2.28-4.08	.005
Local anaesthesia	0.30	0.16-0.58	.0004	0.34	0.17-0.67	.002
Patch closure	0.40	0.24-0.76	.004	0.40	0.22-0.73	.003

Figure 1.9. Multiple logistic regression model of complication rates following CEA[168]

1.4.1.4 Stroke Unit – Organised care

Several studies have demonstrated the utility of comprehensive stroke units in reducing the rates of mortality and morbidity after stroke[169,170,171], with improvement in survival, independence and return to home at 1 year follow up (see Table 1.5 below). Also OR for death and dependency at 5 years was 0.53, 95% CI 0.36-0.80. The benefits of organised care may be attributed to better diagnostic procedures, better nursing care, early mobilisation, prevention of complications, or more effective rehabilitation procedures[170].

Outcome	Stroke Unit	Control	Odds Ratio (95% CI)	Absolute Difference per 100 treated (95% CI)
Home (independent)	546 (39%)	463 (33%)	1.41 (1.19, 1.67) *p<0.01*	+5 (+1, +8)
Home (dependent)	246 (18%)	226 (16%)	1.01 (0.72, 1.41)	0 (-4, +3)
Institutional care	270 (20%)	300 (22%)	0.83 (0.68, 1.03)	-1 (-4, +1)
Dead	320 (23%)	399 (28%)	0.80 (0.67, 0.95) *p<0.05*	-4 (-7, 0)

Table 1.5. Outcomes in stroke unit trials (median follow up 1 year)[172]

1.4.2 Experimental Interventions

1.4.2.1 Neuroprotective Intervention

In the setting of acute stroke, 49 agents with neuroprotective properties had been studied until December 1999[173], with none of them demonstrating clinical applicability. While this lack of benefit could be due to of lack of efficacy, issues with trial design including small sample size, poor patient selection and use of inappropriate outcomes may have played a part also.

Magnesium

Magnesium inhibits pre-synaptic glutamate release[174], blocks NMDA receptors[175], antagonizes calcium channels, and maintains CBF in rats[176]. However, in the Intravenous MAgnesium in Stroke (IMAGES) Study, intervention was associated with no significant overall benefit in functional outcome (Barthel Score <95 and modified Rankin Scale >1 at day 90)[177]. Post hoc analysis suggested improvement in functional outcome in two subgroups: those with MAP > median value (108.3 mmHg), and those with lacunar strokes (pure motor/sensorimotor strokes only). The benefit in those with lacunar strokes persisted after adjustment for baseline factors[178]. Overall lack of benefit may have been due to the large time window for eligibility in this study. The effect of magnesium on infarct growth on serial MRI was studied in the MR IMAGES Study, and results are awaited[179]. A phase III trial (FAST-MAG) aims to determine the efficacy of ultra-early initiation of intravenous magnesium by paramedics[180].

NXY-059

Recently the SAINT-I trial (n=1622) showed some benefit with NXY-059 (free radical trapping agent) compared to placebo, in acute ischaemic stroke[181]. In the active treatment group, 4.4 percent more patients became asymptomatic (modified Rankin Score - mRS, 0), and 3.7 percent more were able to walk without help (mRS, 0-3) at 90 days, compared to the placebo group. However, no benefit was seen in terms of mortality or neurological deficit (National Institute of Health Stroke Scale – NIHSS)[182]. A study of NXY-059 in 603 patients with haemorrhagic stroke within 6 hours of onset showed no difference in mortality or stroke outcomes suggesting the possibility of intervention before formal brain imaging[183]. However the larger SAINT-II trial reported no significant improvement in disability, neurological deficit or symptomatic ICH in association with thrombolysis, and further research was halted[184].

Statins

Various studies suggested a benefit of statin therapy in terms of reduced stroke severity and progression[185,186,187,188,189,190]. A pilot study suggested improved neurological outcome up to 90 days with early statin use[191]. However, the FASTER study which randomly allocated statin-naïve patients to simvastatin or placebo found a trend towards increased stroke recurrence (10.6% vs. 7.3%). As a result of poor recruitment, the trial was terminated early and the resultant sample size disallows any definitive conclusion[117]. While the EXPRESS study reported improved outcomes with early intervention (composite intervention including early statin therapy), it is not possible to ascertain if any individual intervention was responsible for the benefit or indeed harmful[192]. The Neuroprotection with Statin Therapy for Acute Recovery Trial is investigating the value of lovastatin in acute ischaemic stroke (ClinicalTrials.gov identifier: NCT00243880).

Albumin

Albumin may be beneficial following acute stroke due to the following effects: haemodilution; free fatty acid binding; inhibition of free-radical production; improvement in endothelial function; inhibition of platelet activation and maintenance of microvascular patency[193]. Pilot evidence suggests that albumin is safe, alongside thrombolysis, with a small increase in pulmonary oedema[194]. A phase III trial is underway to explore the effects further – Albumin in Acute Stroke (ClinicalTrials.gov identifier: NCT00235495).

Other neuroprotective agents

In a randomized double-blind placebo-controlled study of 40 patients, erythropoietin (EPO) was found to be safe and treatment correlated with reduction of NIHSS, and reduction in neuronal injury marker S100beta at 30 days[195]. The mechanism of action is unclear, but EPO crosses the blood brain barrier, and may have effects on an unknown EPO receptor. Citicoline, a neuronal membrane stabilizer, is being investigated in the International Citicoline Trial on Acute Stroke (ICTUS, ClinicalTrials.gov identifier: NCT00331890). Meta-analysis of four trials showed that a good outcome at 3 months was more frequent in those in the intervention group (OR 1.33, 95% CI 1.10 -1.62)[196].

1.4.2.2 Revascularisation therapy

Intravenous Thrombolysis (non-rt-PA agents)

Desmoteplase

Phase II studies with fixed-dose desmoteplase (3-9 hours after stroke onset), from vampire bat saliva, showed a high rate of symptomatic ICH[197]. However, weight-adjusted doses resulted in lower rates of sICH (2.2%), with reperfusion rates remaining high, 71% in the high-dose desmoteplase group (125 microgram/kg) vs. 19% in the placebo group[197]. Favourable composite outcome (NIHSS, mRS and BI) at 90 days was seen in the higher dose group in 60% of subjects, compared to 22.2% of placebo group subjects[197]. In this study, presence of diffusion-perfusion mismatch on MRI was an inclusion criterion. In another study of similar design, the higher dose (125microgram/kg) group had a trend towards increased reperfusion compared to the placebo group, with no sICH[198]. If the preliminary results are confirmed in the ongoing Phase III DIAS2 study (ClinicalTrials.gov identifier: NCT00111852), more widespread applicability of intravenous thrombolysis may result.

Tenecteplase

A preliminary phase II study of tenecteplase within 3 hours of acute stroke concluded that this agent was safe[199], and an ongoing phase IIb trial is comparing different doses with standard rt-PA, for patients presenting within 3 hours of onset (ClinicalTrials.gov identifier: NCT00252239).

Intra-arterial Thrombolysis

Intra-arterial (IA) thrombolysis may have better applicability due to a longer therapeutic window, and lower bleeding risk due to lower total dose of thrombolytic. IA thrombolysis was associated with higher proximal middle cerebral artery recanalisation rates compared to intravenous thrombolysis (71% vs. 30%), and may be more suitable for large intracranial vessel occlusions[200]. One must keep in mind that recanalisation is not associated with good outcome universally. Overall, early ICH rates were higher immediately post-thrombolysis, but delayed ICH rates were not significantly different from placebo (see Table 1.6). Combination intravenous and IA thrombolysis has been investigated, with higher recanalisation rates, but no improvement in clinical outcomes[201].

% active (placebo)	PROACT-I[202]	PROACT-II[203]	IA urokinase[204]
Early ICH at 24 hours	42 (7)	35 (13)	4.8
Early sICH at 24 hours	15 (7)	10 (2)	-
Delayed ICH	50 (36) day 90	68 (57) day 10	-

Table 1.6. ICH rates in IA thrombolysis trials - percentages: active (placebo)[201]

Combined intravenous thrombolysis with other interventions

Sonolysis

Concomitant transcranial Doppler (TCD) can improve fibrinolytic activity of thrombolytic agents[205]. Whilst earlier use of low frequency ultrasound was associated with increased ICH[206], high frequency (2 MHz) ultrasound was associated with increased rate of complete recanalisation or dramatic recovery (49% vs. 30% placebo), and a trend towards better outcomes at 3 months, with no increase in symptomatic ICH compared to placebo (3% in both groups)[207]. Another promising development is the possibility of enhanced thrombolysis with use of micro-bubbles alongside TCD[208], and the Nanobubbles enhanced CLOTBUST treatment for AIS (ClinicalTrials.gov identifier: NCT00507806) aims to provide some answers.

Endovascular mechanical thrombolysis

Endovascular mechanical thrombolysis as rescue is an attractive concept. The Mechanical Embolus Removal in Cerebral Ischaemia (MERCI) retrieval device was approved by the US Food and Drugs Administration (FDA) in 2004, but has not been demonstrated to be beneficial in an RCT. The Multi MERCI trial reported improvement in successful recanalisation (TIMI flow 2 to 3) in the target and downstream vessels with the addition of adjunctive therapy to clot removal with the Merci(R) L5 Retriever, from 57.3% to 69.5% in patients with moderate to severe acute ischaemic stroke[209]. The Interventional Management of Stroke III trial aims to clarify if intra-arterial recanalisation (using one of concentric retrieval device, EKOS ultrasound catheter, or intra-arterial thrombolysis) following intravenous rt-PA is beneficial (ClinicalTrials.gov identifier: NCT00359424). Many other devices are in development.

Fibrinogen depleting agents

A meta-analysis of 2926 patients participating in 5 trials (Cochrane collaboration) of fibrinogen depleting agents suggested a 10% RRR for death and disability with treatment[210]. However, a subsequent large RCT (ESTAT[211]) showed no difference in clinical outcomes with ancrod

treatment within 6 hours of stroke onset, compared to placebo, and more evidence is required before any definite conclusions can be drawn.

1.4.2.3 Physiological intervention

BP lowering and induced hypertension

BP modification is considered in more detail in the next section.

Hyperglycaemia

Whether routine lowering of elevated glucose values would result in improved outcomes or not, was investigated in the GIST-UK (Glucose Insulin Stroke Trial-UK) study[212]. In the intervention group, glucose potassium infusion (median time from symptom onset to start of infusion – 14 hours) reduced mean plasma glucose by 0.57 mmol/l compared to the placebo group, with no significant difference in outcome (death at 90 days: OR 1·14, 95% CI 0·86–1·51). In addition, significant unexpected BP differences were seen (control group: mean SBP 9 mmHg lower), which may have complicated the association. Moreover the actual difference in glucose between groups was much lower than anticipated, and the study was underpowered. Therefore, significant benefit cannot be ruled out entirely. It should be noted that the median baseline glucose was 7.6-7.8, and the results may not apply to those with higher glucose levels. Though lowering of glucose is common practice, there is no direct evidence of benefit, and three other studies are currently studying glucose lowering in acute stroke - clinicaltrials.gov identifiers - NCT00282867 (GRASP); NCT00472381 (INSULINFARCT); and NCT00373269.

Hypothermia

Hypothermia can slow down temperature-dependent deleterious processes like oxidative stress and inflammation[213,214]. Improvement in functional recovery and mortality has been demonstrated with hypothermia in survivors of out-of-hospital cardiac arrest[215,216]. A pilot study of 25 patients with large MCA infarcts demonstrated reduced intracranial pressure and increased cerebral perfusion pressure, with reduced mortality compared to historical controls[217]. Early hypothermia has been associated with reduced DWI lesion volume[218]. Thus hypothermic therapy has promise, and ongoing trials aim to establish the applicability and benefits of hypothermia following acute stroke: Intravascular Cooling for the Treatment of Stroke-Longer window (ICTuS-L), Nordic Cooling Stroke Study (NOCSS), Controlled Hypothermia in Large Infarction (CHILI) and Combined Cytoprotection rt-PA Stroke Trial.

Oxygen therapy

Hypoxia in the acute post-stroke situation can be due to partial airway obstruction, hypoventilation, aspiration pneumonia, and atelectasis. Since hypoxia worsens brain injury, monitoring of oxygen levels and supplementation to avoid hypoxia is expected to minimise further deterioration. Hyperbaric oxygen therapy failed to show clinical efficacy in human trials, and is complicated to administer. On the other hand, normobaric oxygen therapy is inexpensive, readily available and easy to administer. A pilot study reported reversal of DW-MRI abnormalities and reduced infarct volume[219], and ongoing clinical trials aim to establish the appropriate dose and benefits of normobaric oxygen therapy following acute stroke (ClinicalTrials.gov identifier: NCT00414726, and the Stroke Oxygen Study: www.so2s.co.uk).

Decompressive Craniectomy

Malignant middle cerebral artery (MCA) infarction occurs in up to 10% of patients with stroke, and case-fatality rates can be as high as 80%[220]. Cerebral oedema results in increased intracranial pressure and subsequent herniation and death, and hemicraniectomy is expected to prevent these complications. A pooled analysis of 3 randomized controlled trials (93 patients) suggested that decompressive surgery undertaken within 48 h of stroke onset (malignant MCA infarction) reduced mortality at 12 months (OR 0.10, 95% CI 0.04-0.27) and reduced dependency (mRS>3) at 12 months (OR 0.33, 95% CI 0.13-0.86)[220]. There was also an increase in dependent survival. The conclusions are limited to younger patients with malignant MCA infarction, as the trials excluded older patients (age >60 years).

1.5 BP AND STROKE

Abnormal BP is the most prevalent physiological disturbance following stroke, and consequently the issue of intervention to optimise BP is an important one. This thesis studied the feasibility and safety of optimization of BP in the acute post-stroke stage. The complex relationship between BP and stroke is now summarised.

1.5.1 BP as a Risk Factor for Stroke

BP and first stroke

The linear association between increasing BP levels and first stroke has been demonstrated convincingly, with the risk of cardiovascular events doubling for every 20mmHg SBP or 10mmHg DBP rise across the range of BP values from 115/75 to 185/115[221]. This association is present irrespective of sex, but weaker when considering older age groups. However in the elderly, the higher absolute incidence of stroke translates to a larger absolute increase in population stroke risk for a given BP rise.

At the lower end of the spectrum, there is a suggestion of a J-shaped curve[222] i.e. worse outcome with BP lowering below a certain point, however this association may be confounded and represent general ill health rather than the effects of BP lowering, as suggested by an individual patient meta-analysis of five randomised clinical trials incorporated in the INDANA (Individual Data Analysis of Antihypertensive intervention trials) project, which showed a J-shaped curve in both, treated and untreated individuals[223].

There is also good evidence that reduction of BP reduces the risk of a first stroke[224], with the magnitude of BP reduction being important, irrespective of the choice of initial anti-hypertensive agent used. The threshold for intervention as well as target BP levels has been reduced progressively, with lower targets advocated for those with multiple risk factors.

BP and recurrent stroke

Patients with a prior history of cerebrovascular disease are generally considered separately, because of the possibility of persistent impaired cerebrovascular autoregulation, whereby BP reduction may result in potentially harmful reduction of cerebral blood flow. When considering stroke survivors, the relationship between BP and outcome remains debatable, though recent studies are attempting to clarify the association.

An early study (368 subjects) suggested a 'J'-shaped relationship between post-stroke diastolic BP (DBP), but not SBP, and stroke recurrence, with the nadir at 80-84mmHg[225]. However 69% of patients received anti-hypertensive therapy and it is possible that co-morbid conditions associated with low BP rather than the effects of treatment per se were responsible for this association, an explanation not dissimilar from that proposed for patients with no history of cerebrovascular disease. The J-shaped association was not seen in the Leigh Valley Recurrent

Stroke Study[226], a population-based prospective cohort study of 535 patients, wherein those with lowest follow up DBP (<80 mmHg) had a reduced risk of recurrent stroke compared to those with DBP 80-89 mmHg (RR 0.4, p=0.02). For SBP, those with levels ≥140 mmHg had a RR of 2.4 compared to patients with SBP<140 mmHg for stroke recurrence.

Additionally, large prospective randomised controlled trials have failed to show a J-curve relationship[227,228]. In a retrospective analysis of 2201 patients in the UK-TIA trial[227], there was a strong positive linear relationship between usual SBP and stroke risk (hazard ratio (HR) more than doubled per 20 mmHg rise in SBP and 10 mmHg rise in DBP), similar to the association demonstrated for patients with no previous history of cerebrovascular disease (see Figure 1.10 below). Also, in a post-hoc analysis of patients in the PROGRESS study[228], a continuous association between achieved BP and stroke incidence was noted (SBP range 112-168 mmHg, DBP range 72-102 mmHg (see Figure 1.11 next page). PROGRESS included previously treated hypertensives as well as those with "normal" BP levels. No detrimental effects were observed in the subgroup with lowest baseline BP (SBP<120 mmHg), who achieved on-treatment BP of 115/75 mmHg, associated with a lower incidence of stroke, compared with other BP subgroups[228].

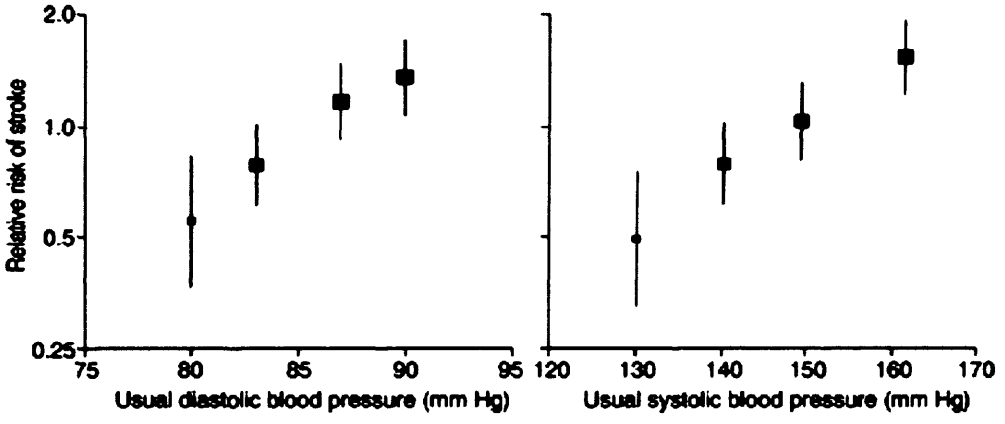

Figure 1.10: Relative risk of stroke by usual diastolic and systolic BP – UK-TIA study[227]

It is inevitable that BP reduction beyond the lower limit of autoregulation would result in cerebral hypoperfusion and its consequences, including an increased risk of stroke recurrence. However this limit has not been defined clearly and a reduction in BP would appear beneficial for stroke prevention irrespective of baseline levels, in the ranges commonly seen in clinical practice.

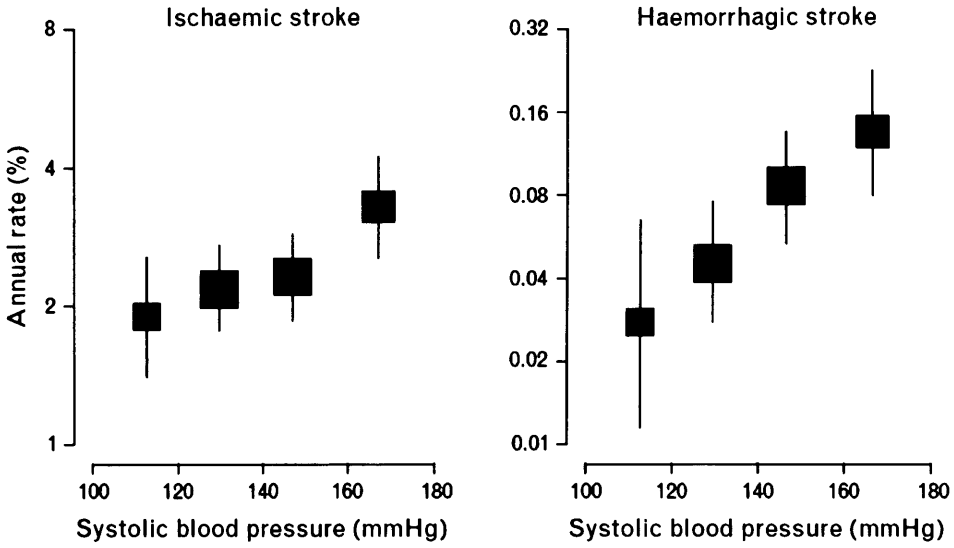

Figure 1.11: Annual rates of ischaemic and haemorrhagic stroke according to achieved follow-up systolic blood pressure levels – PROGRESS[228].

1.5.2 BP Trend Following Acute Stroke

Elevated BP levels are common following acute stroke – the International Stroke Trial (IST)[130] and the Chinese Acute Stroke Trial (CAST)[129] reporting that 54% and 48% of patients, respectively, had a systolic BP (SBP) >160 mmHg within the first 48 hours. BP levels tend to decline over the first week following ictus[229], and over the course of hospitalization[230], the decline being greater for those with higher initial BP values[230], and occurring earlier in large artery atherosclerotic and lacunar strokes, compared to those with cardioembolic strokes or stroke of undetermined cause[231]. However following discharge, casual BP levels[232] increase in more than two-thirds of patients, and persist at these higher levels for several months from ictus, irrespective of BP levels prior to stroke onset. Interestingly, 24 hour BP levels[3] do not show a similar trend post-discharge, which suggests that methodological factors with respect to BP measurement complicate any demonstrated association.

In patients with acute intracerebral haemorrhage, elevated BP is seen more frequently (up to 90% of patients), and initial BP levels are typically higher compared to those with acute ischaemic stroke, with a third of patients remaining hypertensive on the 10th day post ictus[233].

On the other hand, relative hypotension (SBP<140mmHg) immediately post-stroke, though less common than elevated BP, does occur in a significant minority, with a prevalence of 18% and

25% in the IST[130] and CAST[129] Trials, respectively. As yet, no follow up studies have investigated the trend of BP in these patients.

1.5.3 Prognostic value of acute post-stroke BP

Sustained elevated BP may be harmful, increasing the risk of cerebral oedema and haemorrhagic transformation[234]. A systematic review of observational data from studies suggested that elevated BP in the acute stroke period is associated with a poor short and long-term prognosis, in terms of death and disability[235], though because of variation in the timing and method of BP estimation, the validity can be questioned. Individual studies have provided variable results, higher baseline BP associated with worse outcome[236,237], improved outcome[55,238] or not associated with outcome[239].

Since cerebrovascular autoregulation is impaired following acute stroke[240], blood flow may become dependent on systemic BP, and reduction in BP may risk viability of the penumbra (relatively ischaemic potentially viable tissue surrounding the infarct). Some studies have shown that low BP levels in the acute post stroke period are also associated with poor short[241] and long-term[242] prognosis.

A U-shaped relationship between baseline SBP and early (2-week) death and late (6-month) death and dependency has been seen in a retrospective analysis of the IST[241]. Early death increased by 17.9% for every 10mmHg below 150mmHg, and by 3.8% for every 10mmHg above 150mmHg. This U-shaped pattern persisted after adjustment for other important baseline prognostic factors including age, sex, most severe clinical syndrome (Total Anterior Circulation Stroke), time to randomization, level of consciousness and atrial fibrillation.

Because of the lack of standardisation in BP measurement in the IST and other studies along with the natural increased variability in BP following stroke[237], studies using 24 hour BP recordings have been undertaken. In a study of 136 acute stroke patients within 24 hours of admission, the odds ratio for one month death or dependency associated with every 10 mmHg increase in 24 hour SBP at admission was 1.88 (95% CI 1.27-2.78)[237]. In fact the relationship between 24 hour SBP and outcome was almost linear, with no worsening of outcome at lower SBP level. In addition, the lack of a day-night SBP fall was associated with an increased likelihood of dependency (OR for 10 mmHg SBP fall 0.28, 95% CI 0.11-0.70, p=0.006). Studies have suggested that moderate BP reduction in acute stroke may facilitate recovery[243,239].

Shorter 10 minute beat-to-beat readings may yield adequate prognostic information. A study of 92 patients with acute stroke using beat-to-beat finger BP monitoring (Finapres) showed an association between beat-to-beat DBP levels, MAP levels and variability and poor outcome at 30 days[244]. No relationship between casual BP parameters and outcome was observed.

In patients with ICH, higher admission MAP was associated with increased mortality for thalamic and putaminal haemorrhages, but not subcortical, cerebellar or pontine locations[238].

1.5.4 Intervention Studies

1.5.4.1 Acute post stroke hypertension – BP lowering as early secondary prevention

The most promising agents are those acting on the renin-angiotensin system. In patients treated within 7 days of AIS, captopril[245] and perindopril[246] have been shown to reduce systemic BP without adverse effects on cerebral blood flow, even in the presence of significant carotid artery disease[247]. Candesartan was assessed in severely hypertensive (mean of at least 2 blood pressure measurements, SBP ≥200 mmHg and/or DBP≥110 mmHg 6-24 hours after admission; or SBP ≥180 mmHg and/or DBP ≥105 mmHg 24-36 hours after admission) AIS patients deemed to need BP lowering medication, comparing acute (<72 hours) and delayed (>7 days) intervention. A 47.5% reduction in fatal and non-fatal vascular events at 12 months was seen with early intervention, most of the reduction being with cardiovascular events[248]. However, there was no effect on subsequent cerebrovascular events and no significant difference in BP between the active and placebo groups during the initial 7 days of the study. The authors suggested non-haemodynamic mechanisms for the significant reduction in cumulative vascular events. Losartan reduced systemic BP levels without a significant reduction of cerebral blood flow as assessed by SPECT, in a study of 16 hypertensive patients with a history of sub-acute stroke (≥4 weeks post-ictus)[249].

There is preliminary evidence to support the use of labetalol as an effective and safe anti-hypertensive agent in both acute haemorrhagic[250] and ischaemic[152] stroke patients. 9% of patients in the placebo arm of the National Institutes of Neurological Disorders and Stroke (NINDS) Trial of thrombolysis were hypertensive (>185/110mmHg) at admission, and received bolus intravenous labetalol therapy[152]. Amongst the hypertensive patients in the placebo arm, mortality at 3 months was significantly reduced with labetalol therapy (OR 0.1, 95% CI 0.1-0.7) compared to those who did not receive BP lowering therapy. However, in the same group of patients, there was a non-significant increase (OR 1.5, 95% CI 0.8-2.9) in 3-month mortality, for

patients who became hypertensive in the 24 hours post-randomisation. Because of the non-randomised use of anti-hypertensives, and post hoc comparisons, the significance of this observation is unclear.

β-blockers (atenolol and propranolol) were associated with a non-significant increase in the odds of early deterioration and death (1.32, 95% CI 0.84-2.06) and end-of-trial death and disability (1.18, 95% CI 0.78-1.84) in the BEST study[251]. A systematic review of the use of calcium channel antagonists in acute stroke concluded that there was no significant beneficial effect on early or end-of-trial mortality, despite effective BP reduction in the first 72 hours[252]. Bendroflumethiazide 2.5 mg daily showed no additional hypotensive effect over placebo in a small study of 36 hypertensive patients (24 hour mean BP >130/80 mmHg, or daytime mean BP >135/85 mmHg) within 10 days of AIS[253]. Topical GTN (patch) significantly lowered SBP and DBP at 24 hours (meta-analysis of 3 trials)[254]. No significant difference in 3 month outcome (mortality, death and dependency) was reported in a Cochrane Review[255].

Overall, there is insufficient data to support routine BP manipulation in acute stroke, as concluded by various guidelines[256,257,258,259] and the Cochrane Review "Interventions for deliberately altering blood pressure in acute stroke"[260].

1.5.4.2 Acute post stroke hypotension/"relative" hypotension – induced hypertension/pressor therapy

As yet, in humans, there are few data as to the benefits or otherwise of pressor therapy in acute ischaemic stroke. There are theoretical reasons why this may be beneficial e.g. increasing BP levels could reduce cerebral injury by increasing intraluminal hydrostatic pressure, and improving perfusion via collateral channels[261].

Volume expansion/haemodilution is commonly instituted alongside pressor therapy. Haemodilution increases CBF, which may be beneficial in recovery from acute cerebral infarction. However, the Cochrane Review on Haemodilution in Acute Stroke (3119 patients, 18 trials) reported no improvement in mortality (at four weeks and 3-6 months) or death/dependency rates (at 3-6 months) with the use of haemodilution alone[262]. Induced hypertension is a standard treatment for cerebral ischaemia in patients with vasospasm after subarachnoid haemorrhage[263]. Experimental or human data to support the use of pressor therapy following AIS is scarce. A systematic review of the use of pressor therapy in acute ischaemic stroke as described in Chapter

2 concluded that pressor therapy appears feasible and well-tolerated, and that the benefit and risks in terms of clinical outcomes remain unknown, with intensive monitoring being advised if such therapy is undertaken[264]. Further trials are required to establish safety and efficacy.

1.6 MANAGEMENT OF BP IN ACUTE STROKE

The Cochrane Review concluded that there is insufficient evidence to advise BP intervention in all patients with an acute stroke[260]. This conclusion has been arrived at by other authorities including the Royal College of Physicians UK[259], the International Society of Hypertension[257], the European Stroke Initiative (EUSI)[256], and the American Stroke Association (ASA)[258,265].

1.6.1 Post-stroke hypertension

The ASA guidelines recommended BP lowering if SBP>220mmHg or DBP>120mmHg, and lower thresholds for patients suitable for intravenous thrombolysis (SBP>185mmHg or DBP>110mmHg)[258]. The advised BP reduction was 15-25% over 24 hours. For ICH, SBP<180mmHg is advised. The EUSI guidance suggested BP lowering for those with SBP>220mmHg or DBP>140mmHg[256]. The recommended SBP was 180mmHg and DBP of 100-105 mmHg, in patients with prior hypertension, and lower values in other cases (SBP 160-180mmHg; DBP 90-100mmHg). Both guidelines advise against the use of sublingual nifedipine, which has been associated with abrupt fall in BP[258,256]. However urgent indications for initiation of anti-hypertensive therapy are recognised, including: concomitant acute myocardial ischaemia; acute pulmonary oedema; acute renal failure; aortic arch dissection; and hypertensive encephalopathy. In patients who have received thrombolysis, there are strict recommendations to keep the SBP below 180 mmHg[256,258], and DBP below 105 mmHg[258].

Whilst pre-stroke hypertension and anti-hypertensive therapy use was reported to be relatively constant in centres across Europe, a significant difference was seen in the continuation of pre-existing anti-hypertensive therapy (56-91%) and the introduction of new anti-hypertensive therapy (9-24%), a reflection of the lack of an evidence-base to guide management decisions[266]. The Stroke Association reported that 6% of physicians would start anti-hypertensive drug therapy on admission, 21% after a few hours, and the rest would wait anything from a few days to few weeks[266]. Similarly Lindenauer et al reported that two-thirds of acute ischaemic stroke patients were treated with anti-hypertensive agents despite the absence of severe hypertension[267]. Underwood et al[268] reported an even higher rate of anti-hypertensive use (98%), while only 22%

of the 50 patients in this observational cohort (in Memphis Tennessee USA) met the ASA criteria for treatment of elevated BP in acute stroke (SBP>220 mmHg/ DBP>120 mmHg). They also reported no association of excessive BP reduction (>10% per day over the first three days) with worsened neurological outcome.

1.6.2 Post-stroke hypotension

Current guidelines about the management of post-stroke hypotension provide no objective clarification as to the appropriate management, which is a reflection of the paucity of evidence in this field, and an indicator of the practical difficulties of carrying out research in the setting of acute stroke[264]. The EUSI guidelines mention that "low cardiac output states may need inotropic support", after potential causes have been treated[256]. The ASA guidelines state that "at present, drug-induced hypertension cannot be recommended for the treatment of most patients with ischemic stroke (grade A)"[265]. The Cochrane Analysis found insufficient data to draw any conclusions[269].

In current clinical practice, up to 12% of patients were reported to receive inotropic support in a European survey of acute physiological stroke management, despite the lack of evidence of benefit from such therapy[270].

1.7 HYPOTHESES

This thesis investigates the feasibility and safety of BP manipulation immediately following stroke, within the context of a multi-centre trial (CHHIPS) studying intervention to alter BP in acute stroke.

1. 50% of all hospitalised acute stroke patients will be suitable for entry into the CHHIPS study.
2. BP lowering can be achieved with an ACE inhibitor (Lisinopril) or an αβ-blocker (Labetalol) in hypertensive acute stroke patients, with significant improvement in terms of death/dependency at 2 weeks, and no increase in adverse events.
3. BP elevation can be achieved with Phenylephrine in relatively hypotensive acute stroke patients, with significant improvement in terms of death/dependency at 2 weeks, and no increase in adverse events.

2 SYSTEMATIC REVIEW - PRESSOR THERAPY IN ACUTE STROKE

2.1 INTRODUCTION

Low/low-normal blood pressure (BP) is reasonably common immediately post-stroke. In the International Stroke Trial[130] and Chinese Acute Stroke Trial[129], 18% and 25% of patients had systolic blood pressure (SBP) <140mmHg, respectively. However, this 'relative' hypotension is of prognostic importance, as demonstrated in a retrospective analysis of 17,398 patients in the IST trial, where early (2 week) death increased by 17.9% for every 10mmHg SBP below 150mmHg[241]. In a study of 304 patients with a first episode of hemispheric ischaemic stroke, relative risk of death at 1-month and 1-year rose by 28.2% and 17.5%, for every 10mmHg decrease in SBP below 130mmHg[242]. A retrospective analysis of 1004 patients with brain infarction, reported that patients with the lowest BP levels at admission had significantly higher risk for death at 30 days (compared to those with SBP 150-169 mmHg and DBP 100-109 mmHg, relative risk: 2.69 and 3.49, for lower SBP and diastolic BP (DBP), respectively[271].

The aetiology of post-stroke hypotension is multi-factorial and associated with different factors in the various stroke subtypes e.g. low blood pressure in cardioembolic stroke has been associated with heart failure[272], in lacunar stroke with coronary disease[272], and in partial anterior circulation infarction with previous myocardial infarction[273]. This suggests that low blood pressure post-stroke results mainly from pre-existing cardiac disease and reduced cardiac output. However, bilateral cerebrovascular disease resulting in damage to the cortical centre maintaining vasomotor tone is an alternative explanation. Thus the relationship of pressor therapy to outcome in acute ischaemic stroke is likely to be influenced by the aetiology of the associated hypotension.

Astrup et al introduced the concept of the "ischemic penumbra", an area of the brain surrounding infarcted tissue, where electrical failure (flattening of EEG signal) is present, but ion pump failure (as evidenced by increased extracellular potassium) has not yet occurred[274]. They hypothesized that increasing cerebral perfusion in these areas might be an important determinant of outcome following human stroke.

Cerebral autoregulation is impaired after acute ischemic stroke[240] i.e. cerebral blood flow (CBF) is passively dependent on the mean arterial pressure (MAP). Olsen et al demonstrated the existence of pressure-passive non-infarcted low-flow areas in 48 patients with ischemic stroke, where an induced BP-rise resulted in an increase in CBF (assessed by scintigraphy after an intracarotid injection of Xenon-133)[275]. Indeed, animal studies have shown that induced hypertension can reduce focal cerebral injury, by increasing intraluminal hydrostatic pressure,

allowing improved perfusion to the penumbra via collateral channels[261]. Also, induced hypertension is recommended for prevention and treatment of cerebral ischemic complications in patients with vasospasm after subarachnoid haemorrhage[263].

Hence, in patients with a recent stroke, an argument can be made to elevate BP levels, and thereby CBF, thus optimizing perfusion and minimizing ischemic brain injury. The actual therapeutic window for benefit is uncertain, though earlier intervention is likely to be more beneficial.

Some of the studies incorporated volume expansion/ haemodilution as part of the treatment regime. Haemodilution increases cerebral blood flow, which may be beneficial in recovery from acute cerebral infarction. However the Cochrane Review on Haemodilution in Acute Stroke[262], which included 3119 patients (18 trials), most recruited within 6 hours of stroke onset, reported no improvement in 4-week mortality, 3-6 month mortality and 3-6 month death/dependency rates with the use of haemodilution. Of note, there was no increased risk of serious cardiac events, and also a trend towards decreased deep venous thrombosis / pulmonary embolism at 3-6 months, but not at 4 weeks.

Current guidelines about the management of post-stroke hypotension provide no objective clarification as to the appropriate management, which is a reflection of the paucity of evidence in this field, and an indicator of the practical difficulties of carrying out research in the setting of acute stroke.

The European Stroke Initiative Recommendations for Stroke Management (Update 2003) mentions that a low or normal-low BP at stroke onset is unusual and may be consequent to a large cerebral infarct, or cardiac failure, or myocardial ischaemia, or sepsis[256]. The document suggests that BP can be raised by adequate patient re-hydration with crystalloid or, occasionally, colloid solutions, though low cardiac output states may need inotropic support. This implies that potential causes for low blood pressure must be looked for and dealt with, and due consideration be given to pressor therapy. *The Guidelines for the Early Management of Patients With Ischemic Stroke* (A *Scientific Statement From the Stroke Council of the American Stroke Association)* states that studies of pressor therapy and iso-/hyper-volaemic haemodilution in the setting of acute ischemic stroke have been inconclusive, but generally negative[265]. They emphasize the requirement of close observation and cardiovascular monitoring, with the use of intravenous vasopressor agents like dopamine and phenylephrine, because of the potential risk of

precipitating myocardial ischemia, congestive heart failure, pulmonary edema, intracranial hemorrhage, hypertensive encephalopathy, and increased brain edema. *The Cochrane Analysis by the Blood Pressure in Acute Stroke Collaboration*, found insufficient data to draw any conclusions, about deliberate alteration of BP within two weeks of a stroke[269]. In view of the inconclusive evidence, an update of current evidence regarding the use of pressor therapy in patients with acute stroke was needed.

2.2 METHODS

The goal of this review was the systematic identification and review of articles reporting BP elevation in the setting of acute stroke, and to assess its effect on neurological outcomes and complication rates. Two reviewers, AKM and TGR searched for articles in the US National Library of Medicine database (MEDLINE) – 1951 to date and the Excerpta Medica database (EMBASE) – 1974 to date, using MESH headings: Stroke and Cerebrovascular Accident, and keywords: Stroke, induced ADJ hypertension, elevation NEAR BP OR elevation NEAR blood ADJ pressure, and pressor ADJ therapy. Articles were also identified from the Cochrane Database (2005 Issue 1). Of the resultant 451 articles, the relevant articles were handpicked by literature review. Reference lists from published reviews were also searched for relevant articles. Inclusion criteria were: All human studies in the setting of acute stroke, where induced hypertension / pressor therapy was employed, with all disagreements between the two reviewers being resolved by an independent observer (JFP).

Authors	Treated/ Placebo or untreated	Design	*Treatment regime* Onset to treatment time	Duration of pressor stimulus	Outcomes	Volume expansion/ haemodilution	*Side effects* Cardiac effects	ICH/ cerebral oedema (%)	Death (%)
PE									
Rordorf et al 1997[276]	33/30	Retrospective case note review	<24 hours	7-576 hours	Morbidity (complications, CXR, Brain scan) Mortality	Normal saline or Albumin	1 (PAF)	0	4/9 no significant difference
Rordorf et al 2001[277]	13	Pilot study/ Case series	7-10 hours	1-6 days	NIHSS	None	0	0	0
Hillis et al 2001[278]	6 (4 PE & 2 IV fluids)	Case series	<7 days	Until function improved or MAP ≥130	Lexical semantics (oral, auditory and picture naming)	IV Normal Saline in 2 patients not receiving PE	---	---	---
Hillis et al 2001[279]	1	Case	24 hours	12 hours	Language	None	---	---	---
Hillis et al 2003[280]	9/6	RT (2 treated: 1 untreated)	<7 days	24-72 hours	NIHSS, cognitive score volume of hypoperfused tissue	Normal Saline (as per clinical indication)	0	0	0/1
Hillis et al 2004[281]	10/5 (8 PE + 2IV fluids)	Case series	<7 days	24-72 hours	NIHSS, cognitive score volume of hypoperfused tissue	Normal Saline (as per clinical indication)	---	---	---
Norepinephrine									
Schwarz et al[282]	19	Observational	6-143 hours	5 minute sessions	CPP & CBF VmMCA	Crystalloids and hydroxyethyl starch	0	0	4 (ICH)
Marzan et al[283]	34	Retrospective	4-26 hours (13+/-5)	14-96 hours	NIHSS	None	1 (AFibr)	1 (3)	4 (12)
Epinephrine									
Meier F et al[284]	30/44	RT	<6 hours	3 x 1 hour sessions	3 week survival	Low molecular dextrans	---	---	---
Dobutamine									
Duke et al[285]	1	Case			Clinical	Volume, not specified	---	---	---
Oliviera-Filho et al[286]	1	Case	?	~48 hours	NIHSS	Volume, not specified	---	---	---
DCLHb									
Saxena et al[287]	40/45	RCT	<18 hours	72 hours (6 hourly infusions)	NIHSS, Rankin, Barthel	Saline in placebo group only	No significant difference	4 oedema, 2/6 HTI	Higher Rx arm
Dexamphetamine									
Martinsson et al[288]	30/15	RCT	<72 hours	5 days	SSS, Barthel, motor function scores	Nil	---	---	20& - Rx arm, 13.3% placebo (NS)

PAF – paroxysmal atrial fibrillation, RT – randomized trial, RCT – randomized controlled trial, ICH – intracranial hypertension, NIHSS – National Institute of Health Stroke Scale, SSS – Scandinavian Stroke Scale, HTI haemorrhagic transformation of infarct, --- not mentioned

Table 2.1: Published Studies of pressor therapy in acute stroke – Study Design – reproduced from Mistri et al[264]

Authors	Treated/ Placebo or untreated	Design	Baseline BP SBP	DBP	MAP	Target BP	End of pressor BP	Change in BP with pressor stimulus	% attained target BP
Phenylephrine (PE)									
Rordorf et al 1997[276]	33/30	Retrospective case note review	152 (+/-34.5)	78.5 (+/-17)	---	>threshold SBP mean 161 (+/-20.1) (range 120-190)	---	---	100% by definition (i.e. threshold BP)
Rordorf et al 2001[277]	13	Pilot study/ Case series	141 (+/-23) nonresp 140 (+/-13) responders	---	---	SBP>160, or Rise of 20% (max 200)	---	---	100% within 60 minutes
Hillis et al 2001[278]	6 (4 PE & 2 IV fluids)	Case series	---	---	---	Increments of 10% MAP (max 130)	---	---	---
Hillis et al 2001[279]	1	Case	---	---	87	MAP 90-100	---	---	---
Hillis et al 2003[280]	10/5 (8 PE + 2IV fluids)	RT	---	---	---	10% increments in MAP until functional improvement (max 130)	---	---	---
Hillis et al 2004[281]	9/6	Case series (2 treated: 1 untreated)	---	---	97.9 (+/-15)	10-20% increment in MAP (within 8 hours), further 10% increments if no functional improvement (max 130-140)	---	---	100% (by 12 hours)
Norepinephrine									
Schwarz et al 2002[282]	19	Observational	---	---	83.6 (+/- 1.6)	MAP increase of 10% (max 130)	MAP 108.9 (+/- 2.0)	MAP 25.3	---
Marzan et al 2004[283]	34	Retrospective	---	---	127(+/- 14)/ 65(+/- 10)	10-20% increase in SBP	---	SBP 17(+/-10) % DBP 18(+/-18) %	---
Epinephrine									
Meier F et al 1991[284]	30/44	RT	---	---	---	SBP 210-220	---	---	---
Dobutamine									
Duke et al 1998[285]	1	Case	---	---	---	---	---	---	---
Dopamine									
Oliviera-Filho et al 2002[286]	1	Case	~120	---		SBP > 160	---	N/A	---
DCLHb									
Saxena et al 1998[287]	40/45	RCT	---	---	113 (+/- 14)	---	MAP 134 (+/- 20), (Control SBP 109 +/- 16)	---	---
Dexamphetamine									
Martinsson et al 2003[288]	30/15	RCT	---	---	---	---	---	SBP +14mmHg DBP +8mmHg	---

RT – randomized trial, RCT – randomized controlled trial, PE – phenylephrine, IV – intravenous, --- not mentioned

Table 2.2 Published studies of pressor therapy in acute stroke – BP characteristics of patients – reproduced from Mistri et al[264]

2.3 RESULTS

13 relevant publications were identified; including 2 randomised controlled trials, 3 randomised trials (with conventional management as comparator), 1 case-control study, 1 observational study, 1 case series, 2 retrospective reviews and 3 case reports (Table 2.1Table 2.2). The review included 366 subjects (age range 42-88 years, 55% male). The pressor agents used included phenylephrine, norepinephrine, epinephrine, dobutamine, dopamine, dexamphetamine and DCLHb. 7 of the studies also incorporated volume expansion. Phenylephrine was the most commonly used agent in 62 of 217 patients receiving pressor therapy. However because of the small numbers, varying entry and outcome criteria, a meta-analysis of outcome variables was not possible.

The study design and BP characteristics of all published studies of pressor therapy in acute stroke are summarized in Tables Table 2.1 and Table 2.2 respectively. Subsequent description of these studies by pressor agent involved is described below, in chronological order.

2.3.1 Phenylephrine (PE)[289]

Pharmacodynamics

PE differs from epinephrine, in not having the β-OH arm, which results in a reduction of α2 and β activity, with only a slight reduction in α1 activity, making it selective for this receptor. Intravenous infusion results in an increase in BP by peripheral vasoconstriction, without substantial direct cerebral vasoconstriction, due to a low density of α1 receptors in cerebral vessels[290]. It does not cause tachycardia/ tachyarrhythmias, having negligible β-agonist action. On the contrary, there is reflex vagal bradycardia, which explains why it was previously used for termination of paroxysmal supraventricular tachycardia.

Rordorf et al[276]

Study Design

Unblinded, retrospective, case note analysis, comparing 30 patients with ischaemic stroke, within 24 hours of ictus, who received PE (with the aim of improving cerebral perfusion) with 33 who received standard treatment, , over a 2.5-year period.

A BP threshold was defined as an SBP below which a sustained, consistent, neurological decline (i.e., new or worsening hemiparesis, aphasia or dysarthria, new gaze deviation, new or worsening sensory loss, decreased level of alertness) occurred at least twice, and above which the decline (lasting more than 5 minutes) was rapidly reversed after the BP was elevated with phenylephrine.

Treatment Regimes

Admission BP was specified only for those patients who had an identified BP threshold for neurological deficits – SBP 152.0 +/- 32.5 mmHg, DBP 78.5 +/- 17.0 mmHg. (All BP values are henceforth expressed as mean +/- SD). Admission BP values for patients in the treated-group who had no threshold and those in the control group were not published. Being a retrospective review, there were no fixed protocols for administering phenylephrine, and no specified BP targets.

Adverse effects

Only 3 of 30 patients receiving phenylephrine developed clinically silent cardiac complications i.e. creatinine phosphokinase elevation, with no electrocardiographic abnormalities. No patient discontinued treatment because of systemic or neurological complications. There were no significant differences in morbidity, mortality, and clinical or radiological complications between phenylephrine-treated patients and control patients.

Outcomes

The threshold SBP for neurological deficit was 161 (+/- 20.1) mmHg, range 120-190 mmHg, in the 10 (out of 30) phenylephrine-treated patients who were observed to have a SBP threshold. No significant difference in mortality or morbidity was reported, while 1 patient in the phenylephrine-treated group developed a brief run of atrial fibrillation.

Rordorf et al[277]

Study Design

A randomised trial of 13 patients with acute ischaemic stroke (baseline NIHSS≥4; no ICH on head CT), studied within 7-10 hours from symptom onset. Exclusion criteria: patients with recent angina or MI (last 3 months); history of ventricular arrhythmia; ECG showing ischaemia or left bundle branch block; seizure at stroke onset; other contraindications to phenylephrine.

Treatment Regimes

Baseline SBP was 141 (+/-23) mmHg for non-responders and 140 (+/-13) mmHg for responders (same definitions as in previous study). Increasing doses of intravenous PE (40-300 mcg/min) were used to increase SBP to ≥160mmHg or by 20% above admission SBP, to a maximum of 200mmHg. The target SBP was achieved in all patients in the first hour. NIHSS improved by ≥ 2 points in 7 of the 13 patients and a BP threshold was found in 6 of these 7 patients. The infusion was continued (maintenance 40-300microg/min) only for these 6 patients, and weaned off after 1-6 days.

Adverse effects

There were no systemic or neurological complications associated with the use of induced hypertension.

Outcomes

Patients with a BP threshold (threshold SBP – 174 (+/-15) mmHg) maintained their improved NIHSS until discharge. Patients benefiting seemed to be patients with large extracranial or intracerebral vessel stenosis or occlusion.

Hillis et al[278]

Study Design

Case series of 6 patients, within 7 days from symptom onset. Inclusion criteria: progressive naming deficits (with or without comprehension deficits); area of hypoperfusion on perfusion-weighted MRI encompassing a core of densely ischaemic tissue on diffusion-weighted MRI. Exclusion criteria: contraindication for MRI; contraindication for phenylephrine; decreased arousal or need for ongoing sedation.

Treatment Regime

Baseline mean arterial pressure (MAP) extrapolated from the graphic representation in the paper was 90.6 (+/-16.9) mmHg. MAP was increased by 10% increments (using PE in 4 patients and IV normal saline in 2), until there was functional improvement, or an MAP of 130mmHg was reached, or adverse effects of hypertension were seen.

Results

All patients showed marked and immediate improvement in naming when mean arterial pressure was increased (actual change in MAP was not reported). No adverse effects of treatment were reported.

Hillis et al[279]

Case Report

Hillis et al published the case of a 55-year old man, who presented with paraphasias and clumsy right hand movements, MRI showing an acute infarct in the left frontal lobe, insula and putamen, with an additional larger area of hypoperfused tissue that included Wernicke's area. Mean arterial pressure (MAP) drop from 107 to 87 mmHg was associated with decline in speech with development of global aphasia. Intravenous phenylephrine was administered with the intent of elevating mean arterial pressure to 90-100 mmHg. The accuracy of all language tasks improved in parallel with MAP and subsequent MRI on treatment revealed improved perfusion of Wernicke's area. Language improvement appeared to be dependent on maintaining a MAP > 90 mmHg.

Hillis et al[280]

Study Design

Randomized trial (no mention of blinding), 15 ischaemic stroke patients (quantifiable, stable or worsening aphasia, hemispatial neglect and/or hemiparesis) with >20% diffusion-perfusion mismatch on MRI, treatment within 7 days of symptom onset

Treatment Regime

Baseline MAP was 104.6 (+/- 29.9) mmHg. Intravenous PE was titrated to bring about a 10-20% increase in MAP within 8 hours of onset of infusion, and if no clinical improvement was observed, further increases of MAP in 10% increments were induced, until there was clinical improvement or MAP of 130-140 mmHg was reached. The final MAP goal was maintained for 24-72 hours, and after 24 hours, oral therapy was instituted with fludrocortisone, midodrine and NaCl, whilst weaning PE, to maintain the MAP in the goal range. MAP at Day 3 was 112.7 (+/- 15) mmHg.

Outcomes

The mean NIHSS (treated vs. untreated) was 10.2 vs. 13.5 at baseline (non-significant), 5.6 vs. 12.6 ($p=0.01$), on day 3, and 2.7 vs. 9.7 at week 6-8 ($p<0.04$). In the treated patients, there was significant improvement of NIHSS ($p<0.002$), cognitive score (58.7% to 27.9%) and volume of hypoperfused tissue (132 to 58ml) on perfusion-weighted imaging. There were no adverse effects (cardiac ischaemia or haemorrhagic conversion of infarct) during the intervention.

Hillis et al[281]

Study Design

(There was an overlap of patients with the aforementioned study – this study was intended to look into the role of MR imaging in identification of suitable patients for pressor therapy).
Randomized trial, 15 stroke patients (quantifiable, stable or worsening aphasia, hemispatial neglect and/or hemiparesis) with >20% and >30 cc diffusion-perfusion mismatch on MRI, treatment within 7 days of symptom onset.

Treatment Regime

Baseline BP and change in BP not mentioned. Regime same as above study.

Outcomes

There was a significantly larger reduction in hypoperfused tissue (identified by perfusion weighted MR imaging) in those showing functional improvement (NIH increase ≥ 3). Mean NIHSS increased from 9.3 at baseline to 4.8 on day 3, in the treated group (untreated group – no difference 12 to 11.8), $p<0.001$. No adverse events were reported.

Conclusions

Phenylephrine would appear to be a suitable pressor agent for studying the effect of BP elevation on outcome following acute stroke. Being selective in its action on vascular $\alpha 1$ receptors, it has little direct cerebral vasoconstrictive effect and less cardiac inotropic and chronotropic effects compared to other potential agents.

2.3.2 Norepinephrine (NE)[289]

Pharmacodynamics

NE differs from epinephrine in lacking the methyl moiety on the amine arm, with a resultant reduction in β2 activity. It causes less coronary vasoconstriction and a tendency to tachycardia, because of its β-adrenergic action. Its pressor effect is therefore, due to a combination of its β1-agonist (inotropic, chronotropic) and α-agonist (vasoconstrictive) properties, the β1 effects being potentially detrimental by causing increased myocardial oxygen demand and a propensity to arrhythmias.

Schwarz et al[282]

Study Design

Monitoring study, 19 consecutive patients with acute >2/3 middle cerebral artery territory infarct, sedated, intubated, ventilated, with monitoring of intracranial pressure and middle cerebral artery blood flow (transcranial Doppler via temporal windows).

Treatment Regime

Baseline MAP was 83.6 (+/- 1.6) mmHg. Fluid resuscitation to maintain CVP 12-16 cm H_2O, and, followed by a continuous infusion of NE if cerebral perfusion pressure was ≤70 mmHg. MAP was raised by 25.3 mm Hg to 108.9 (+/-2.0) mmHg.

Outcomes

Cerebral perfusion pressure and peak mean flow velocity of the middle cerebral arteries improved with no significant increase in intracranial pressure.

Adverse effects

No cardiovascular or pulmonary side effects were reported. No haemorrhagic transformation was reported on follow up CT scans. 4 patients died of uncontrollable intracranial hypertension, 28-84 hours after the last pressor stimulus.

Marzan et al[283]

Study Design

Retrospective case note evaluation, 34 patients with acute stroke, 4-26 hours from symptom onset. Inclusion criteria: NIHSS $\geq$ 5, SBP $\leq$ 140 mmHg and no evidence of hypovolaemia or other treatable cause for hypotension.

Treatment Regime

Baseline SBP was 127 (+/-14) and DBP was 65 (+/-10) mmHg. Intravenous NE (for 14-96 hours, with gradual reduction after the first 12 hours) was used to maintain a target SBP of 10-20% above baseline value. The dose range was 1 to 20microg/min. Actual SBP increase was 17 (+/- 10)% and DBP increase was 18 (+/-18)%.

Adverse effects

1 patient developed a recurrence of paroxysmal atrial fibrillation, with accompanying ventricular tachycardia, necessitating discontinuation of the infusion.

Overall 4 (12%) patients died due to:

1. massive space occupying haemorrhagic transformation
2. uncontrollable intracranial hypertension
3. pneumonia and acute cardiac insufficiency
4. locked-in syndrome

Outcomes

Early (within 8 hours) neurological improvement (NIHSS rise $\geq$2) occurred in 9 (27%) patients. No deaths were reported during the infusion.

Conclusions

Norepinephrine may not be the ideal agent, because of its cardiac side effects, especially taking into account the high coincidence of ischaemic heart disease with cerebrovascular disease. Also the high prevalence of raised intracranial pressure is of concern, as the effects of noradrenaline on cerebral autoregulation are unknown.

2.3.3 Epinephrine (Adrenaline)[289]

Pharmacodynamics

Epinephrine has agonist activity at all subtypes of receptors. The only difference from norepinephrine is additional activity at β2 receptors, with resultant bronchodilatory properties and increase in heart rate.

Meier et al[284]

Study Design/Treatment Regime

Meier et al assessed the clinical efficacy of a short-term rise in BP (for 1-hour intervals using intravenous adrenaline – 0.025-0.05 mgs, on 3 occasions) during simultaneous treatment with low-molecular dextrans, in a randomized trial of 81 patients with acute ischaemic cerebral stroke[284]. SBP was intermittently elevated to 210-220 mmHg for 5 minutes.

Outcome

Significantly more patients in the intervention group survived to 21 days (62.2% vs. 36.4%, p=0.02). There were no significant improvements in level of consciousness or severity of paresis.

Conclusions

Because of its indiscriminate stimulation of all sympathetic receptor subtypes, epinephrine has a higher risk of side effects than phenylephrine.

2.3.4 Dobutamine[289]

Pharmacodynamics

Dobutamine is primarily a β1 agonist, having positive inotropic and chronotropic effects similar to norepinephrine, with additional effects on α1 and β2 receptors. Its peripheral vascular effects are minimal, the vasoconstrictive effects of α1 stimulation being counterbalanced by the vasodilatory effects of β2 stimulation, though tolerance can develop if used for more than 24-72 hours.

Case Description

Duke et al used dobutamine, in a patient who developed an ischaemic stroke 8 hours following carotid endarterectomy, demonstrating reperfusion on angiography, alongside BP elevation and associated clinical improvement[285].

2.3.5 Dopamine[289]

Pharmacodynamics

The pressor effects of dopamine are due to its β-agonist activity (inotropic effect) and at higher levels, α-agonist activity (peripheral vasoconstriction). It also causes selective vasodilation in vascular beds that contain dopamine receptors (e.g. renal)

Case Description

Oliviera-Filho et al reported a case of an 81 year old lady with multiple infarcts in the posterior circulation, who had worsening neurological deficits (NIHSS = 8) coincident with fall in BP, where induced hypertension with dopamine was followed by rapid clinical improvement (NIHSS improved to 2, within 30 minutes). The infusion was weaned off over a period of 2 days, the patient remaining stable. At 6 months, the patient was independently mobile, with no recurrent cerebrovascular events (NIHSS = 0).

Conclusions

The pressor effects of dobutamine and dopamine are primarily due to cardiac stimulation and this is not ideal for the population being studied, with a high coexistence of ischaemic heart disease, which may be asymptomatic.

2.3.6 Diaspirin Cross-Linked Haemoglobin (DCLHb)[291]

Pharmacodynamics

DCLHb is a cell-free, haemoglobin-based oxygen-carrying solution, which offers the potential advantage of haemodilution without a decrease in oxygen delivery. In animal models, it induces a hypertensive response, with significant reductions in extent of brain injury, and in healthy human volunteers, it causes a dose-dependent increase in mean arterial pressure. It may also be a nitric oxide scavenger, and its effects are not simply related to BP changes.

Study Design

Randomised placebo-controlled trial, 40 patients with symptoms of an acute anterior circulation ischaemic stroke, within 18 hours of symptom onset

Treatment Regime

Baseline MAP was 113 (+/- 14) mmHg. Patients were randomly assigned to DCLHb or saline placebo, and three different doses were tested, with infusions every 6 hours for 72 hours (12 doses). MAP increased to 134 (+/-20) mmHg in treatment group, versus 109 (+/- 16) mmHg in the control group.

Outcome

DCLHb resulted in a rapid rise in BP, with the duration of the pressor effect being dose-dependent[291]. Outcome at 3 months was significantly worse in the treatment group (unfavourable outcome (Rankin score 3-6 at 3 months): 85% in treated patients, and 51% in untreated patients, p=0.002), and more serious adverse events and deaths occurred. However effects other than elevating BP, including a dose-dependent increase in endothelin-1 levels[287] and baseline stroke severity, may have contributed to the negative outcome.

2.4 DISCUSSION

There have been only 3 structured randomised trials to date (2 with overlapping patients), looking specifically at pressor therapy in acute stroke. All used phenylephrine as the pressor agent, and reported no systemic or neurological complications in the studied patients. The results of the two randomised controlled trials (using DCLHb and dexamphetamine) are difficult to interpret in view of the non-pressor effects of the agents employed.

Furthermore, all studies have shown the importance of monitoring for adverse events. Atrial fibrillation has been reported secondary to both PE and NE, and suggests the importance of cardiac monitoring during pressor therapy. However, mortality in the case note review by Rordorf et al was not significantly different in the treated and untreated groups[277].

We would suggest that phenylephrine is perhaps the best suited pressor agent in acute stroke populations, in view of the following:

1. It is the agent that has been studied the most in the setting of acute stroke
2. Due to its selective action, it is less likely to cause β-receptor mediated tachyarrhythmias.
3. It has little positive inotropic activity, therefore does not directly increase myocardial oxygen demand as much as other β-agonist agents.

An ideal patient more likely to have net benefit from induced BP elevation would have the following characteristics:

1. SBP below 130-150 mmHg – it has been demonstrated that prognosis of acute stroke is worse in these patients[271,241,242].
2. Severe ipsilateral large extracranial or intracerebral vessel carotid stenosis or occlusion[278,279,281]).
3. Because of the short-lived existence of the ischaemic penumbra, only patients presenting early after symptom onset are likely to benefit. The exact duration for which the penumbra remains viable is unclear at present, but is unlikely to be greater than 36 hours after onset of symptoms. However, specialised tests can now identify persistence of the penumbra (e.g. MRI diffusion-perfusion mismatch, CT perfusion, PET), and have been used to select subjects for two of the studies cited in this review[277,279], thus increasing the window of eligibility for time-sensitive therapy, like thrombolysis for ischaemic stroke, and pressor therapy.
4. Patients without evidence of diffuse cerebrovascular disease and ischaemic heart disease are less likely to have complications / side effects.
5. Knowledge of individual patient physiology (cardiac output and peripheral resistance) may guide the selection of appropriate pressor agent. β-receptor stimulation causes positive inotropic effect, and this may be preferred in patients with low cardiac output state, while α–receptor stimulation mainly increases peripheral vascular resistance, and may be suitable when it is expected that there is no cardiac dysfunction.

Obstacles to clinical application of pressor therapy would include: Delayed recognition of symptoms by patient / carers; pre-hospital triage and transport; delay in recognition of patient suitability; narrow time window for initiating treatment; issues surrounding appropriate patient consent; need for urgent neuroradiology support (to exclude haemorrhage prior to treatment);

frequent coexistence of coronary artery disease and arrhythmia which would preclude treatment with many of the pressor agents; requirement of intensive monitoring; and availability of additional nursing and medical input. In the CHHIPS study[264], the three major reasons for exclusion of patients were: admission beyond 12 hours of onset (window for initiating pressor therapy), poor baseline functional status (modified Rankin Scale >3) and pre-existing anti-hypertensive therapy.

2.5 SUMMARY

- Though small studies have shown that BP elevation can be carried out safely in acute stroke (with close monitoring), no large-scale trial has been carried out to date.
- Interpretation of the results of published studies reviewed here is complicated by the fact that all studies used differing inclusion criteria and protocols for administering pressor therapy, and lack of standardization of outcomes. The small size of what are mostly pilot trials limits reliable conclusion as to the effects on outcomes – both benefits and harms.
- The balance of benefit versus harm with induced hypertension in acute stroke needs to be demonstrated in a well-structured randomised controlled trial.
- Phenylephrine, with fluid replacement, is the most studied pressor agent in acute stroke populations, with some theoretical advantages compared to other pressor agents.
- Pressor therapy should ideally be restricted to the early stages after a stroke, when a viable ischaemic penumbra exists. Specialized investigation may be warranted to demonstrate the penumbra before instituting potentially hazardous pressor therapy beyond the early stage.

3 METHODOLOGY

This study was carried out within the confines of a UK-based multi-centre acute BP intervention trial: the "Controlling Hypertension and Hypotension Immediately Post-Stroke" (CHHIPS) Pilot Study[292]. The study and my post as overall trial coordinator and research fellow in Leicester were supported wholly by funding from the National Health Service Research and Development Health Technology Assessment Programme.

3.1 STUDY OBJECTIVES

1. To identify the proportion of acute stroke patients eligible for a trial of BP manipulation, and to establish reasons for non-eligibility/non-recruitment.
2. To establish the safety of early BP manipulation following stroke, from suspected serious adverse reactions (both unexpected and expected), treatment-related adverse events, treatment discontinuations, and trial withdrawals.
3. To prospectively study the temporal trends in BP following stroke over 2 weeks, within the context of a randomised controlled trial.
4. To investigate the effects of BP lowering on short term outcome (neurological deterioration at 72 hours, death/dependency at 2 weeks)
5. To investigate the relationship between the BP responses and
    i. Stroke type (ischaemic/haemorrhagic)
    ii. Stroke severity
    iii. Time to intervention
    iv. Swallowing status at admission
    v. Anti-hypertensive therapy: type and administration route.
6. To review current evidence for the role of pressor therapy in acute stroke and undertake preliminary safety studies.

3.2 STUDY DESIGN

3.2.1 Study Population

It was planned to recruit 1650 hypertensive patients with suspected stroke (ischaemic and haemorrhagic confirmed on head neuroradiology either CT or MRI) to the depressor arm, and 400 stroke patients, with ischaemic stroke confirmed by brain imaging and relative hypotension to the pressor arm. Patients were recruited from Acute Stroke or Medical Units of United Kingdom Teaching and District General Hospitals to this prospective, randomised, double-blind, placebo-controlled, titrated-dose trial. Inclusion criteria: age ≥18 years; stroke onset ≤24 hours (amended to ≤36 hours subsequently) for depressor arm and ≤12 hours for pressor arm, for patients waking with suspected stroke, time of onset was taken as last time patient documented to be asymptomatic; clinical diagnosis of suspected stroke, with neuroimaging before (requirement for the pressor arm of trial) or following study entry to exclude non-stroke diagnoses and to define ischaemic and haemorrhagic stroke; hypertension was defined as supine SBP ≥160mmHg, "relative" hypotension as supine SBP ≤140mmHg (defined by mean of six BP recordings over 10 minutes, using a semi-automatic BP monitor (UA-767: an oscillometric device, validated to British Hypertension Society (modified) and Association for the Advance of Medical Instruments criteria, in patients without arrhythmia, with mild to moderate hypertension[293]) with an appropriate size cuff; informed patient consent, or relative/ independent clinician assent (with later patient confirmation). The trial was designed to be as pragmatic as possible, whilst recognising significant factors contra-indicating the intended treatments. The following exclusion criteria applied: indications for urgent anti-hypertensive therapy (e.g. hypertensive encephalopathy, co-existing cardiac or vascular emergency, SBP>200mmHg or DBP>120mmHg in association with intracerebral haemorrhage); pre-existing anti-hypertensive therapy providing patients are not dysphagic (see below); contraindications to trial therapy; significant co-morbidity (pre-morbid dependence (modified Rankin Score (mRS) >2), co-existing life-threatening condition with life expectancy <6 months); non-stroke diagnoses (on subsequent neuroimaging); impaired conscious level (NIHSS 1a score ≥2); females of childbearing potential. Patients on anti-hypertensive treatment prior to stroke onset, who were not dysphagic, were considered for the Continue Or Stop post-Stroke Antihypertensive Collaborative Study (COSSACS)[294], which was running in parallel to the CHHIPS trial. However patients that were dysphagic and had been taking anti-hypertensive medication up to the time of stroke were included in the dysphagic depressor arm of the CHHIPS trial.

3.2.2 Randomisation

SBP level (mean of 6 readings), time of stroke onset and swallowing status (standardised bedside swallow assessment by appropriately trained personnel) were be assessed prior to randomisation. Patients fulfilling trial inclusion criteria were then randomised by secure internet central randomisation to receive either active treatment or matching placebo in a ratio of 1 active treatment: 1 matching placebo (pressor arm) and 1 active treatment (labetalol): 1 active treatment (lisinopril): 1 matching placebo (depressor arm).

3.2.3 Study Outcomes

Appropriately trained research staff at the participating centres performed all study measurements. Staff were provided training packages on videotape (NIHSS) or DVD (mRS), and had to pass a certification test.

The primary outcome measure was the proportion of patients who were dead or dependent (mRS >2) at 2 weeks following stroke onset. Secondary outcome measures included: early neurological deterioration (increase in the NIHSS score $\geq$4 at 72 hours of stroke onset); causes of treatment discontinuations and trial withdrawals; serious adverse events; treatment-related adverse events; changes in casual BP levels at 24 hours and at 2 weeks; fatal and non-fatal stroke recurrence at 2 weeks.

3.2.4 Study Treatment Plan

All other routine aspects of stroke patient management were continued as was standard local practice including aspirin use, but patients who received thrombolysis were excluded. Baseline assessments included mRS[295], NIHSS[296] and the Oxfordshire Community Stroke Project (OCSP)[297] Classification.

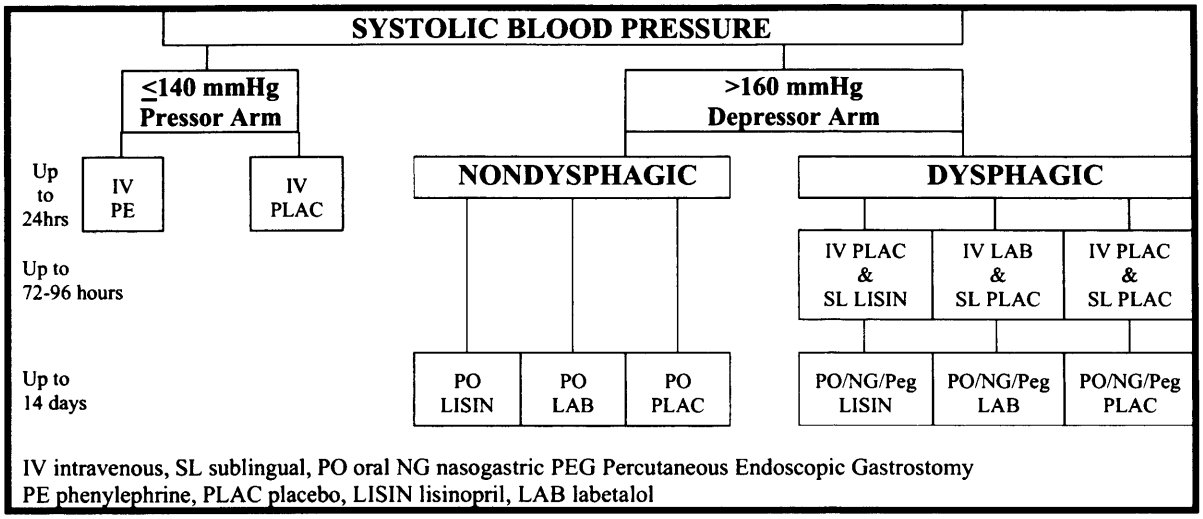

Figure 3.1 Schematic diagram of treatment allocation in the CHHIPS study

3.2.5 Depressor Arm

Hypertensive (defined as SBP≥160 mmHg – average of six readings with UA-767 semi-automatic BP monitor) non-dysphagic patients recruited within 24 hours of stroke onset, were assigned randomly to receive a test dose (either oral lisinopril 5mg or oral labetalol 50mg or oral matching placebo). Casual BP was monitored at 30-minute intervals (UA-767) for 4 hours following any test dose. In those patients not achieving target SBP of 150mmHg (range 145 to 155mmHg) or a ≥15mmHg reduction in SBP from baseline values at 4 and 8 hours, the initial test dose was repeated using the same protocol.

The established treatment regime was continued till day 14 post-stroke onset. The cumulative test dose was administered once daily for active lisinopril (with placebo lisinopril to give a twice daily regimen), with active or placebo labetalol also being administered twice daily. The treatment schedule was designed to ensure that there was no unbinding (lisinopril 5, 10 or 15mg in the morning plus matching oral placebo in the evening, labetalol 50, 100 or 150mg BD, or placebo 1 to 3 matching capsules BD).

Hypertensive, dysphagic patients whether previously untreated or treated with anti-hypertensive agents received a sublingual (tablets crushed and dissolved in 2 ml of water) and intravenous test dose (either sublingual lisinopril 5mg and intravenous placebo or, intravenous labetalol 50mg and sublingual placebo or, sublingual and intravenous placebo). Intravenous bolus medication was administered over a period of at least 1 minute and patients remained supine for 30 minutes following the injection. Casual BP was monitored every 30 minutes, and repeat test doses

administered if target SBP is not achieved at 4 and 8 hours, similar to the regime for non-dysphagic patients. Dysphagic patients received the established treatment regimes for 72 hours (sublingual lisinopril 5, 10 or 15mg OD, sublingual placebo OD and intravenous placebo BD; or intravenous labetalol 50, 100 or 150mg bolus injection (over ≥1 minute) BD with sublingual placebo BD; or sublingual placebo BD and intravenous placebo BD). At 72 - 96 hours, dysphagic patients had their swallow reassessed, to decide if medications could then be administered orally, as per the non-dysphagic regime, or via nasogastric or PEG tube (in the form of crushed tablets dissolved in 30ml of water).

3.2.6 Pressor Arm

Patients with "relative" hypotension (SBP<140 mmHg – average of six readings with UA-767 semi-automatic BP monitor) recruited within 12 hours of stroke onset were randomised in the pressor arm, after brain imaging to exclude cerebral haemorrhage or non-stroke diagnosis. Eligible patients included those with dysphagia but not those who had received anti-hypertensive treatment in the previous 7 days or who had potential contraindications to phenylephrine i.e. uncontrolled angina, occlusive vascular disease, current or recent use of monoamine oxidase inhibitors etc. To reduce the risk of potential hypovolaemia, normal saline at 100mls/ hour was infused throughout the treatment period in all subjects. BP monitoring and treatment was carried out in an Acute Stroke or High Dependency Unit during the medication infusion period. Patients had continuous ECG recording and Finapres/Portapres non-invasive beat-to-beat BP monitoring. Patients receive either IV Phenylephrine at a rate of 60 microgram/minute or matching placebo, which was continued for up to 24 hours after stroke onset (minimum pressor stimulus 12 hours). The infusion rate was adjusted at 30 microgram/minute increments (max. 180 microgram/minute) at 30-minute intervals to maintain an increase in SBP to target SBP of 150mmHg (range 145 to 155mmHg) or a 15mmHg increase above baseline values, based on casual BP readings (UA-767) taken every 15 minutes. The infusion was to be discontinued immediately, in patients developing any of the following:

1. Cardiac-type chest pain,
2. Cardiac arrhythmias,
3. Sustained tachycardia (>120 beats/ minute) or bradycardia (<40 beats/ minute).

Intravenous infusion was via a Venflon sited in the antecubital fossa, and the infusion site regularly inspected, as extravasation of phenylephrine may cause local tissue necrosis.

3.2.7 Early Monitoring

The NIHSS score was repeated at 24 hours following randomisation, to identify those patients who made a full recovery within 24 hours indicating that the initial event was a transient ischaemic attack, and at 48 and 72 hours to identify those with early neurological deterioration (increase in the NIHSS score of ≥4 from baseline).

For patients in the depressor arm, study medication was discontinued in those patients developing any of the following:

1. Doubling of baseline creatinine or absolute value ≥200mg/dl (venous blood samples taken at admission and again at 24 hours)
2. Symptomatic wheeze (requiring bronchodilator or steroid therapy)
3. Bradycardia (<40 beats/ minute)

3.2.8 Follow-Up Assessments at 14 Days

Functional assessments included mRS, NIHSS and the Barthel Index[298]. The length of hospital stay and final discharge destinations was recorded. Casual BP levels were measured supine using the UA-767 monitor. Subsequent management of BP levels after 2 weeks was at the discretion of the supervising clinician. At 3 months the central coordinating centre collected data on causes of death from the NHS register on all patients in the trial.

3.2.9 Good Clinical Practice

The study was 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. Consent was obtained according to the requirements of the multi-centre and local research ethics committees. Management of all personal data was in compliance with the Data Protection Act 1998. Results have been presented in line with the guidelines set out in the Revised CONSORT statement[299].

3.2.10 Statistical Considerations

The study was designed to have a statistical power of 80% to detect a relative reduction of 15% in death and dependency, between either of the treatment groups and the placebo group (depressor arm), and a relative reduction of 25% in death and dependency between active treatment and placebo groups (pressor arm), with a two-sided significance of 0.05.

This would mean a sample size of 1650 for the depressor arm and 550 for the pressor arm, assuming 60% death and dependency in the placebo arm, and a 15% dropout rate.

The primary analysis was on an intention-to-treat basis, comparing the proportions of subjects who were dead or dependent at 2 weeks post-randomisation. Logistic regression analysis was used to assess the effect of depressor treatment on death and dependency at 2 weeks after adjustment for age, sex, time to treatment, and stroke type. BP measurements at baseline, 24 hours and 2 weeks were compared between active treatment and placebo groups using a random effects model with adjustment for prognostic factors, for both depressor and pressor arms, separately.

3.3 STUDY ORGANISATION

The CHHIPS Pilot Trial was an independent, investigator-led study performed by a United Kingdom collaborative research group. The trial was coordinated from the CHHIPS Trial Office at the University of Leicester and the Coordinating Centre was responsible for individual site monitoring. The Trial Steering Committee oversaw the management of the trial, and an independent Data and Safety Monitoring Committee reviewed the proportion of patients with neurological deterioration, serious adverse events and treatment-related adverse events throughout the course of the trial. The pilot trial was funded by a grant from the NHS Research and Development Health Technology Assessment Programme.

3.4 SUMMARY

- Hypertension and relative hypotension following acute stroke are associated with significant, but potentially reversible, morbidity and mortality.
- There is great uncertainty about management of BP in the acute post-stroke period.
- Preliminary experience with both depressor and pressor agents has demonstrated that therapeutic BP manipulation is achievable in acute stroke.
- However, the effects of acute BP manipulation on cerebral blood flow and the penumbra are unclear, as are the timing, dose, route and titration of appropriate treatment regimes.
- The uncertainty with regards to the risks and benefits of BP manipulation justified the current study (within the confines of the CHHIPS study) to assess whether hypertension and hypotension should be therapeutically manipulated following acute stroke.

4 FEASIBILITY OF BP LOWERING IN ACUTE STROKE

4.1 INTRODUCTION

A variable association of elevated BP in the immediate post-stroke period with worse outcome[244,300,238] and improved outcome[301,243,302,303], and indeed a lack of association with outcome[304,305] has been demonstrated in individual studies. However, two independent systematic reviews concluded that elevated BP in the acute post-stroke period is associated with poor outcome[306,307]. On the other hand, low BP has also been associated with worse outcome[241,242], though this was not confirmed in a 24 hour BP study[244]. Larger BP drops (SBP fall >20mmHg or DBP fall >20 mmHg in the first 24 hours following an ischaemic stroke)[304,308] and increased pulse pressure[309] have also been associated with worse outcome.

The likely multi-factorial explanation for this apparently contradictory evidence includes:

- Baseline BP and magnitude of BP change

Very high BP values are associated with complications i.e. cerebral oedema and haemorrhagic transformation in acute ischaemic stroke (AIS)[234,310], and haematoma growth in primary intracerebral haemorrhage (PICH)[311]. Since cerebrovascular autoregulation is impaired following acute stroke[240], lower BP values or sudden drops would result in reduced cerebral blood flow (CBF), thus reducing cerebral perfusion, and hampering recovery of the penumbra (potentially viable brain tissue surrounding areas of acute stroke)[264]. Thus the impact of BP change on outcome would be a function of the baseline BP *and* the magnitude of BP change in the acute stages.

- Patient selection in individual studies

Due to differing underlying pathophysiology, elevated BP is likely to have a differential impact on stroke outcome, depending on stroke subtype i.e. small vessel disease, large vessel disease, cardioembolic stroke. Additionally patients with pre-existing hypertension need to be considered as a distinct group, as they tend to have higher BP levels immediately post-stroke[312,313]. Also cerebral autoregulation is reset at a higher level consequent to chronic hypertension and a higher BP level may be optimal following acute stroke in chronic hypertensives, as compared to non-hypertensives[314].

- Trial methodology

Inconsistent continuation of pre-stroke anti-hypertensives, variable time window for subject inclusion, variable use of de novo anti-hypertensives and bias associated with retrospective design may all be responsible for the variable results.

- Blood pressure variability (BPV)

BPV is increased following stroke[237,315] and a standardised method of BP measurement averaging multiple readings over a period of time is essential, some studies using single BP readings only[301,316,238].

- Degree of vessel recanalisation

The natural course of elevated SBP is associated with the degree of vessel recanalisation[317]. Thus occurrence of spontaneous recanalisation may also be important in predicting outcome, as seen in experimental stroke in rats[318].

The issue of elevated BP as a prognostic factor remains a matter of continual debate. A large observational database with standardised methodology is required for definitive clarification of the true association. Nonetheless, BP lowering to improve outcome is an attractive intervention, and a small BP reduction in the early stages may be beneficial by reducing the risk of the aforementioned complications in both AIS and PICH. Anti-hypertensive use has been associated with a significant reduction in fatal and non-fatal vascular events at 12 months in a pilot study of patients with acute ischaemic stroke who were hypertensive. However intervention did not result in a significant difference in BP between active and placebo groups during the treatment period or at outcome assessment (12 months), and BP change was thus unlikely to be related to the altered outcome[248].

Little research has been undertaken into the feasibility of BP lowering in the acute post-stroke situation. The larger trials have investigated BP lowering in patients beyond the acute stage i.e. weeks to months after the onset of stroke (e.g. PROGRESS[319], HOPE[320], PATS[321]). The small trials that have demonstrated the feasibility of BP reduction in the acute post stroke stage have not been powered to investigate the impact on clinically relevant outcomes, and were of limited duration[246,322,323]. Moreover, few trials have included patients with impaired swallowing (e.g. IV nimodipine[324]). BP reduction is likely to be beneficial where the absolute BP is higher, with avoidance of precipitous falls due to the danger of compromising CBF and cerebral perfusion. Thus, a cautious approach using low doses, with further titration may be beneficial. It remains uncertain whether intervention to lower BP following a stroke has an impact on outcome, even in the context of thrombolysis, due to lack of randomised controlled studies.

A suitable anti-hypertensive for use in acute stroke would have the following features:

- Effective for acute treatment and secondary prevention;
- Gradual and predictable BP lowering;
- No significant decline in CBF (less likely to need intensive monitoring);
- Suitable formulation for patients who are unable to swallow; and
- Applicable to the majority of patients with stroke i.e. AIS and PICH.

Since elevated pulse pressure (PP)[309], impaired baroreceptor sensitivity (BRS)[325] and increased BP variability (BPV)[326,237] in acute stroke are associated with worse outcome, additional desirable qualities would include:

- Reduction of PP;
- Increase in BRS; and
- Reduction of BPV.

Routine considerations with respect to any drug used include: low cost, few side effects, few drug interactions; and the possibility of incremental dosing.

The available evidence with respect to the individual drug classes in human studies is summarised in Table 4.1 (next page).

Drug type	First author, publ year (Study)	n (A,P)	Window	Entry BP criteria	Baseline BP (A,P)	BP fall, mmHg A,P (parameter)	Outcome	OR (05% CI)	Safety difference
ACE inhibitor									
Lisinopril	Eveson 2007	18,22	24 hours	≥140/90	174/91, 169/94	20/6, 11/8 - 4h 25/11, 5/2 - 14d	14 day NIHSS, Barthel, mRS	NS	Rise in creatinine & difference in SAE – NS
Perindopril	Dyker 2001	12,12	--	≥170/95	171/94, 173/91	18/11	CBF change (reduction in MCA velocity)	NS	No SAE
Captopril (Nic, clon)	Lisk 1993	3-5-2,6	72 hours	>170/95	125, 128 (MAP)	Titration to achieve fall of 10-15%	CBF (SPECT MCA ratio) 72h	Larger MAP fall associated with smaller increase in CBF	Suggestion that MAP fall >16% will impair CBF
Angiotensin Receptor Blocker (ARB)									
Losartan	Nazir 2004	14,10	7 days	>110 (MAP)	115.5, 115.3 (MAP)	9.5 (MAP)	Global and focal cerebral perfusion, ICA flow	No fall	Change in GFR - NS
Candesartan	Schrader 2003 (ACCESS)	173,166	72 hours	>180/105	188/99, 190/99	NS	Vascular events at 12 months	47.5% reduction	NS
αβ-blockers									
Labetalol	Patel 1993	10	unspecified	--	152-184/ 50-99	11-35 mmHg (6-19%)/ 3-21 mmHg (3-26%)	Observational study	N/A	No adverse haemodynamic or mental status changes
Labetalol	Brott 1998 (NINDS) *POST HOC ANALYSIS*	22,43 pre-thrombolysis	3 hours	≥185/110	--	--	Death at 3 months sICH at 36 hours	0.1 (0.1-0.7) NS	--
		80,115 post-thrombolysis			--	28/25 (maximal MAP decline)	Death at 3 months sICH at 36 hours	1.5 (0.8-2.9) NS	--
β-blockers									
Atenolol, propranolol	Barer 1983 (BEST)	101-101,100	8 hours			Aten 9%, propr 6% P 2% (MAP)	Death at 6 months	NS increase, especially in elderly	Confounded by baseline differences in stroke severity
CCB reviews	Horn 2001	6877 in total	--	--	--	--	Mortality Death or dependency (mRS>3) Adverse events	RR 1.07 (0.98-1.17) RR 1.04 (0.98-1.09) RR 1.17 (0.97-1.41)	No significant benefit, trend towards worse outcomes
	Mohr 1994	4324 in total	<48 hours	--	--	--	Death Clinical deterioration		No significant benefit, ?benefit <12 hours from onset
BFZ	Eames		24-96h	Mean>135/85 (day)/>130/80 (24h)					
Nitrates (GTN patch)	Willmot 2006					23/NS (peripheral) 22/NS (central)			
	Rashid 2003					6.2% (amb MAP) - day 1, NS - day 10			
	Bath 2001	16,21	5d		167/96, 157/87	13.0/5.2 - day 1 9.3/5.8 - day 8	Case fatality, dependency(mRS>3)	NS	Platelet function unaffected
Magnesium	Lees 2004 (IMAGES)					4/3	Death or dependency at 90 days (mortality; time to death)	NS (NS)	Difference in SAE - NS

Table 4.1. Characteristics of studies investigating BP lowering in acute stroke, within 2 weeks of stroke onset

A active; amb ambulatory; Aten Atenolol; BP blood pressure; CBF cerebral blood flow; Clon Clonidine; ICA internal carotid artery; MAP mean arterial pressure; MCA middle cerebral artery; mRS modified Rankin Scale; N/A not applicable; NIHSS National Institutes of Health Stroke Scale; Nic Nicardipine; NS non significant; OR odds ratio; P placebo; Propr propranolol; publ publication; RR relative risk; SAE serious adverse event; sICH symptomatic intracerebral haemorrhage; SPECT single photon emission computed tomography

4.1.1 ACE Inhibitors/Angiotensin II Receptor Blockers (ARBs)

Theoretically, angiotensin converting enzyme (ACE) inhibitors are the prime candidates as they shift the lower limit of cerebrovascular autoregulation to the left, thus maintaining cerebral blood flow at lower systemic blood pressures[327]. In a pilot study of 40 patients with acute stroke within 24 hours of symptom onset, oral lisinopril (5 mg) reduced BP significantly, with a maximal placebo-adjusted reduction of 19/7 mmHg at 4 hours post-dose[328]. In acute ischaemic stroke with BP>170/95 mmHg, perindopril treatment started about 3 days from stroke onset was associated with a placebo-adjusted BP reduction of 19/11 mmHg[246].

Since the proposed effects of ACE inhibitors are due to reduction in angiotensin II-mediated small vessel vasoconstriction, similar effects may be expected of angiotensin II receptor antagonists (ARB's). In addition, ARBs may reduce local oxidative stress and improve nitric oxide bioavailability[329]. Losartan in mild early AIS without significant carotid artery disease, within 2-7 days of onset resulted in a placebo-adjusted MAP reduction of 9.5 mmHg[322]. Indeed, the ACCESS study reported a significant benefit with the use of candesartan in acute stroke 6-36 hours after hospital admission (47.5% reduction in vascular events). No difference in BP was seen between active and placebo groups throughout the trial, suggesting an alternative mechanism for the observed benefit[248].

4.1.2 Beta-blockers

Beta-blockers may be beneficial following stroke by reducing catecholamine-mediated cardiac[330] and neurological[331] damage, and by reducing the metabolic demands on the brain[332]. Also observational evidence suggested benefit in terms of less severe stroke, for patients who were on β-blockers pre-stroke, compared to those who were not[333]. However, this was not borne out in the BEta blocker Stroke Trial (BEST) study, where mean BP fell by 9% with atenolol (50 mg daily), 6% with slow release propranolol (60 mg daily), and 2% with placebo, in the first 24 hours post stroke, and there was a trend towards higher mortality in both the beta blocker groups, compared to placebo[251]. There was some imbalance in baseline characteristics, with subjects in the intervention arms having more severe symptoms at baseline.

4.1.3 Alpha-beta blocker - Labetalol

Labetalol was the anti-hypertensive of choice in the National Institutes of Neurological Disorders and Stroke (NINDS) Trial of thrombolysis in acute ischaemic stroke[152], and has also been used in a study of patients with intracerebral haemorrhage[250]. 9% of patients in the placebo arm (not thrombolysed) of the NINDS Trial of thrombolysis were hypertensive (≥185/110mmHg) at admission, and received bolus intravenous labetalol therapy. The odds ratio for death at 3 months was significantly reduced (0.1, 95% CI 0.1-0.7) compared to hypertensive patients in the placebo group who did not receive BP lowering therapy[152]. However, in the same group of patients, there was a non-significant increase (OR 1.5, 95% CI 0.8-2.9) in 3-month mortality, for patients who became hypertensive and received labetalol in the 24 hours post randomisation. Because of the non-randomised use of anti-hypertensives, and post hoc comparisons, the significance of these observations is unclear. An observational study in patients with intracerebral haemorrhage or subarachnoid haemorrhage concluded that small bolus doses of intravenous labetalol (5-20 mg) did not have significant adverse effects, including worsening neurological deficit, hypotension or altered mental status[250]. Duration from stroke onset was not specified.

4.1.4 Calcium Channel Blockers (CCBs)

CCBs have been associated with reduced infarct size in experimental stroke[334]. Reduction in calcium-induced damage to hypoxic cells due to reduced intracellular calcium influx is the proposed mechanism. As a result, CCBs have been studied extensively in the setting of acute stroke, with demonstrated efficacy in terms of lowering BP[324,335,336,337,338,339,340], the effect being dose-dependent[324] and route-dependent (larger drops being seen with intravenous administration compared to oral[324]). A small study suggested that use of nicardipine results in fall in CBF which may be detrimental in acute stroke[245]. Sublingual use of nifedipine has been associated with abrupt drops in BP, and with ischaemic stroke, and this route of administration is best avoided[341].

However, despite efficacy in BP lowering, no overall significant improvement in outcome has been demonstrated. Whilst an earlier review suggested possible benefit with early use of nifedipine (<12 hours from stroke onset)[340], this was not confirmed in a more recent review (Horn, 2001)[252,342]. Larger DBP drops (>20%) were associated with worse outcome in subgroup analysis in one study[324].

4.1.5 Bendroflumethiazide (Thiazide Diuretic)

Bendroflumethiazide 2.5 mg daily showed no additional hypotensive effect over placebo in a small study of 36 hypertensive patients (24 hour mean BP >130/80 mmHg, or daytime mean BP >135/85 mmHg) within 10 days of AIS[253]. Also, there was no significant change in beat-to-beat BPV, CBF or cerebral autoregulation.

4.1.6 Others

4.1.6.1 Glyceryl Tri-Nitrate (GTN)

GTN functions as a nitric oxide donor, which causes vascular smooth relaxation. Other putative benefits include: inhibition of platelets and leucocytes, and attenuation of NMDA receptor activity. A meta-analysis of 3 trials studying GTN in acute stroke (93 active treatment and 52 control) showed that topical GTN (patch) significantly lowered SBP (weighted mean reduction: 9.8 mmHg) and DBP (weighted mean reduction: 4.43 mmHg) after initial treatment (24 hours)[254]. Moreover, in one study, no cerebral steal phenomenon was seen[323]. Transdermal administration is attractive as it is unlikely to result in rapid fall in BP, and suitable for the 22-65% patients who are dysphagic following acute stroke[343]. However, tachyphylaxis with loss of BP lowering effect occurs by about 8 days, and this may be reduced by increasing the dose after a few days[344].

4.1.6.2 *Magnesium*

Magnesium is neuroprotective in various animal models, the mechanism being uncertain[177], but possibilities include: reduced glutamate release in the brain[174]; blockade of N-methyl D-aspartate receptors[175]; blockage of voltage-gated calcium channels; and improved cerebral perfusion secondary to cerebral vasodilatation[176]. In the Intravenous MAgnesium in Stroke (IMAGES) Study, overall BP was lowered by 4/3 mmHg in the intervention arm, with no significant overall benefit in functional outcome (Barthel Score <95 and modified Rankin Scale >1 at day 90)[177]. Post hoc analysis suggested improvement in functional outcome in two subgroups: those with MAP > median value (108.3 mmHg), and those with lacunar strokes (pure motor/sensorimotor strokes only). The benefit in those with lacunar strokes persisted after adjustment for baseline factors[178].

4.1.7 Non-Tablet Formulations

Both enalapril and lisinopril are absorbed via the buccal mucosa, though to a lesser extent than their corresponding oral absorption[345]. Whether this is due to different modes of absorption from the buccal and intestinal mucosa, or due to practical difficulties with

administration of the crushed medication is unclear. Thus sublingual administration of these agents is feasible, though efficacy in lowering BP with this mode of administration has not been studied. Parenteral drugs used as infusions allow titration of dose to achieve desired BP fall, however an intensive monitoring environment is required, thus limiting its applicability for all patients. In the INWEST study, intravenous nimodipine was effective at lowering BP, average SBP during the first 48 hours fell by 2.1% from baseline with placebo, 6.6% with low-dose, 1mg/hour (p=0.008 vs. placebo), and 11.4% with high-dose nimodipine treatment, 2mg/hour (P<0.001 vs. placebo). Corresponding average DBP fall was 1.7% with placebo, 7.7% with the low-dose (P=0.005 vs. placebo), and 14.1% with the high-dose nimodipine treatment (P<0.001 vs. placebo). Larger DBP fall (>20%) was associated with poor outcome.

A retrospective analysis of nitroprusside use in 11 patients with haemorrhagic stroke reported that 90% had a rise in intracranial pressure >50%, but these were short-lived (0.4-1.6 hours) and were not associated with poor outcome[346]. While other agents are recommended for parenteral use in some guidelines (e.g. nicardipine), there are no published studies involving patients with acute stroke, where BP lowering efficacy has been studied. A large RCT is investigating the use of transdermal Glyceryl TriNitrate in acute stroke.

Lisinopril and labetalol were considered suitable BP lowering agents for the CHHIPS Pilot study[292], the reasons being summarised in Table 4.2 below.

Attribute of candidate drug	**Lisinopril**	**Labetalol**
Previous use in acute stroke	Yes[328]	Yes[152]
Effective at lowering BP in acute stroke	Yes[328]	Yes[152]
Alternative formulation for dysphagic patients	Yes[345]	Yes[152]
Effective for secondary prevention	--	--
Reduction of Pulse Pressure	Yes (hypertensives)[347]	--
Increase in Baro-Receptor Sensitivity	Yes (hypertensives)[348]	--
Reduction of Blood Pressure Variability	--	--
Preserves Cerebral Blood Flow	--*	Yes (healthy[349], ICH[350])

Table 4.2: Desirable attributes of candidate anti-hypertensive agents

* Preservation of cerebral blood flow despite significant BP lowering has been demonstrated for other ACEI (perindopril) and A2RA (losartan, candesartan) in small studies including subjects with acute stroke, and is likely to be a class effect, thus applying to lisinopril also.

4.2 AIMS

Since elevated BP following acute stroke is associated with worse prognosis, it is important to establish whether BP can be lowered in the acute stages, and which drugs may be suitable for this purpose. The aims of this study were:

1. To demonstrate the feasibility of SBP reduction following acute stroke, active therapy being compared to placebo.
2. To compare the effects of labetalol and lisinopril on SBP following acute stroke.
3. To study the temporal trends in SBP following acute stroke, in the study participants.

4.3 METHODS

4.3.1 Subjects

The study population was recruited as part of the CHHIPS Pilot study (from January 2004 to December 2006), funded by the UK National Health Service Research & Development Health Technology Assessment (NHS R&D HTA) program. CHHIPS was a prospective, multi-centre, randomized, double-blind, placebo-controlled, titrated-dose trial.

Patients were eligible if the following criteria were satisfied: age >18 years; stroke onset <24 hours (subsequent amendment to allow onset within 36 hours); clinical diagnosis of suspected stroke (neuroimaging to exclude non-stroke diagnoses and to define stroke type); informed patient consent, or relative/ independent clinician assent. Hypertension was defined as systolic BP > 160 mmHg (average of six readings using a semi-automated machine validated to BHS criteria[351]). No DBP criteria were specified. We excluded those with pre-specified exclusion criteria: indication for urgent anti-hypertensive therapy, hypertension with an SBP>200mmHg or DBP>120mmHg in association with intracerebral haemorrhage; contraindication to trial therapy; significant co-morbidity (pre-morbid dependence i.e. modified Rankin Score >2 (subsequently amended to mRS>3); life expectancy <6 months; non-stroke diagnosis; impaired conscious level (NIHSS 1a score >2); females of childbearing potential. Those receiving thrombolysis were excluded, due to the requisite BP limits set for these patients, as per guidelines. Dysphagic patients on prior anti-hypertensives were later included if they were dysphagic. The amendments resulted in an overall increase of ~22% in recruitment.

4.3.2 Trial Design and Conduct

A 3-tiered process of consent was approved by the Trent MREC. Informed patient consent was obtained wherever possible. Otherwise, informed relative or independent clinician assent were sought in that order, with subsequent confirmation by relative/patient, as soon as possible. Witnessed consent was allowed if the patient indicated an understanding of the relevant information and agreed to participation, but was unable to sign.

Since it was felt that local randomisation may lead to treatment imbalance, a centralized online randomisation service operated and maintained by Imperial College, London was employed. After recording baseline data, patient number and treatment number was allocated, randomisation being done in fixed blocks of six, and stratified by dysphagia status. This database also collected data from all trial visits.

Ethical approval was given by the Trent Multi-centre Research Ethics Committee (Reference MREC 03/4/001), regulatory approval by the Medicines and Healthcare products Regulatory Authority (CTA No. 21662/0001/001-0001), and the Research & Development (R&D) departments at the participating sites. Patients were recruited at 6 UK sites, while 3 other sites which had the requisite approvals failed to recruit any patients. The trial conformed to International Conference on Harmonization Good Clinical Practice standards, and the European Clinical Trials Directive. All sites were monitored with source data verification from patient notes.

The Trial Steering Committee (which included a lay representative) supervised the trial; reviewed 3-monthly reports prepared by the Trial Coordinator, and recommended amendments to improve recruitment rates. An independent Data Safety & Monitoring Committee did interim safety analyses.

4.3.3 Statistical Analysis

The primary outcome of the study was death and dependency (modified Rankin Scale - mRS>3) at 2 weeks. Secondary objectives were: to establish the safety of BP lowering (<36 hours from onset of acute stroke) as assessed by the absence of early neurological deterioration (increase in NIHSS score of 4 or more points at 72 hours); to investigate the influence of stroke type (ischaemic versus haemorrhagic) on the effects of BP manipulation; to determine if alternative therapeutic routes (sublingual, intravenous) are effective at lowering BP in dysphagic stroke patients; to investigate if beneficial or detrimental effects of

BP manipulation are influenced by time to treatment; and to assess cost effectiveness of active treatment versus placebo.

Based on an expected 60% death or dependency rate at 2 weeks in the placebo arm of the trial[177] and an estimated dropout rate of 15%, recruitment of 1650 (550 in each group) subjects would have 80% power at the 5% significance level to detect a relative reduction of 15% in death and dependency between either of the two treatment groups and the placebo group. However, recruitment did not allow for this number of patients to be randomised, as discussed further in Chapter 6.

The significance level was fixed at 5%. The primary outcome was death and dependency at 2 weeks. Subsequent exploratory data analyses were carried out. Mann-Whitney U test and Chi-squared test were used to assess for differences in baseline characteristics. Repeated measures ANOVA was carried out for changes in BP parameters, the Scheffe method being used to adjust for multiple comparisons. Logistic regression was used to estimate the impact of baseline BP parameters on primary outcome. Cumulative survival rates were presented in the form of a Kaplan-Meier curve.

4.3.4 Interventions

Participants were randomized to receive one of three interventions: lisinopril, labetalol or placebo (1:1:1). Drug dose was titrated to achieve a target SBP of 145-155 or a reduction of 15mmHg from baseline during the titration phase. Test doses (lisinopril 5 mg; or labetalol 50 mg; or matched placebo) were given at baseline, and repeated at 4 and 8 hours, if the target (average of half-hourly SBP monitoring in the preceding 4 hours) was not reached. A maximum of 3 test doses were allowed. If the target was reached at either 4 or 8 hours, no further test doses were administered. Dysphagic patients received sublingual lisinopril with intravenous placebo; or intravenous labetalol with sublingual placebo; or intravenous and sublingual placebo. Dysphagia screening was carried out by trained personnel, usually undertaking a protocol-driven dysphagia screen. Treatment discontinuations and serious adverse events were monitored during the titration phase and for the planned duration of drug schedule (14 +/- 2 days).

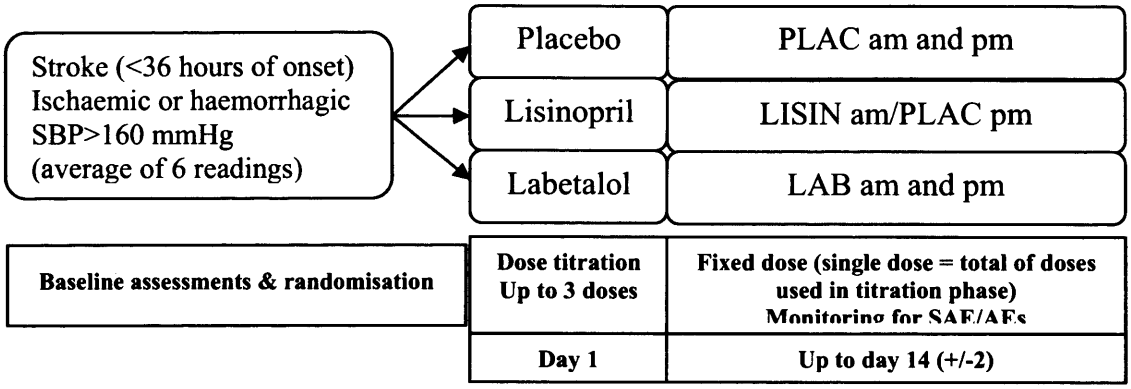

Figure 4.1. Drug schedule

4.3.5 Funding

The National Health Service Research & Development Health Technology Assessment Program was the sole funding agency and sponsor for the trial. They were provided regular reports, and gave feedback, but had no influence on the conduct of the study, or its interpretation.

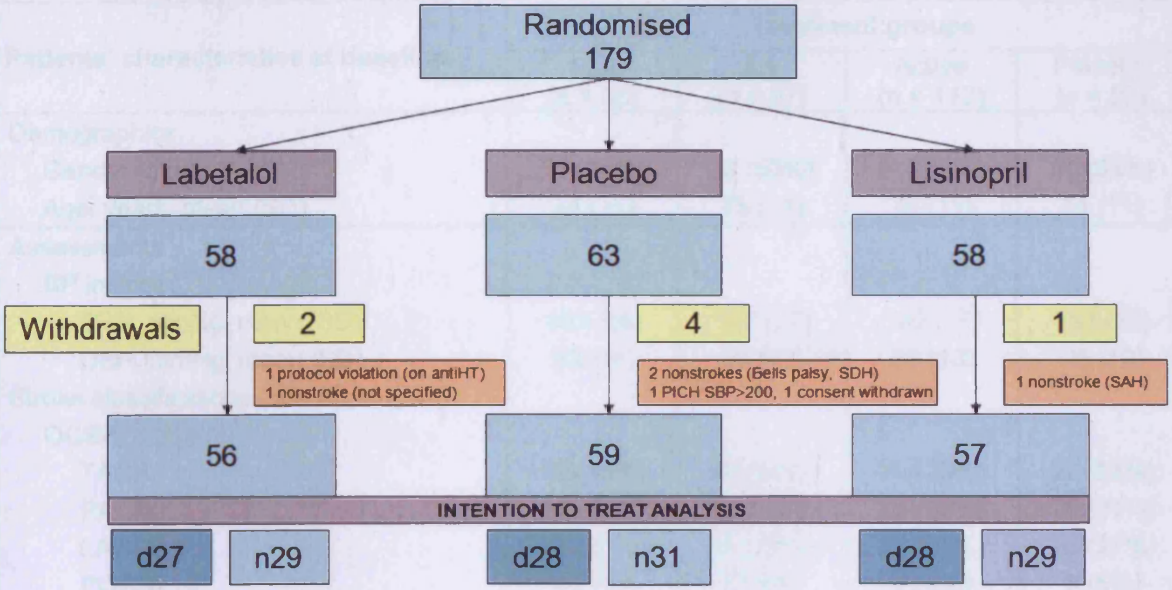

Figure 4.2. Distribution of patients by randomised group

AntiHT anti-hypertensive; d dyphagic; n nondysphagic; PICH primary intracerebral haemorrhage; SAH subarachnoid haemorrhage; SDH subdural haematoma

4.4.1 Baseline Characteristics

Random patient allocation to the three groups is summarised in Figure 4.2 above. 179 patients were randomised into the depressor (BP lowering) arm. Baseline demographic characteristics, neurological deficit (NIHSS), Oxfordshire Classification of Stroke Project classification (OCSP), dysphagia status, delay from stroke onset to randomisation, and vascular risk factors (previous stroke, previous TIA, previous ischaemic heart disease, previous diabetes, previous hypercholesterolemia and smoking status were not significantly different (see Table 4.3 below). Mean age was 74 years (SD 11), and median baseline NIHSS was 9 (interquartile range, IQR 5-16) on a 42-point scale.

Patients' characteristics at baseline	Treatment groups			
	Lab (n = 56)	Lis (n = 57)	Active (n = 113)	Placebo (n = 59)
Demographics				
Gender (male), n (%)	34 (61%)	30 (53%)	64 (57%)	31 (53%)
Age, years, mean (SD)	74 (11)	75 (11)	74 (11)	74 (11)
Assessments				
BP indices				
SBP, mmHg, mean (SD)	181 (16)	182 (17)	182 (17)	181 (16)
DBP, mmHg, mean (SD)	93 (14)	96 (12)	95 (13)	96 (12)
Stroke classifications (see Appendix I)				
OCSP, n (%)				
TACS	19 (35%)	20 (34%)	39 (35%)	22 (37%)
PACS	15 (27%)	21 (36%)	36 (32%)	18 (31%)
LACS	17 (31%)	11 (19%)	28 (25%)	16 (27%)
POCS	4 (7%)	5 (9%)	9 (8%)	3 (5%)
Unknown	1	0	1	0
Pre-morbid mRS, n (%)				
0	42 (75%)	38 (67%)	80 (71%)	44 (75%)
1	7 (13%)	12 (21%)	19 (17%)	9 (15%)
2	5 (9%)	4 (7%)	9 (8%)	5 (8%)
3	2 (4%)	3 (5%)	5 (5%)	1 (2%)
NIHSS score, median (IQR)	9 (6-16)	10 (5-16)	9 (5-16)	9 (4.5-17.5)
Dysphagic, n (%)	27 (48%)	28 (49%)	55 (49%)	28 (47%)
Comorbidity				
Previous stroke, %	5	12	9	5
Previous TIA, %	9	9	9	7
Previous IHD, %	16	9	12	8
Previous diabetes, %	7	7	5	5
Previous hypercholesterolemia, %	29	25	27	37
Atrial fibrillation at presentation, %	14	18	16	24
Smoking status, n (%)				
Never smoked	24 (42%)	33 (58%)	57 (50%)	24 (42%)
Ex-smoker	21 (38%)	15 (26%)	36 (32%)	19 (32%)
Current smoker	11 (20%)	9 (16%)	20 (18%)	16 (27%)
Time to treatment, hours, mean (SD)	19.2 (6.6)	20.5 (8.5)	19.8 (7.6)	17.4 (6.6)
Type of stroke on CT, n (%)				
Ischaemic	33 (59%)	31 (54%)	64 (57%)	35 (61%)
PICH	9 (16%)	9 (16%)	18 (16%)	7 (12%)
No relevant abnormality	14 (25%)	17 (30%)	31 (27%)	15 (26%)
Died before CT done	0	0	0	2

Table 4.3. Baseline characteristics of participants

Trial withdrawals and treatment discontinuations

There were seven withdrawals, as indicated in Figure 4.2 above, due to non-stroke diagnoses (4), protocol violations (2), and withdrawal of consent (1). 126 patients (73.3%) completed the full protocol-specified two weeks of trial treatment (treatment discontinuation rates: 20.3% placebo, 28.6% labetalol, 31.6% lisinopril, 30.1% active treatment, no significant difference, Chi-squared test). Most of the discontinuations occurred in the first 72 hours, with a higher rate, as expected, in the dysphagic group (Figure 4.3). There were 18 treatment discontinuations due to serious adverse events (six labetalol, eight lisinopril, four placebo group), and five of these patients (one labetalol, two lisinopril, two placebo group) subsequently suffered a fatal event. There was no significant difference between groups.

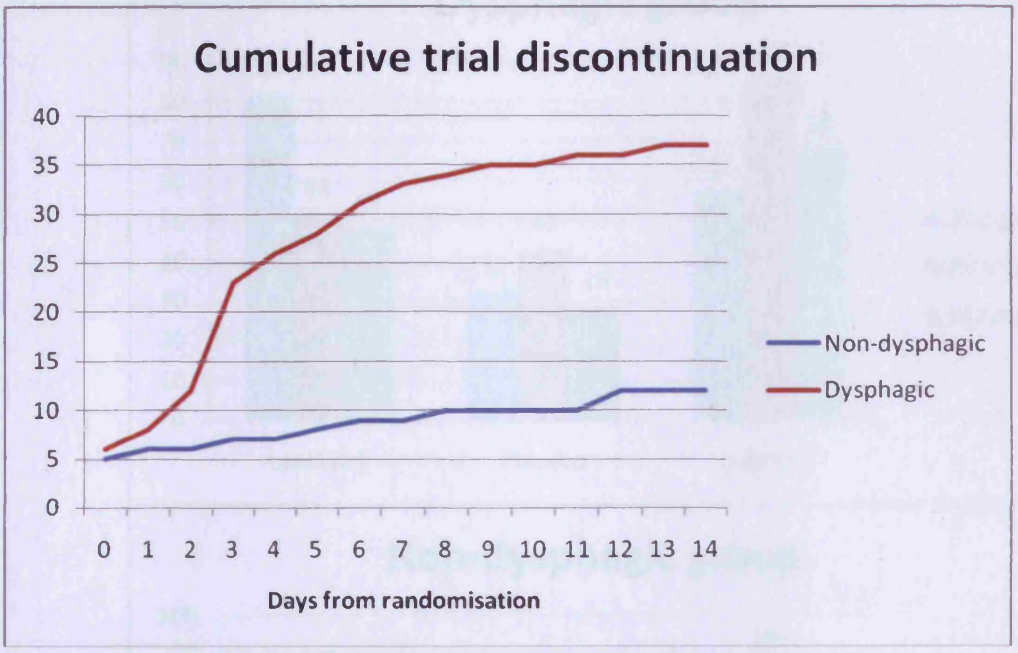

Figure 4.3. Cumulative trial discontinuation by dysphagia status

4.4.2 Attainment of target SBP

The protocol specified SBP target was 145-155 mmHg or a fall from baseline ≥15 mmHg. SBP target achievement at 4, 8 and 24 hours from randomisation is indicated in Figure 4.4. In the labetalol group, a high percentage achieved target SBP at 4 hours. The rates at subsequent time-points were generally lower, and this was more pronounced in the dysphagic group. In the placebo group, target achievement was low, as expected. In the lisinopril group, target achievement at 4 hours was lower than the labetalol group, however rates continued to rise at the 8 hour time-point, and subsequently declined at 24 hours.

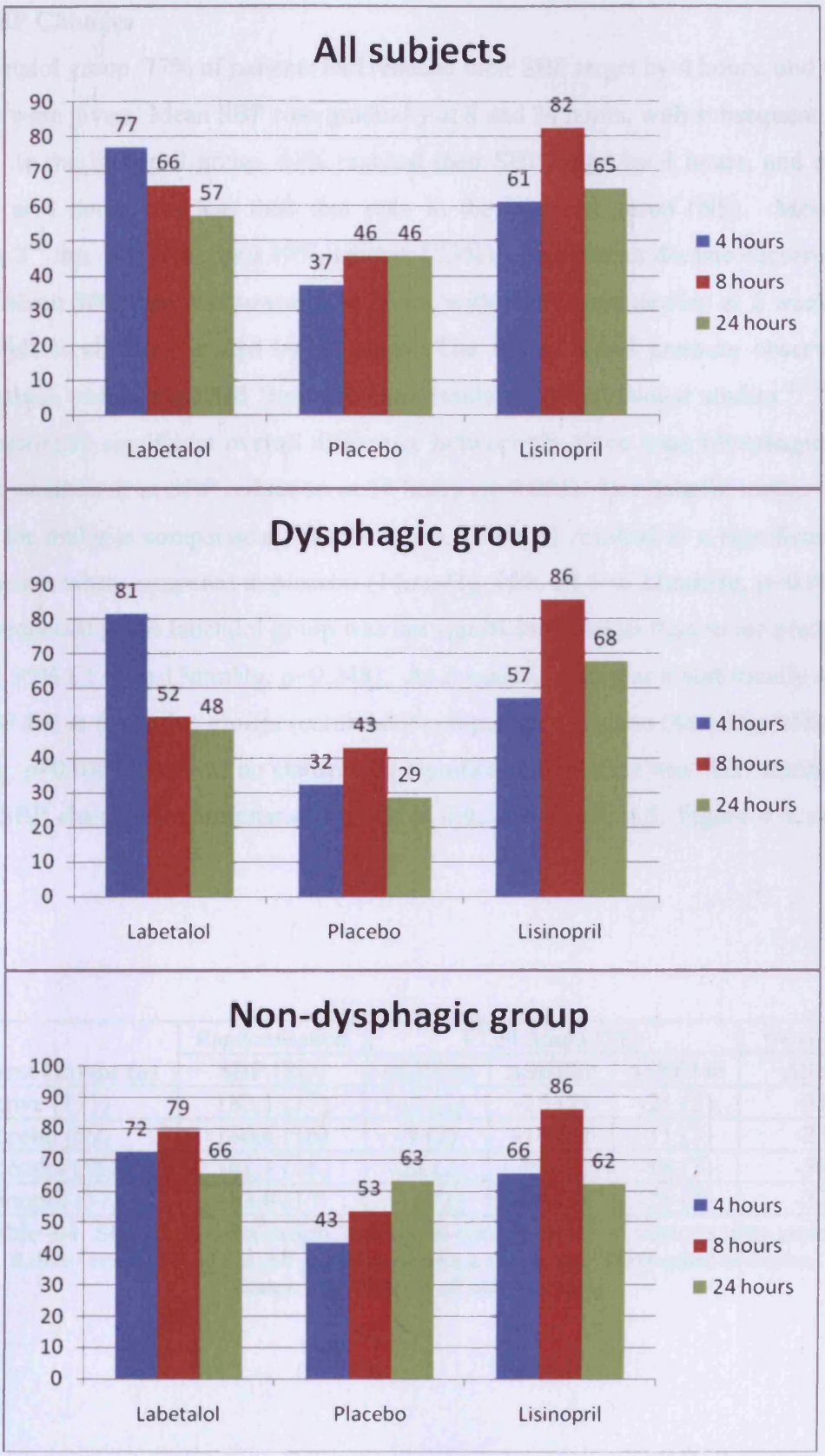

Figure 4.4. Percentage maintaining target SBP at various time points
a) all b) dysphagic and c) nondysphagic subjects
Target SBP was 145-155 mmHg OR SBP fall ≥15 mmHg from baseline

4.4.3 SBP Changes

In the labetalol group, 77% of patients had reached their SBP target by 4 hours, and no further test doses were given. Mean SBP rose gradually at 8 and 24 hours, with subsequent decline at 2 weeks. In the lisinopril group, 61% reached their SBP target by 4 hours, and mean SBP reduction at 4 hours was less than that seen in the labetalol group (NS). More patients received a 2nd test dose (lisinopril 39%, labetalol 23%), and a further decline occurred towards 8 hours. Mean SBP then rose towards 24 hours, with subsequent decline at 2 weeks. Blood pressure fell in all three groups by 24 hours. The fall in blood pressure observed in the placebo group was as expected from previous results in observational studies[352,229]. There was a statistically significant overall difference between the three arms (dysphagic and non-dysphagic combined) in SBP reduction at 24 hours (p=0.005). The Scheffe method was used to adjust for multiple comparisons. At 24 hours, lisinopril resulted in a significantly larger SBP reduction when compared to placebo (14mmHg, 95% CI 5 to 22mmHg, p=0.005), while the SBP reduction in the labetalol group was not significantly larger than in the placebo group (7mmHg, 95% CI -1 to 15mmHg, p=0.248). At 2 weeks, there was a statistically significant larger SBP fall in the active groups (combined) compared to placebo (8mmHg, 95% CI 0.2 to 16 mmHg, p=0.045), however no statistically significant difference was seen across the three groups. SBP changes are summarised in Table 4.4, and Figure 4.5, Figure 4.6, and Figure 4.7.

	Randomisation	1st 24 hours (SE)			14 +/- 2 days
Treatment Groups (n)	SBP (SD)	ΔSBP4h	ΔSBP8h	ΔSBP24h	ΔSBP2w
Active (113)	182.1 (17)	-19 (2)	-25 (2)	-21 (2)	-31 (2)
Placebo (59)	180.6 (16)	-9 (2)	-14 (3)	-11 (3)	-23 (4)
Labetalol (56)	181.1 (16)	-22 (2)	-20 (3)	-18 (3)	-31 (3)
Lisinopril (57)	183.0 (17)	-16 (2)	-29 (3)	-25 (3)	-32 (3)

Table 4.4. SBP at randomisation, and mean change in BP at various time points
Active - labetalol and lisinopril groups combined; n sample size; SD standard deviation;
Δ change from baseline, all units in mmHg

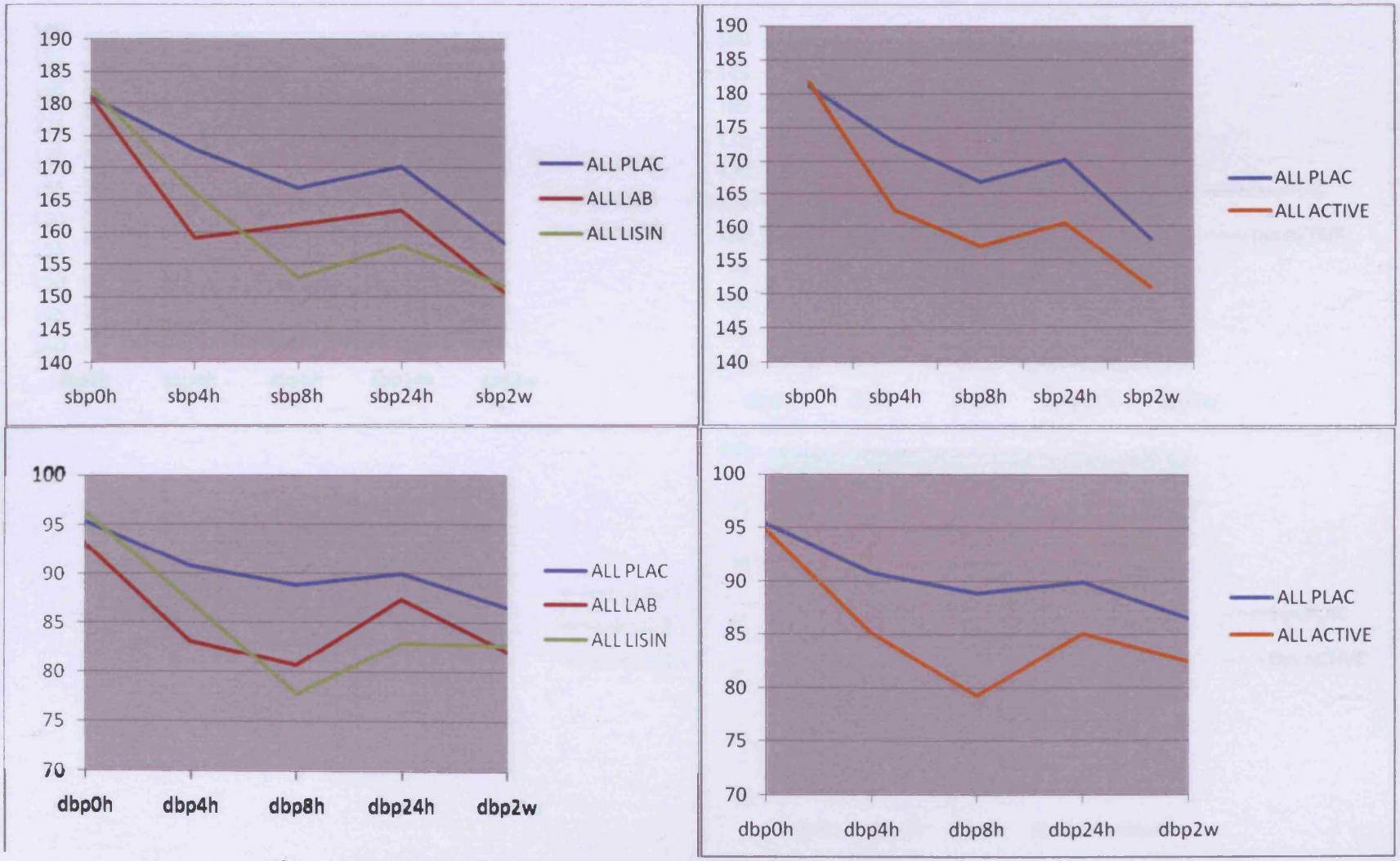

Figure 4.5. SBP and DBP changes in all patients, by three groups, and active therapy versus placebo

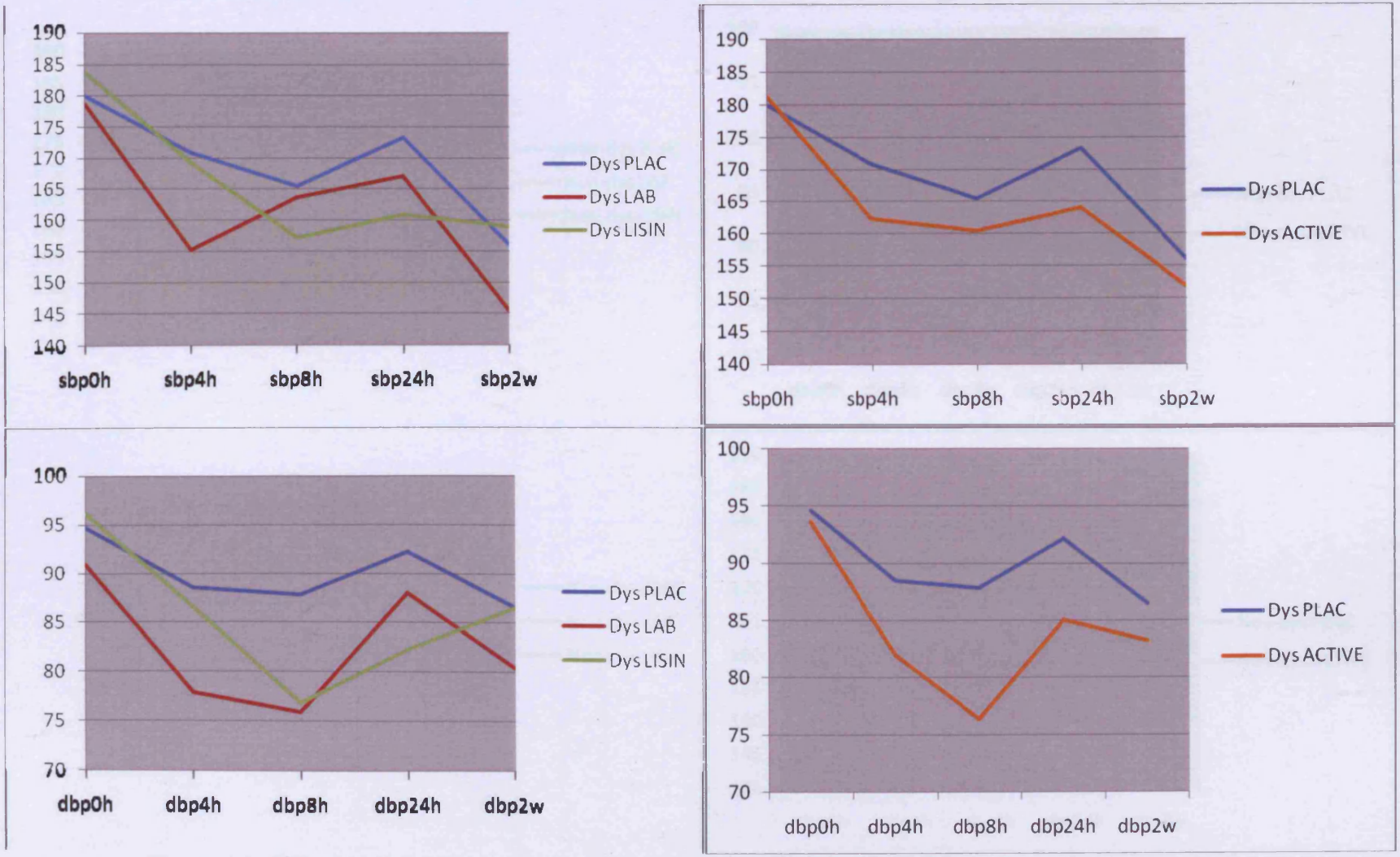

Figure 4.6. SBP and DBP changes in dysphagic (Dys) patients, by three groups, and active therapy versus placebo

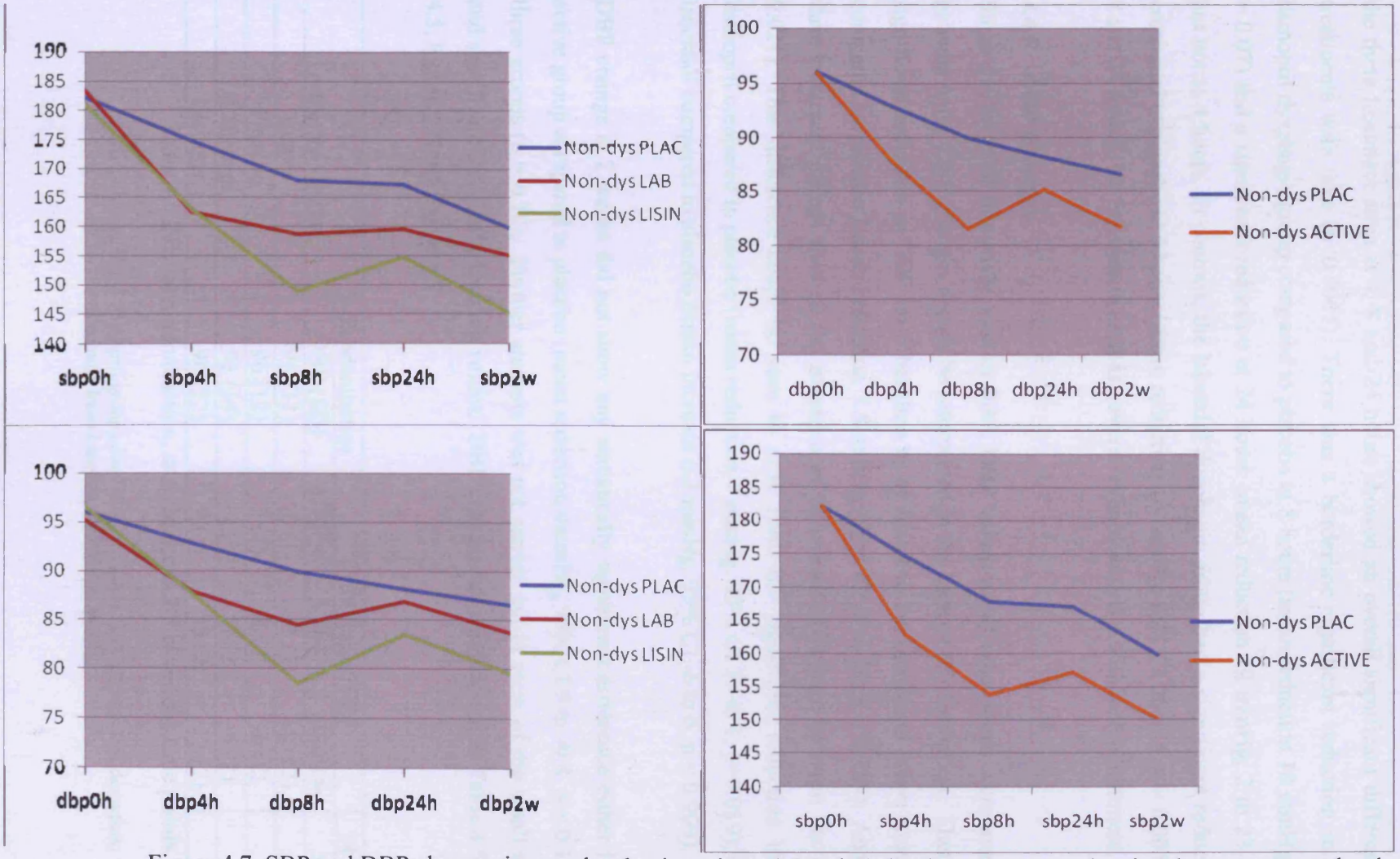

Figure 4.7. SBP and DBP changes in non-dysphagic patients (Non-dys), by three groups, and active therapy versus placebo

4.4.4 Dysphagic Patients

83 patients with dysphagia were recruited in the study. Repeated measures analysis for SBP for the three treatment arms at 4, 8 and 24 hours showed an overall significant difference between treatments with time ($p<0.0001$). There was a borderline significant reduction in SBP in the lisinopril dysphagic group compared to placebo at 8 hours (mean reduction 10 mmHg, -1 to 21, $p = 0.07$) and a significant reduction at 24 hours (mean reduction 12 mmHg, 2 to 23, $p = 0.024$), but not at 4 hours. In contrast, the labetalol dysphagic group had a significant reduction in SBP compared to placebo at 4 hours (mean reduction 16 mmHg, 95% CI 26 to 5, $p = 0.005$), but not at 8 and 24 hours. No increase in serious adverse events was seen with active treatment.

4.4.5 DBP Changes

Since the focus of this study was on SBP, DBP values at all time points were available in 99 patients only. DBP changes should be interpreted in the light of this limitation. There was a non significant reduction in DBP from baseline to 24 hours in the combined active treatment group compared to placebo (mean reduction 3.5 mmHg, 95% CI 9 to -2, $p = 0.189$). Analysis across three treatment groups showed the presence of an overall difference between the groups ($p = 0.021$). This difference could be seen to arise from the significant reduction in DBP with lisinopril compared to placebo (mean reduction 7 mmHg, 95% CI 13 to 1, $p=0.019$), but not with labetalol compared to placebo (mean increase 0.3 mmHg, 95% CI -6 to 6, $p = 0.909$).

DBP change at 2 weeks did not show any statistically significant difference either in combined active group compared to placebo (mean reduction 4mmHg, 95% CI 9 to -0.8, $p = 0.10$) or across three groups ($p = 0.12$). Further analysis was not carried out in view of the small sample size, and significant bias due to missing values. DBP changes are summarised in Table 4.5 and Figure 4.5, Figure 4.6 and Figure 4.7.

	Randomisation	1st 24 hours (SE)			14 +/- 2 days
Treatment Groups	DBP (SD)	ΔDBP4h	ΔDBP8h	ΔDBP24h	ΔDBP2w
Active	95 (13)	-10 (1)	-15 (1)	-10 (2)	-13 (1)
Placebo	96 (12)	-5 (1)	-6 (3)	-6 (2)	-9 (2)
Labetalol	93 (14)	-10 (1)	-13 (2)	-6 (2)	-11 (2)
Lisinopril	96 (12)	-9 (1)	-18 (2)	-13 (2)	-15 (2)

Table 4.5 DBP at randomisation, and change in BP at various time points

Active - labetalol and lisinopril groups combined; n sample size; SD standard deviation;
Δ change from baseline, all units in mmHg

4.4.6 Pulse Pressure and Mean Arterial Pressure

Exploratory analyses of pulse pressure (PP) and mean arterial pressure (MAP) were carried out. PP fell from 86.53 (SE 1.14) at baseline to 69.62 (SE1.48) mmHg (difference 16.93, 95% CI 14.32 - 19.53 mmHg). PP change from baseline to 2 weeks did not differ significantly between the individual groups. Similarly, MAP fell from 123.81 (SE 0.94) at baseline to 106.9 (SE1.32) mmHg. MAP change from baseline to 2 weeks did not differ significantly between the individual groups. Using logistic regression, every 1 mmHg increase in baseline pulse pressure was associated with a 2.1% increase in the odds of death or dependency at 2 weeks (OR 1.021, CI 0.999-1.043, p 0.061), and every 1 mmHg increase in baseline mean arterial pressure was associated with a 2.5% reduction in the odds of death or dependency at 2 weeks (OR 0.975, CI 0.950-1.000, p 0.047).

Treatment group		PP Randomisation	PP 2 weeks	MAP Randomisation	MAP 2 weeks
Labetalol	Mean	87.95	68.35	122.49	104.94
	SD	13.99	17.51	13.30	17.96
	n	56	55	56	55
Placebo	Mean	85.53	71.62	124.07	110.41
	SD	15.60	19.56	11.28	17.41
	n	59	53	59	53
Lisinopril	Mean	86.19	68.93	124.82	105.39
	SD	15.19	19.16	12.44	14.29
	n	57	52	57	52
Total	Mean	86.5388	69.62	123.81	106.90
	SD	14.90	18.68	12.31	16.74
	n	172	160	172	160

Table 4.6 Pulse pressure and mean arterial pressure at randomisation and 2 weeks
PP pulse pressure; MAP mean arterial pressure; SD standard deviation; n number of observations

4.5 DISCUSSION

This study (CHHIPS) is the first to compare different routes of administration as well as different anti-hypertensive agents in the acute stroke situation. Administration of depressor agents to stroke patients who are dysphagic (this group comprising nearly 50% of the trial population) has been difficult and usually implies using intravenous agents, with the associated problems. The CHHIPS depressor trial set out to lower BP acutely following ischaemic and haemorrhagic stroke using agents not previously studied in a large number of patients or with a placebo control (labetalol and lisinopril) and using novel methods of administration i.e. the sublingual route.

Spontaneous fall of BP following stroke has been reported in observational studies[352,229], and this was reproduced in the placebo group within the first 24 hours and by day 14 in the current study. The active treatments studied (labetalol and lisinopril) were more effective than placebo at reducing post-stroke BP within 24 hours of randomisation, and this difference was statistically significant for the treatment groups combined, and for lisinopril, but not labetalol, compared to placebo. The BP changes at 24 hours for the active group combined are similar to those obtained in previous studies intravenous nimodipine[324] or transdermal glyceryl trinitrate[323]. Beta-blocker therapy in the BEST trial[251] resulted in half the depressor effect seen here, while other placebo-controlled studies using oral nimodipine[335] and oral candesartan[248] found no BP lowering effect of these agents acutely.

In the dysphagic group, sublingual lisinopril appeared to be an effective and well-tolerated alternative to the intravenous route of administrating anti-hypertensive agents in acute stroke, opening up the possibility of acute administration by paramedics on initial patient contact or by nurses in the Accident & Emergency department on patient arrival before a formal swallow assessment has taken place. While intravenous labetalol produced a significant SBP fall by 4 hours compared to placebo, an earlier SBP reduction than that seen with the oral preparations of labetalol or lisinopril or with sublingual lisinopril, this was not sustained at 8 or 24 hours (roughly 50% at target). Since a large proportion of subjects achieved the target SBP at 4 hours, subsequent test doses were not administered (as per protocol), and this coupled with the short duration of action of labetalol may explain the lack of a significant SBP difference over the 24-hour period. Thus frequent dosing or a continuous infusion is likely to be needed to maintain target BP levels.

Based on observational data[241], treatment targets were set to an optimum SBP level for decreased death and disability, with a target SBP of between 145 to 155 mmHg by 4 and 8 hours from randomisation, and if the target was not achieved, additional therapy was given. This is the first study to employ an incremental dosage approach to achieve goal BP levels. By 4 hours 77% of patients receiving labetalol (oral and intravenous routes combined) had achieved target SBP reduction, but by 24 hours this had fallen to just under half. Lisinopril was able to achieve target BP by 4 hours in 60% of patients, and this was maintained at 24 hours, with little difference in achieved targets between sub-lingual and oral routes. Compared to the labetalol group, fewer subjects achieved the target SBP at 4 hours, and more at 24 hours, indicating a slower onset of action, but sustained BP lowering. Whether rapid early BP reduction as achieved with labetalol is better in terms of a greater reduction in death and disability or the slower anti-hypertensive effect achieved with lisinopril cannot be concluded from this study due to inadequate sample size.

At 2 weeks, SBP was significantly lower in the active treatment groups combined, by a mean of 8 mmHg compared to placebo, but not DBP. Few other studies have continued anti-hypertensive treatment for this duration, one study using bendroflumethiazide found no anti-hypertensive effect compared to placebo by day 7[253], and another study using transdermal GTN reported a significant reduction in BP at day 8 (9/5 mmHg)[353]. Since secondary prevention trials of blood pressure lowering post-stroke have shown the effectiveness of ACEI's or ARB's and/or thiazide-like diuretics beyond the first two weeks, it was felt unethical to continue trial treatment longer than the 14 days.

Noting the limitations of the small sample size, no significant increase in adverse events was noted, this is considered in more detail in the next chapter.

4.6 SUMMARY

- This study showed that SBP reduction is feasible in patients hospitalised following an acute stroke using and incremental dose approach, significant SBP reduction being achieved with active intervention compared to placebo, over the first 24 hours, and at 2 weeks.
- Whilst SBP targets were achieved in the majority of patients in both intervention groups, only about half retained this target SBP level at 24 hours, and BP differences decreased by 2 weeks. The need for dose increase should be considered if SBP reduction is to be maintained beyond the first few days.
- No significant difference between groups in terms of effects on other BP parameters (including DBP, PP and MAP) was demonstrated.
- Both oral lisinopril and oral labetalol were effective SBP lowering agents in acute stroke, and would be suitable for a larger definitive trial of BP lowering in acute stroke.
- In dysphagic patients, sublingual lisinopril is a novel mode of administration with similar efficacy to oral lisinopril and oral labetalol and easy applicability requiring less intensive monitoring that intravenous labetalol.

5 SAFETY OF BP LOWERING IN CHHIPS

5.1 BACKGROUND

A pilot study is designed to test practicality and gather information prior to a larger study, in order to improve the latter's quality and efficiency. Pilot studies may reveal deficiencies in the design of a proposed study, allowing these to be addressed before embarking on a resource-intensive large scale study. Given the delicate physiological balance that exists following an acute stroke, a pilot study to establish safety of a new intervention is of paramount importance.

Typical pathophysiology seen in stroke includes: high or low BP; elevated glucose; pyrexia, hypoxia and dehydration[270]. Some of these physiological abnormalities are associated with worse outcome e.g. high and low BP[241,242], elevated serum glucose[354,355,356], elevated temperature[80,77]. Ongoing studies aim to provide the evidence to guide appropriate management of these alterations, which is uncertain at the moment, as reflected in existing guidelines[265,258,257,256]. Optimisation of physiological derangements may be helpful in the setting of acute stroke. This situation is typified by the clinical dilemma faced in acute stroke where high blood pressure is a frequent occurrence in the early post-ictal phase, and, while there is accumulating evidence of associated complications, there is no evidence-base to guide management.

Early studies with calcium channel blockers and beta blockers showed that BP reduction was feasible, but no significant benefit in terms of clinical outcome (mortality at 3 months to a year) was demonstrated[251,252]. In fact, there was a trend towards increased risk of early death with beta-blocker treatment in the BEST study[251], and increased adverse events with calcium channel blockers in a systematic review[252]. More recently, the ACCESS study reported a significant benefit (mortality at 12 months) with the early use of candesartan, however no BP differences were apparent between the two groups and the mechanism for this benefit remains unclear[357]. Elevated BP has been associated with complications following both ischaemic and haemorrhagic stroke in individual studies[311,234,310], and this conclusion has been supported by two independent systematic reviews[307,235]. Nonetheless, at present, there is no conclusive evidence to guide management of elevated BP in the acute situation, and this has been the conclusion of a Cochrane Review on the topic[269].

When considering pressor therapy in acute stroke with 'relative hypotension', two systematic reviews of published studies (mainly pilot trials) have suggested that 'induced hypertension' is feasible and safe with intensive monitoring, but the impact on clinical outcome remains uncertain[264,358]. The CHHIPS Pilot trial was established to study the feasibility and safety of acute BP manipulation following a stroke, and to clarify the need for a large-scale trial[292].

5.2 AIMS

While BP reduction in the early stages post-stroke is feasible, there remain concerns about worsening stroke deficit secondary to reduced cerebral perfusion. The aims of this study were to

1. Establish the safety of early SBP reduction following acute stroke, in terms of
    a. Early neurological deterioration
    b. Death and dependency
    c. Adverse events
    d. Treatment discontinuations
    e. Large SBP drops
2. Assess if there was a differential effect of BP reduction in various stroke subtypes.

5.3 METHODS

The study population was recruited as part of the CHHIPS Pilot study (from January 2004 to December 2006), funded by the UK National Health Service Research & Development Health Technology Association (NHS R&D HTA) program. The CHHIPS pilot was a prospective, multi-centre, randomized, double-blind, placebo-controlled, titrated-dose trial. Eligibility criteria, randomisation and trial interventions have been specified in Chapter 3.

The safety outcomes studied were:

- early neurological deterioration, defined as an increase in NIHSS $\geq$4 points at 72 hours
- composite outcome of death and dependency (mRS>3) at 2 weeks
- serious adverse events
- drug-related adverse events
- mortality at 3 months
- Association of larger drops in BP with early neurological deterioration – exploratory analysis, previous studies have suggested that larger drops in BP were associated with worse outcome[304,242].

Statistical analysis

The significance level was fixed at 5%. The primary outcome was death and dependency at 2 weeks. Mann Whitney U test was used to assess for difference in baseline characteristics. Cumulative survival rates were presented in the form of a Kaplan-Meier curve, and Cox proportional hazards test was used for mortality at 3 months.

5.4 RESULTS

179 patients were randomised into the depressor (BP lowering) arm. Baseline demographic characteristics, neurological deficit (National Institutes for Health Stroke Scale - NIHSS), Oxfordshire Classification of Stroke Project (OCSP) classification, dysphagia status, delay from stroke onset to randomisation, and vascular risk factors (previous stroke, previous TIA, previous ischaemic heart disease, previous diabetes, previous hypercholesterolemia and smoking status) were not significantly different between the groups (see Table 4.3. Baseline characteristics of participants in 'Feasibility Chapter'). Mean age was 74 years (SD 11), and median baseline NIHSS was 9 (IQR 5-16) on a 42-point scale.

5.4.1 Early Neurological Deterioration

Early neurological deterioration at 72 hours occurred in ten subjects overall (5.8%), with seven subjects in the active treatment group (6%) and three in the placebo group (5%), see Table 5.1. No significant difference between-groups was noted (p=0.56, Chi squared test). There was one death at 72 hours in the active treatment group, compared to three in the placebo group.

Outcomes at 72 hours	**Treatment groups**			
	Labetalol (56)	**Lisinopril (57)**	**Active (113)**	**Placebo (59)**
NIHSS increase ≥4 or death, n (%)	1 (2%)	7 (12%)	8 (7%)	6 (10%)
active vs. placebo, p = 0.56; across 3 groups, p = 0.09				
NIHSS increase ≥4, n (%)	1 (2%)	6 (10%)	7 (6%)	3 (5%)
NIHSS no significant change (change ≤ 3 from baseline)	4 (7%)	2 (4%)	6 (5%)	1 (2%)
NIHSS decrease ≥4, n (%)	51 (91%)	48 (84%)	99 (88%)	52 (88%)
Death, n (%)	0 (0%)	1 (2%)	1 (1%)	3 (5%)

Table 5.1. Change in Neurological Status at 72 hours

5.4.2 Stroke Subtype

The effect of stroke sub-type on outcome was also studied. Stroke subtypes were defined as CT /MRI confirmed relevant infarct including haemorrhagic transformation of infarct, primary intracerebral haemorrhage, or other (this group includes those whose neuroimaging was reported as normal). Two patients randomised to the placebo arm died before neuroimaging, and therefore are not included in the figures, stroke subtype being labelled 'unknown'. The numbers in each group were too small to allow useful statistical analysis (see Table 5.2). However, in patients with radiologically confirmed haemorrhage (n=25), the possibility of worse outcomes in the active treatment group compared to the placebo group in terms of early neurological deterioration at 72 hours (2,11% vs. 0, 0%), and death and dependency at 2 weeks (14, 77% vs. 3, 43%) was noted. There was no statistically significant imbalance of baseline stroke severity between active and placebo groups in this subgroup (median NIHSS: active group - 11, placebo - 6, p=0.495, Mann Whitney U test).

Treatment groups (n)	**Increase in NIHSS ≥4 at 72 h, n (%)**	**SBP change at 24 hours (SE), mmHg**	**SBP change at 2 weeks (SE), mmHg**	**DBP change at 2 weeks (SE), mmHg**	**Death and dependency at 2 weeks (mRS>3), n (%)**
Ischaemic (99)					
Active (64)	4 (6.2%)	-23 (3)	-30 (3)	-14 (2)	44 (68)
Placebo (35)	2 (5.7%)	-9 (3)	-25 (5)	-10 (3)	19 (54)
Haemorrhage (25)					
Active (18)	2 (11%)	-18 (5)	-31 (6)	-9 (3)	14 (77)
Placebo (7)	0	-17 (10)	-34 (8)	-12 (5)	3 (43)
Other (46)					
Active (31)	1 (3.2%)	-20 (3)	-24 (3)	-13 (2)	11 (35)
Placebo (15)	0	-17 (5)	-15 (7)	-5 (4)	11 (73)

SE standard error, - indicates a fall from baseline

Table 5.2. Neurological Deterioration, SBP change and Death and Dependency at 2 weeks, by stroke subtype

OCSP (n)	NIHSS change at 72 hours, median (IQR)	Early neurological deterioration	%
TACS (61)	-3 (-5 to 1)	5	8.20
PACS (54)	-2 (-4 to 0)	4	7.41
LACS (44)	-1 (-2 to 0)	1	2.27
POCS (12)	-1 (-2 to 0)	0	0.00

Table 5.3. Median NIHSS change/early neurological deterioration (NIHSS increase≥4) by OCSP

As expected, syndromes with a likely cortical stroke (TACS/PACS) had a higher rate of early neurological deterioration, compared to LACS and POCS.

5.4.3 Death and Dependency at 2 Weeks

The primary endpoint of the study was death and dependency (dependency defined as mRS >3) at two weeks. There was no significant difference in death and dependency at two weeks between the active treatment and placebo groups (p=0.82, Chi squared test) or across the three groups (p=0.97, Chi squared test). This lack of difference persisted after adjusting for time to first treatment dose. The data for each group are presented in Table 5.4. Given the small sample size and pilot nature of this trial, the possibility of a Type II error cannot be excluded. The total number of deaths at 2 weeks was too small to allow any statistically significant conclusions by group. A lower number of deaths was noted in the labetalol group.

Death or dependency	**Treatment groups (n)**			
	Labetalol (56)	Lisinopril (57)	Active (113)	Placebo (59)
Yes (%)	34 (61)	35 (61)	69 (61)	35 (59)
No (%)	22 (39)	22 (39)	44 (39)	24 (41)
active vs. placebo, p = 0.82; across 3 treatment groups, p = 0.97				

Table 5.4. Death and dependency (mRS >3 at 2 weeks) by treatment arms

Cause of Death	**Treatment groups (n)**		
	Labetalol	Lisinopril	Placebo
Neurological (stroke)	1	4	2
Respiratory (pneumonia)	0	1	4
Total	1	5	6

Table 5.5. Cause of Death by treatment group at 2 weeks

5.4.4 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) were categorised as advised by the Medicines and Healthcare products Regulatory Agency (MHRA) in terms of commonly occurring adverse events following a stroke. 96 serious adverse events were reported, in 58 patients. 23 patients had multiple SAEs, with 17 patients having two, two patients had three, three patients had four, and one patient had five. There was no significant difference in the number of SAEs reported by treatment allocation (labetalol 28, lisinopril 33 and placebo 35, p=0.43, Chi squared test) – the distribution of SAEs is shown in Figure 5.1. In each group there were more SAEs reported in the dysphagic compared to the non-dysphagic arm (labetalol group: 18 dysphagic vs. 10 non-dysphagic; placebo group: 25 dysphagic vs. 10 non-dysphagic; lisinopril group: 17 dysphagic vs. 16 non-dysphagic). It is likely that the higher SAE rate reflects increased stroke severity in those with dysphagia. To

account for multiple SAEs in the same subject, the number of patients having one or more SAEs is also shown. The largest discrepancies were found in the dysphagic placebo group (2.6 SAE per patient) and the dysphagic labetalol group (1.9 SAE per patient). The overall results remained non-significant, but a trend was noted with more patients having an SAE in the lisinopril group (p=0.08, Chi squared test).

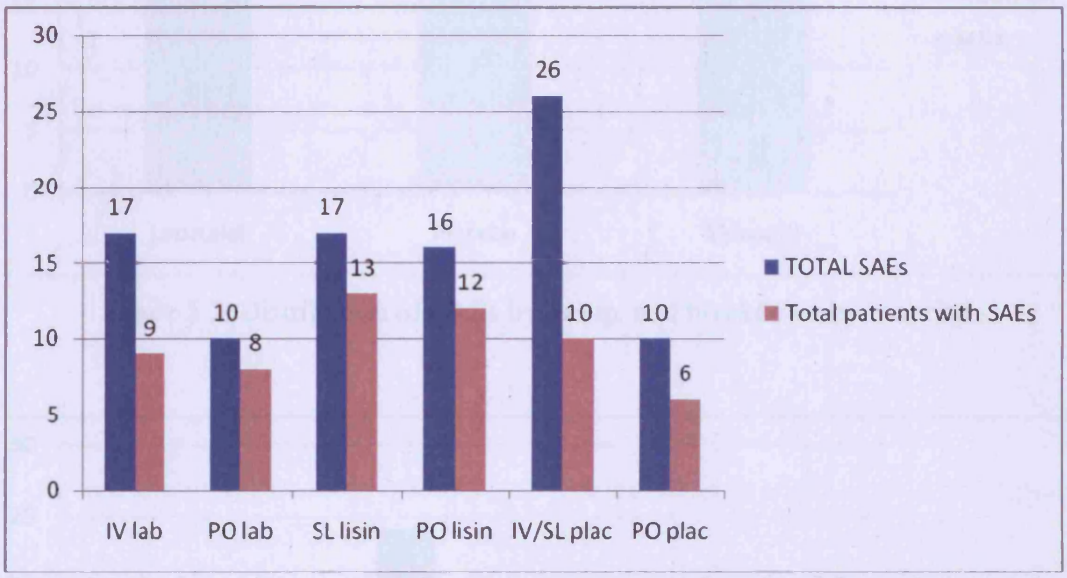

Figure 5.1. Serious adverse events by treatment group and mode of drug administration

Severity of SAE

There were 12 fatal SAEs reported at the 2 week follow up, exclusively due to neurological or respiratory causes (NOTE: one patient in the placebo group had two fatal SAEs reported: one neurological and one respiratory). There was one fatal SAE in the labetalol group, seven in the placebo group and five in the lisinopril group. Cause of death as reported by local investigators is presented in Table 5.5. All fatal SAEs up to 2 weeks were classified as either respiratory or neurological (see Figure 5.4). One patient in the placebo group had two fatal events reported, due to coexistence of pneumonia and significant increase in NIHSS score. Figure 5.2 illustrates the severity of SAE by treatment group, and Figure 5.3 shows the difference between treatment groups by dysphagia status.

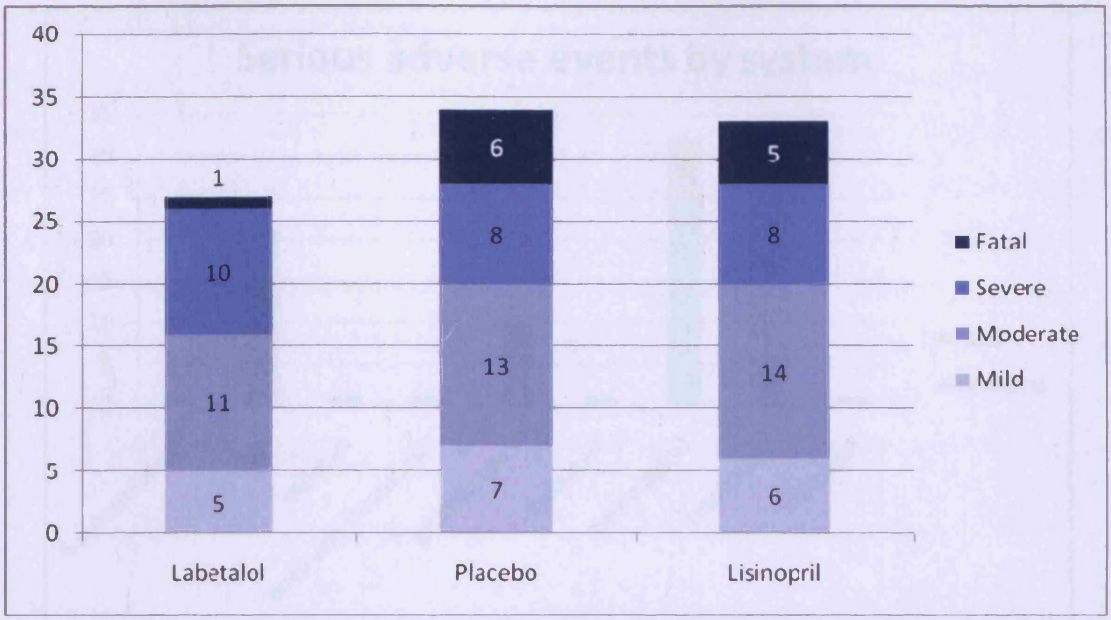

Figure 5.2. Distribution of SAEs by group, and breakdown by severity

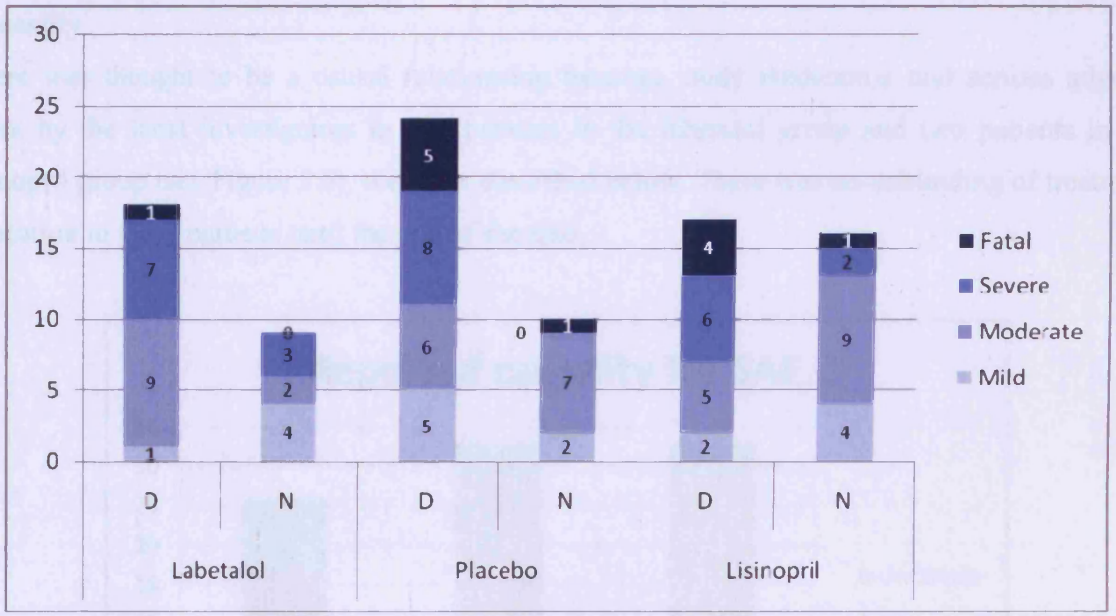

Figure 5.3. Severity of SAE by group and dysphagia status at randomisation

D dysphagic; N non-dysphagic

NOTE: Includes two fatal SAEs for one patient in dysphagic placebo group

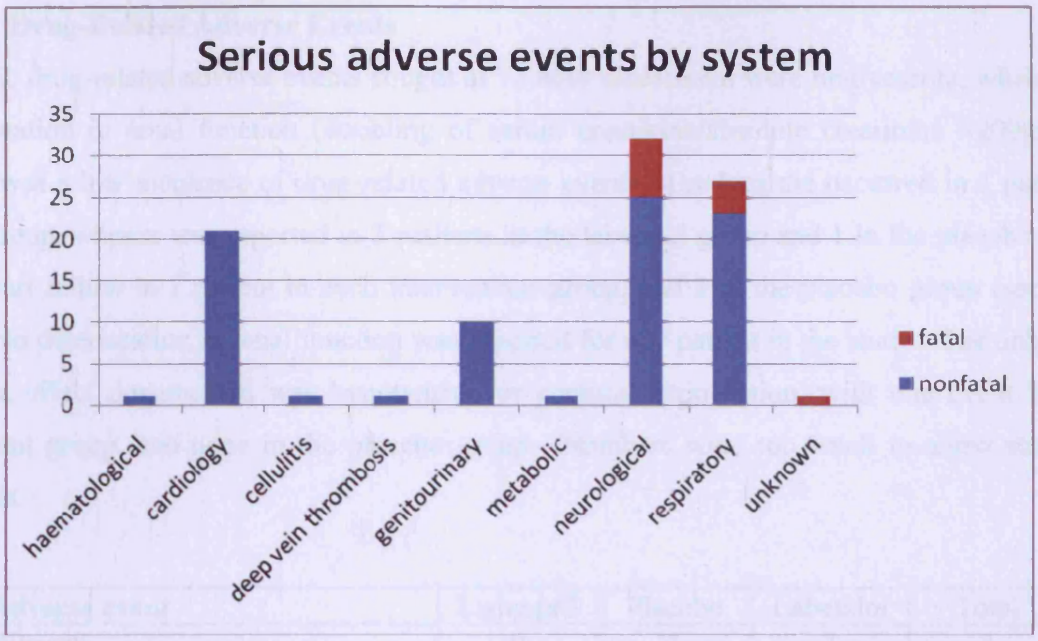

Figure 5.4. Serious Adverse Events by system and fatality

Causality

There was thought to be a causal relationship between study medication and serious adverse event by the local investigators in two patients in the labetalol group and two patients in the lisinopril group (see Figure 5.5), these are described below. There was no unblinding of treatment allocation in these patients until the end of the trial.

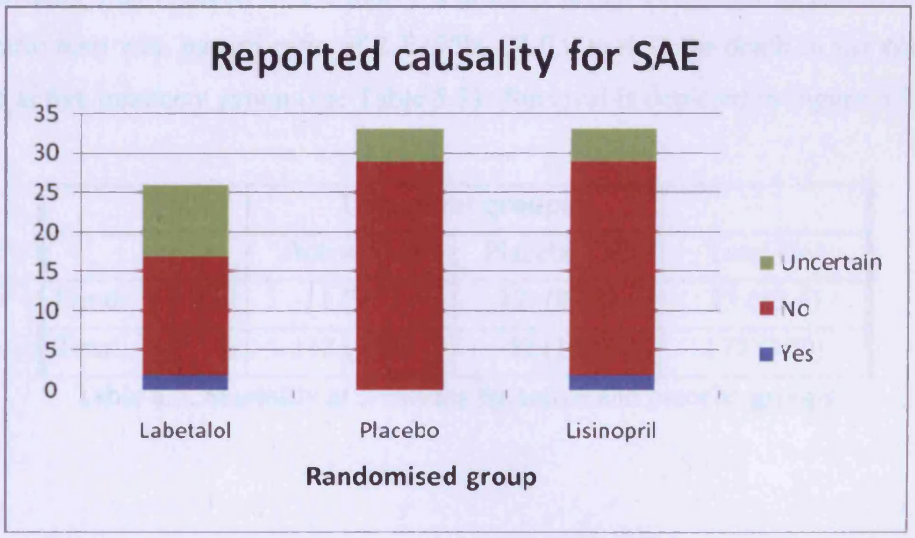

Figure 5.5. Causality of SAEs according to treatment type as assessed by investigators

5.4.5 Drug-Related Adverse Events

Specific drug-related adverse events sought at 72 hour assessment were bradycardia, wheeze and deterioration in renal function (doubling of serum creatinine/absolute creatinine >200μmol/l). There was a low incidence of drug-related adverse events. Bradycardia occurred in 1 patient in each group, wheeze was reported in 3 patients in the labetalol group and 1 in the placebo group, and heart failure in 1 patient in each intervention group, and 2 in the placebo group (see Table 5.6). No deterioration in renal function was reported for any patient in the study. The only other adverse effect documented was hypotension or postural hypotension, with one event in each treatment group, and none in the placebo group. Numbers were too small to allow statistical analysis.

Adverse event	Lisinopril	Placebo	Labetalol	Total
Wheeze	0	1	3	4
Bradycardia	1	1	1 (1)	3
Heart failure	1	2 (1)	1 (1)	4
Deterioration in renal function	0	0	0	0
Hypotension/postural hypotension	1	0	1 (1)	2
TOTAL	3	4	6	13

Table 5.6. Drug-related adverse events at 2 weeks (and 72 hours)

5.4.6 Mortality at 3 months

3 month mortality was reduced in the active treatment group compared to placebo (p = 0.057, likelihood ratio test) with hazard ratio of 2.1 (95% CI 0.9 to 4.7) for death in the placebo group compared to active treatment group (see Table 5.7). Survival is depicted in Figure 5.6.

	Treatment groups		
	Active (%)	Placebo (%)	Total (%)
Dead	11 (9.7)	12 (20.3)	23 (13.4)
Total	113 (100)	59 (100)	172 (100)

Table 5.7. Mortality at 3 months by active and placebo groups

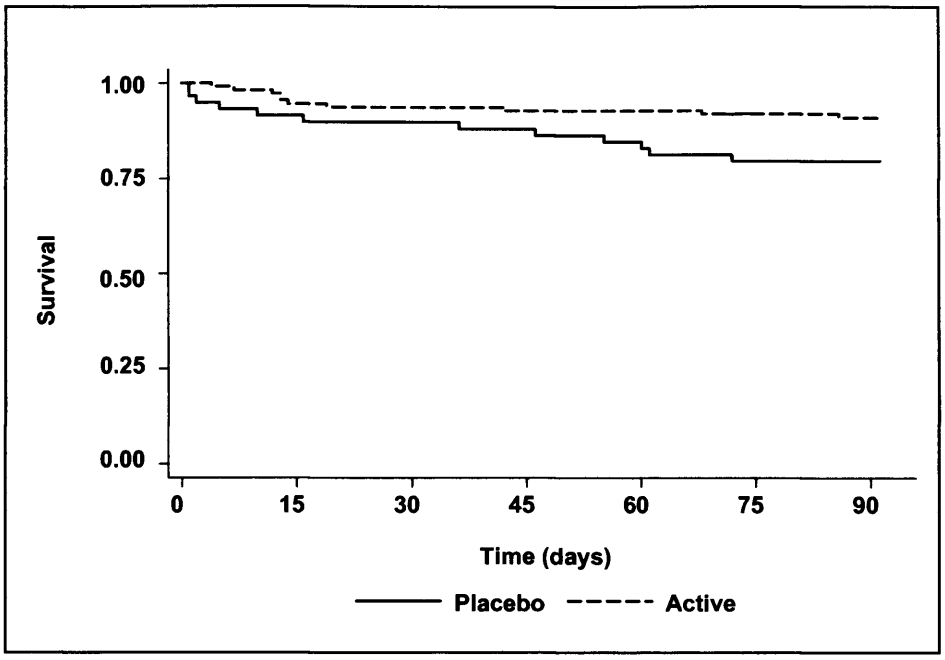

Figure 5.6. Kaplan-Meier survival – active treatment versus placebo

5.4.7 Large SBP Drops

SBP change at 4 hours	n	median NIHSS change at 72h	IQR
Fall>40 mmHg	16	-2	-4.5 to 0
Fall 21-40 mmHg	48	-1.5	-4 to 0.5
Fall 1-20 mmHg	81	-2	-4 to 0
Rise	27	-1	-3 to 0

Table 5.8. NIHSS change in subgroups of SBP change at 4 hours

Dead by 2 week assessment (n)	NIHSS change at 72h Median (IQR)	NIHSS increase >=4 points	Mean SBP change (mmHg) at 4 hours (SD)	Mean SBP change (mmHg) at 24 hours (SD)
YES (12)	0.5 (-4.8 to 12.3)	4 (66.67%)	-18.9 (52.0)	-19.0 (21.7)
NO (160)	-1.5 (-3.25 to 0)	6 (3.75%)	-16.3 (16.6)	4.1 (20.5)

Table 5.9. NIHSS change at 72h and SBP at 4 hours, by death status at 2 weeks

Systolic blood pressure fell from values at randomisation in each of the three groups by 24 hours and remained lower at two weeks. The NIHSS change at 72 hours was similar when patients were stratified based on magnitude of early SBP change - randomisation to 4 hours (see Table 5.8). When patients were split by death status at 2 weeks, there was a difference in mean SBP change at 24 hours (alive: -19.0 mmHg, dead: 4.1 mmHg), but not at 4 hours (alive: -16.23 mmHg; dead: -18.9 mmHg), as seen in Table 5.9. Increasing SBP change from baseline to 24

hours was associated with an increased odds of death (OR 1.054 95% CI 1.041 – 1.067 p=0.002, per unit increase in SBP change) i.e. fall in SBP at 24 hours was protective.

5.4.8 Dysphagic Group

Mean changes in SBP levels over the first 24 hours and 2 weeks with DBP changes at 2 weeks by treatment groups in dysphagic and non-dysphagic patients are shown in Table 5.10. Repeated measures analysis for SBP at 4, 8 and 24 hours in the dysphagic group for the three treatment arms, showed an overall significant difference between treatments with time (p=0.0001). There was a borderline significant reduction in SBP in the lisinopril group compared to placebo at 8 hours (mean reduction 10 mmHg, 95% CI 21 to -1, p = 0.07) and a significant reduction at 24 hours (mean reduction 12 mmHg, 95% CI 23 to 2, p = 0.024), but not at 4 hours. In contrast, the labetalol dysphagic group had a significant reduction in SBP compared to placebo at 4 hours (mean reduction 16 mmHg, 95% CI 26 to 5, p = 0.005), but not at 8 hours and 24 hours (see **Table 5.10**).

	Baseline		**24 hours**	**2 weeks**	
Treatment groups (n)	**SBP (SD) mmHg**	**DBP (SD) mmHg**	**ΔSBP (SE) mmHg**	**ΔSBP (SE) mmHg**	**ΔDBP (SE), mmHg**
dysphagic (83)					
Labetalol (27)	179 (15)	91 (12)	-11 (4)	-34 (5)	-11 (3)
Lisinopril (28)	184 (18)	96 (12)	-23 (4)	-27 (6)	-12 (3)
Placebo (28)	180 (18)	95 (14)	-7 (4)	-25 (6)	-9 (4)
non-dysphagic (89)					
Labetalol (29)	183 (16)	95 (16)	-24 (4)	-28 (3)	-11 (2)
Lisinopril (29)	181 (18)	97 (13)	-26 (4)	-36 (3)	-17 (2)
Placebo (31)	182 (13)	96 (11)	-15 (4)	-22 (4)	-9 (2)

Table 5.10. Change (Δ) in SBP at 24 hours and 2 weeks and DBP at 2 weeks

5.5 DISCUSSION

	Active treatment	Placebo	P
Early Neurological Deterioration at 72 hours	6%	5%	0.56
Death at 72 hours	1%	5%	
Death or dependency 2 weeks	61%	59%	0.82
Serious Adverse Events	54%	59%	
Drug-related adverse events	8.0%	6.8%	
Death at 3months	9.7%	20.3%	0.054

Table 5.11. Safety outcome rates: active vs. placebo groups (p shown where calculated)

In this study of 179 subjects, SBP lowering with a target of 145-155 mmHg, or a fall of ≥15 mmHg from baseline was not associated with a significant change in outcome, in terms of early neurological deterioration at 72 hours, death and dependency at 2 weeks, and rate of serious adverse events, as summarised in Table 5.11. While there was a borderline reduction in mortality at 3 months with active treatment compared to placebo (p=0.054), this must be interpreted with caution in view of the small numbers.

Early neurological deterioration following stroke due to cerebral oedema especially in larger strokes[359], and recurrent stroke in lacunar syndromes[360], has been associated with increased mortality. No increase in early neurological deterioration at 72 hours in the active treatment group compared to placebo was seen. The sample size was too small to make any definite conclusions as to the clinical benefits of BP lowering therapy in acute stroke; however since no worrying trends were identified in terms of early neurological deterioration, a larger pragmatic trial seems justified. There was no significant difference in early SBP change (from baseline to 4 hours) between those with early neurological deterioration and those without.

While the number of events was too small to establish any association between stroke subtype and effect of intervention, the possibility of a two-fold increase in early neurological deterioration in patients with intracerebral haemorrhage was raised. Baseline stroke severity did not account for this trend. Additionally, this finding is in contradiction to the recent results of the INTERACT study, where intensive BP lowering in PICH, compared to standard BP lowering, appeared safe and well tolerated[361], and has led to an ongoing Phase III study.

Intervention did not result in a significant change in the primary outcome (2-week death and dependency), which is unsurprising, given that recruitment was far short of the sample size predicted by power calculation. Thus a type II error is possible, and clinically significant effects have not been excluded.

There was no significant difference in the number of serious adverse events reported by group, or the number of patients reported to have a serious adverse event. Wheezing was noted as a side effect of labetalol therapy, no deterioration in renal function due to lisinopril was observed.

Labetalol resulted in early BP drops (significant at 4 hours), as compared to the sustained BP drop seen with lisinopril (significant at 24 hours). However, this was not associated with an increased rate of adverse events. Whether early rapid lowering is beneficial or harmful is unclear at present. It is tempting to hypothesise that an earlier BP drop may be cerebroprotective, reducing the known complications of cerebral oedema and haemorrhagic transformation.

Strengths of the study

This is the first acute stroke study using a titrated-dose regime to achieve early targetted BP lowering within 24 hours. While the ACCESS study also employed a titrated-dose regime, the dose escalation was carried out on day two, with some patients receiving intervention for severe hypertension. Subjects were randomised to receive one of two BP lowering medications or placebo, and a prospective safety analysis was carried out, with early neurological deterioration at 72 hours being a secondary outcome.

Weaknesses of the study

Overall, the number recruited was too small to draw any definitive conclusions with regard to the clinical benefits or harms, of early BP lowering following stroke. Analyses were carried out using the combined treatment groups due to the small number of patients in the pilot study, and no comment can be made on effects of individual treatments. The patients were not stratified based on clinical (OCSP) or radiological (ischaemic versus haemorrhagic) stroke types, which prevents any conclusions to be made with regard to differences between these types.

5.6 SUMMARY

- In this pilot study of 179 patients, early BP lowering following acute stroke, with either labetalol or lisinopril was not associated with an increase in early neurological deterioration at 72 hours, serious adverse events, or death and dependency at 2 weeks.
- A large randomised controlled trial of anti-hypertensive therapy in acute stroke is justified to confirm the lack of harm seen in this pilot trial and establish clinically relevant benefits.

6 REASONS FOR EXCLUSION FROM ACUTE STROKE BLOOD PRESSURE STUDIES

6.1 BACKGROUND

Recruitment to clinical trials involving patients with acute stroke presents practical challenges, and recruitment rates tend to be poor due to a variety of reasons: small time window of eligibility, difficulties with consent, exclusion of those with pre-existing functional dependence, or more severe strokes. The smaller sample sizes result in reduced statistical power to detect significant differences in outcome[362] and/or prolongation of proposed recruitment period with financial consequences. Such difficulties have been faced by recent trials in acute stroke e.g. FASTER[117], GIST[212].

The power of a trial can be improved or sample size reduced by changes to trial design including the use of prognosis-adjusted end points[363], the appropriate use of disability end points[376]; and stratification based on severity of baseline neurological deficit[364]. Reduction in the delay from symptom onset to contact with a hospital (pre-hospital delay), review by a stroke specialist and access to neuro-imaging (intra-hospital delay) are important[365] and could potentially increase the number of patients eligible for thrombolysis as a clinical intervention, as well as for participation in acute stroke trials studying thrombolysis, physiological optimisation or promising neuroprotective agents.

Delays to specialist review need to be studied further if future research is to be successful in answering commonly faced clinical dilemmas in the management of acute stroke. Thus it is crucial to understand the temporal profile of stroke onset, the delays to reaching a hospital and to being seen by a specialist, who will be able to make decisions about thrombolysis for acute ischaemic stroke and participation in clinical trials, as well as the reasons for delay to specialist review.

Until the introduction of the recent CONSORT statements, few publications reported the number of patients reviewed and excluded. Amongst published trials of thrombolysis for acute ischaemic stroke, only two have reported the number of patients enrolled as a percentage of those screened: MAST-I[366] and NINDS[367], which enrolled 4.4% of patients screened within 6 hours of stroke onset, and 3.6% of patients screened within 3 hours of stroke onset, respectively. No further information regarding reasons for exclusion was given. The FASTER study seeking patients with TIA or minor stroke within 24 hours of onset recruited 12.8% of all patients screened and provided detailed information about reasons for exclusion[117], and future trials would be expected to provide similar information so that clinical relevance and applicability may be understood.

Published data regarding delays in hospital admission for patients with stroke exists mostly in the context of trials investigating thrombolysis for acute ischaemic stroke, the only evidence-based treatment in acute stroke with significant benefit on composite outcome. Factors reported to have a significant association with increased delay to hospital admission include: overnight onset (between midnight and 6 am)[368]; gradual or fluctuating onset[369]; milder deficit[369,370]; black race[371]; initial reaction of patient (waiting versus contacting someone else)[369,372]; living alone[368,371,373,370]; stroke at home (versus at work)[374]; unemployed or retired[370]; pre-morbid dependence in any activity of daily living[375]. Previous transient ischaemic attack[370], reduced conscious level[376]; contacting someone else - emergency services, a relative, carer or health professional[369,372] significantly decreased the relative risk of delayed admission[369,368,371,377].

The data for two acute stroke blood pressure trials are reported, including an analysis of the reasons for exclusion of patients, and the time intervals from symptom onset to hospital admission and review by a research team member.

6.2 AIMS

With the advent of thrombolysis, more patients reach a hospital earlier following an acute stroke. When conducting acute stroke trials and assessing the applicability of results to the general population, it is important to understand the difference in characteristics between those subjects that were included and those who were not. The aims of this study were:

1. To identify the proportion of stroke patients eligible for the CHHIPS and COSSACS studies.
2. To establish reasons for exclusion of patients from acute stroke BP studies

6.3 METHODOLOGY

6.3.1 Subjects

All patients presenting with suspected stroke were systematically identified and screened for potential participation in two multi-centre trials, the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) and the Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) Study, at four study centres – Bournemouth, Exeter, Leicester and Newcastle. The 2 trials were complementary, and the eligibility criteria did not allow for patients to be eligible for both studies. Patients admitted to hospital with a clinical diagnosis of stroke were actively sought by dedicated researchers alongside an

advertisement program encouraging frontline clinicians to refer potentially eligible patients to the research team. Screening for both these studies had been approved by the appropriate ethical committees and NHS trusts. Though patients who had their strokes whilst an inpatient were potentially eligible, these may have been missed as recording of occurrence of inpatient strokes was not uniform amongst the centres. The screening was carried out by dedicated research fellows and nurses with special interest in the two studies, and assessment of swallowing was carried out by trained personnel as per local guidelines. Each site developed their own comprehensive program for identification of patients presenting with an acute stroke syndrome.

6.3.2 Data Collection

Data were prospectively collected from the medical notes or from the patient/ carer/ admitting doctor with regards to the inclusion and exclusion criteria for the two studies. Screening information was recorded in a standardised Excel database for subsequent analysis, data being gathered at a single visit. Inclusion criteria were: clinical diagnosis of stroke; age>18 years; clinical diagnosis of suspected stroke (with neuroimaging before or after randomisation to exclude non-stroke diagnoses and to define ischaemic and haemorrhagic stroke); informed patient consent or relative/ carer assent. Criteria specific to the COSSAC Study were: stroke onset <48 hours; current anti-hypertensive therapy (within 48 hours of last dose) and retained ability to swallow. Criteria specific to the depressor arm of CHHIPS were: stroke onset <36 hours; and hypertension defined as a systolic blood pressure >160mmHg (mean of multiple BP recordings over 15 minutes). The pressor arm considered similar patients with stroke onset <12 hours with 'relative' hypotension (SBP<140 mmHg).

Exclusion criteria were: indications for urgent anti-hypertensive therapy (e.g. hypertensive encephalopathy, co-existing cardiac or vascular emergency, hypertension with SBP>200mmHg or DBP>120mmHg in association with intracerebral haemorrhage); contraindications to trial therapy (lisinopril or labetalol or placebo in CHHIPS); significant co-morbidity (pre-morbid dependence in personal activities of daily living (modified Rankin Score (mRS) >3), co-existing condition with life expectancy <6 months); non-stroke diagnoses (on subsequent neuroimaging); impaired conscious level (NIHSS 1a score >2); females of childbearing potential. Patients and/or carers were questioned further if all the information was not documented in the clinical notes.

Specific data considered in the current analysis included Oxfordshire Classification of Stroke Project (OCSP) classification of stroke (as documented in the clinical notes, or following patient review if not documented in the notes), first BP recorded in hospital, use of anti-hypertensives prior to admission (medical notes), dysphagia status at admission, existence of diabetes (medical notes) and atrial fibrillation (medical notes or admission electrocardiogram), time of symptom onset (defined as the time when neurological symptoms were noticed by the patient or an observer, and if this was not known, the last known time when the patient was known to be normal was considered the time of onset), time of first review by a doctor in hospital (as documented in the medical notes) and time of review by researcher. The primary aim was to identify patients that were eligible for the two studies.

Reasons for exclusion with a view to potential changes (to inclusion and exclusion criteria, and trial design) that might improve recruitment rates of the ongoing trials, and to inform the design of future trials were noted. Where exact times were available, a statistical analysis of time delay from stroke onset to hospital admission and from stroke onset to review by researcher was carried out.

6.3.3 Statistical Analyses

The time intervals analysed were: onset to admission: OA-delay, and onset to screening (review by researcher): OS-delay. The two outcome measures for delay were all found to be non-normally distributed and log-transformation resulted in normal distribution, allowing parametric analysis. Descriptive statistics are presented for the covariates analysed: stroke subtype (OCSP classification); comorbidity (pre-morbid hypertension or diabetes and atrial fibrillation at presentation); baseline dependency (modified Rankin Scale); swallowing status; symptom onset time; hospital admission time; and researcher screening time.

Methods of multiple linear regression were used in SAS version 9.1 to identify factors associated with each of the two outcome measures for delay. In order to build the "best" model, the individual significance of each factor upon outcome was established and then a forward selection approach was taken. Each factor was entered into the model in order of its individual significance and the appropriate degrees of freedom and the sum of squares were used to compare the models, taking account of missing values where necessary. Missing values were assumed to be missing at random.

6.4 RESULTS

The four main centres participating in CHHIPS and COSSACS (Bournemouth, Exeter, Leicester and Newcastle) kept a record of all patients screened for participation over an average period of 16 months. Information from a total of 3236 patients presenting with an acute stroke syndrome were reviewed in total, including 509 stroke mimics and 368 transient ischaemic attacks. 94 had been discharged or were deceased before the researcher could review them. All patients were included in the screening analysis, however only those with a clinical stroke syndrome and availability of all three time points under study were considered in the multivariate analysis.

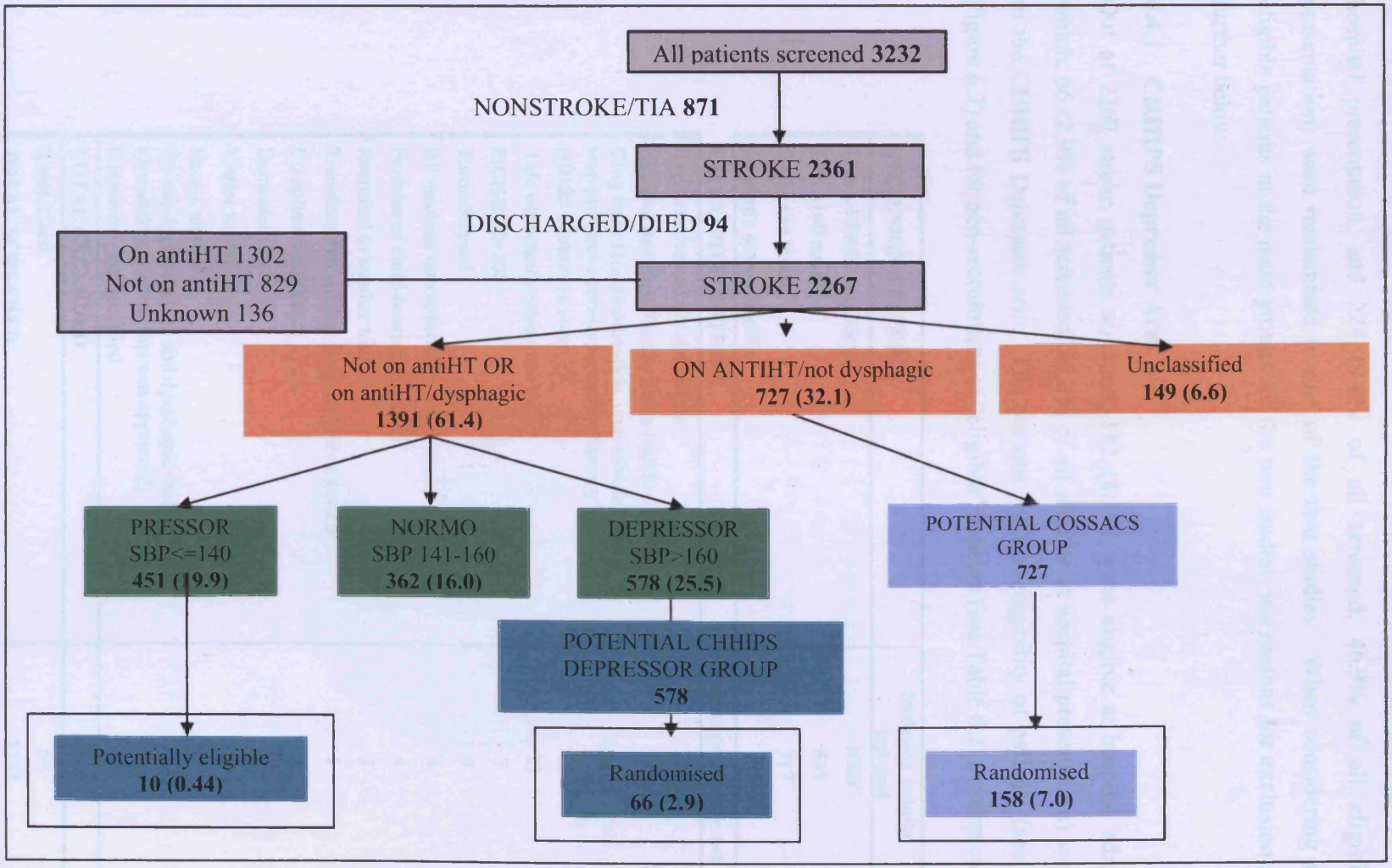

Figure 6.1. Schematic breakdown of patients screened for the CHHIPS and COSSACS studies over 16 months (average)
Note: Figures in brackets are percentages out of total strokes screened (n=2267)

Out of those with a clinical impression of stroke, 21.1% (478/2267) were eligible for trial entry at hospital presentation, and 224 (9.9% of all screened, 46.9% of all eligible at hospital presentation) were randomised to one of the two studies. When considering the potentially eligible patients in the main groups for the two studies, the reasons for exclusion are considered further below.

6.4.1 CHHIPS Depressor Arm

Out of 2267 stroke patients screened, 182 (8.1%) were eligible at hospital admission, out of which, 66 (2.9% of all screened, 36.3% of all eligible at hospital presentation) were randomised to the CHHIPS Depressor arm. The reasons for non-eligibility of patients (see Table 6.1 and Figure 6.2) and for non-recruitment of "eligible" patients (see Table 6.2) are depicted below.

INCLUSION CRITERIA	Inclusion criteria **not met**
Clinical stroke syndrome	1028
SBP >160 mmHg	835
Onset <36 hours	217
Consent / assent feasible	28
EXCLUSION CRITERIA	Exclusion criteria met
Hypertensive and not dysphagic	706
Baseline modified Rankin Score (mRS>3)	130
Drug issue (contraindication, unavailable, unable to stop pre-stroke anti-hypertensive therapy)	80
NIHSS Section 1a score ≥2	75
Life expectancy <6months	23
PICH/SBP>200	7
Thrombolysed	9
BP machine uncomfortable	4
Females of child-bearing potential	4
Recruited to another trial	2
Transferred to another hospital before review	1
Compliance unlikely	1
Dementia	1
Visitor to area	1
Excess alcohol	1
On anti-hypertensives and dysphagic (before amendment to allow this was approved)	1
Unknown – not specified	12
TOTAL EXCLUDED	**3166**
Randomised	66
TOTAL SCREENED	**3232**

Table 6.1. CHHIPS Depressor Arm: Reasons for exclusion of patients screened

OUTCOME	NUMBER
Randomised	66
Within time window at admission, but outside by the time reviewed by researcher	64
Declined participation/ unable to consent/no relative assent feasible	26
SBP>160 documented at admission, but lower (<160) when reviewed by researcher, therefore not eligible	25
?eligible, no reason on file for exclusion	1
Eligible at admission	**182**

Table 6.2: Outcomes amongst patients eligible for the depressor arm of CHHIPS at initial hospital contact

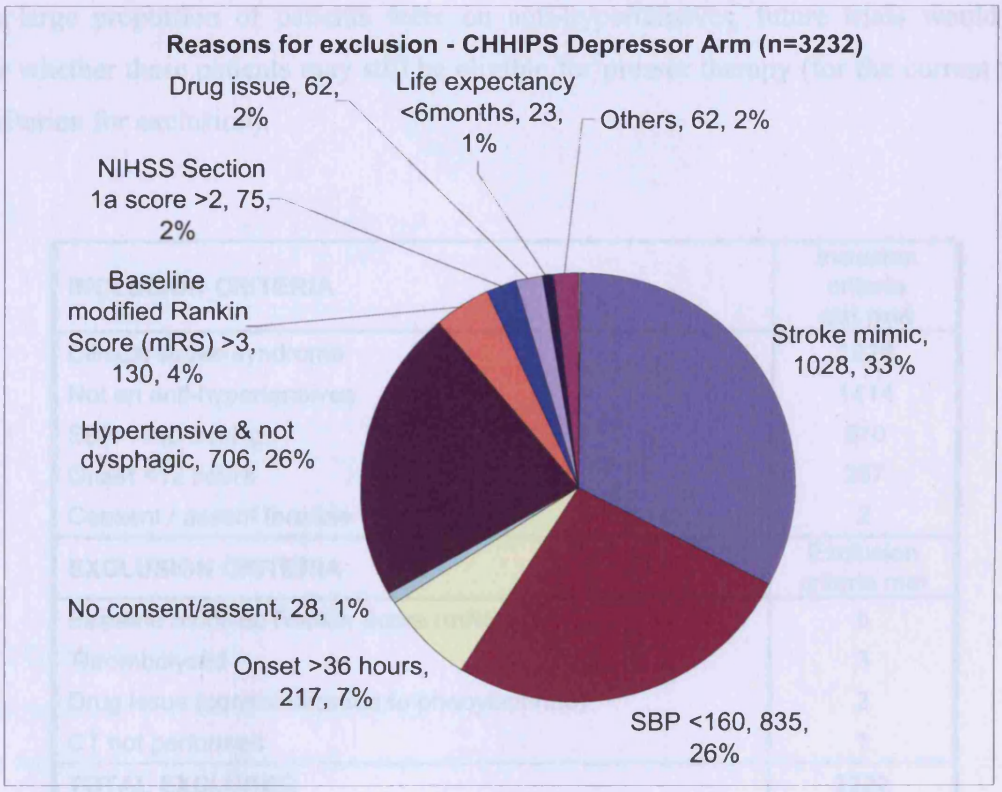

Figure 6.2: Breakdown of patients ineligible for CHHIPS pressor group

6.4.2 CHHIPS Pressor Arm

(SBP<140 mmHg and not on anti-hypertensive therapy)

For the pressor arm, those categorised into the "pressor group" with SBP<140 mmHg and not previously on anti-hypertensive therapy were considered (see Table 6.3 below). Some patients may have been on anti-hypertensive agents, due to other medical indications e.g. ischaemic heart disease, cardiac failure. Only 10 patients were potentially suitable at hospital admission (0.31% of all screened, 0.44% of all stroke syndromes screened). 6.7% were excluded because they were reviewed outside the trial eligibility window (180 admitted >11.5 hours from onset plus 77 reviewed outside the 12 hour window). Among the ten patients who were potentially suitable, there was no indication why three were not recruited, and the remaining seven presented after discontinuation of the pressor arm of the study, due to lack of suitable subjects (see Table 6.4). Since a large proportion of patients were on anti-hypertensives, future trials would need to consider whether these patients may still be eligible for pressor therapy (for the current trial, this was a criterion for exclusion).

INCLUSION CRITERIA	Inclusion criteria **not met**
Clinical stroke syndrome	1028
Not on anti-hypertensives	1414
SBP <140 mmHg	510
Onset <12 hours	257
Consent / assent feasible	2
EXCLUSION CRITERIA	Exclusion criteria met
Baseline modified Rankin Score (mRS>3)	5
Thrombolysed	3
Drug issue (contraindication to phenylephrine)	2
CT not performed	1
TOTAL EXCLUDED	**3222**
Potentially eligible	10
TOTAL SCREENED	**3232**

*Assumes that unknown onset-admission delay equates to >12h i.e. ineligible

Table 6.3: Breakdown of patients in CHHIPS "pressor group"

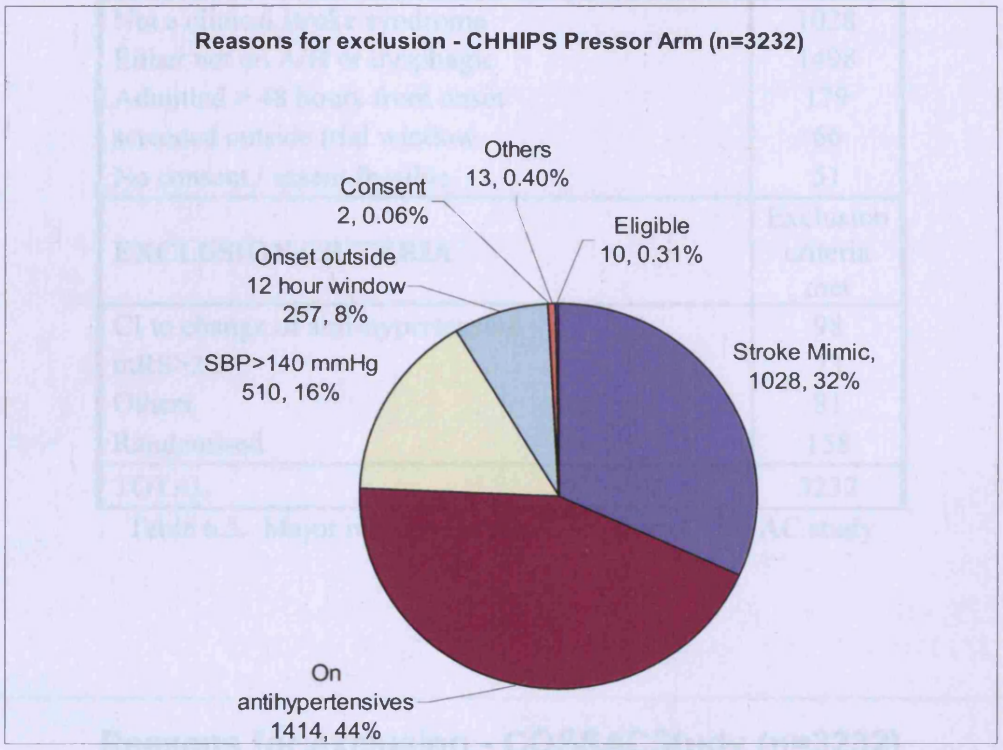

Figure 6.3: Breakdown of patients in the CHHIPS "pressor group".

No clear reason for non-recruitment	3
After Pressor arm discontinuation	7
TOTAL	10

Table 6.4: Outcome of potentially suitable "pressor group" patients

6.4.3 COSSACS Patients

(on anti-hypertensives and not dysphagic)

Patients on anti-hypertensive medication who were not dysphagic post-stroke were considered potentially eligible for the COSSACS study, and only 32.1% of all patients fell into this category. This was lower than expected, and it is likely that a significant proportion of potentially eligible patients did not seek hospital attention, were incorrectly labelled as transient ischaemic attacks outside hospital, or were referred to outpatient clinics for urgent review. Reasons for exclusion are summarised in Table 6.5 and Figure 6.4 (next page).

INCLUSION CRITERIA	Inclusion criteria not met
Not a clinical stroke syndrome	1028
Either not on A/H or dysphagic	1498
Admitted > 48 hours from onset	179
screened outside trial window	66
No consent / assent feasible	51
EXCLUSION CRITERIA	**Exclusion criteria met**
CI to change of anti-hypertensive	98
mRS>2/3	73
Others	81
Randomised	158
TOTAL	3232

Table 6.5. Major reasons for exclusion from COSSAC study

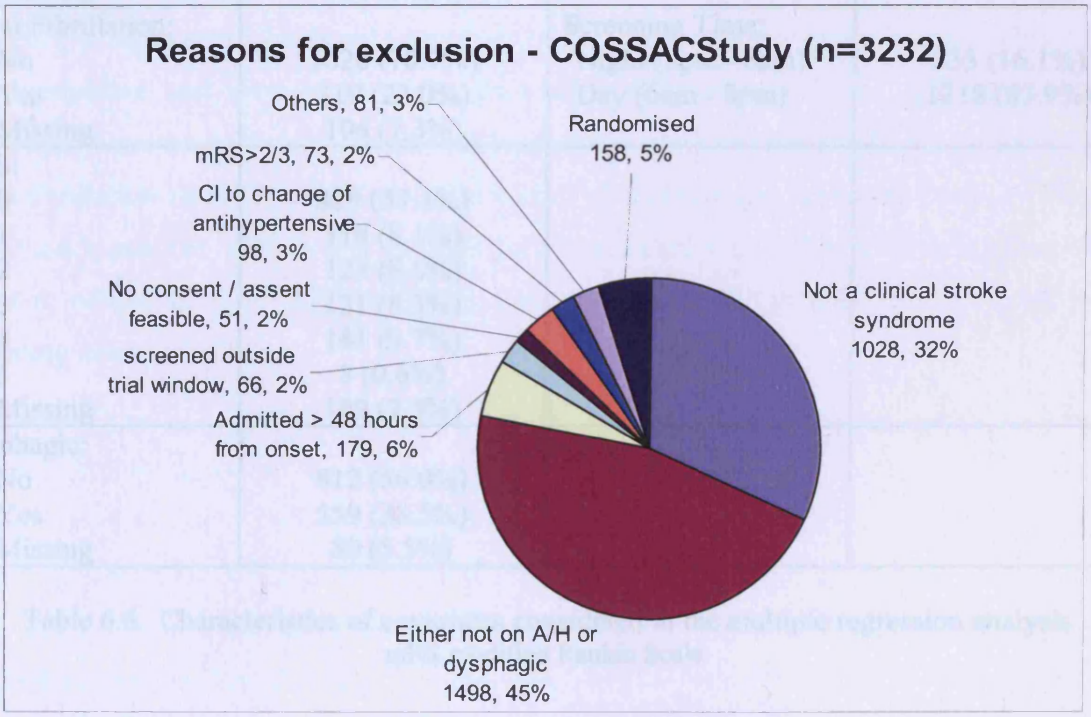

Figure 6.4. Major reasons for exclusion from COSSAC study

6.4.4 Analysis of Time Delays

Reliable timings (stroke onset, admission to hospital and review by researcher) could be elucidated for 1448 patients with stroke (63.9% of all presenting with a stroke syndrome). Median delay from symptom onset to hospital admission was 8.83 hours (interquartile range, IQR: 3.50-19.21), and median delay from admission to screening was 13.75 hours (IQR: 3.00-22.00). 210 patients out of 2398 with an admission diagnosis of stroke (8.75%) were successfully randomised. A further 8.5% were potentially suitable at hospital admission, but were outside the trial window when reviewed by the researchers. The remaining 72.75% did not fulfil the inclusion and/or exclusion criteria.

Covariate	n (%)	Covariate	n (%)
Hypertension:		Onset Time:	
No	552 (38.0%)	Night (8pm - 6am)	636 (43.8%)
Yes	861 (59.3%)	Day (6am - 8pm)	815 (56.2%)
Missing	38 (2.6%)		
Diabetes:		Admission Time:	
No	1133 (78.1%)	Night (8pm - 6am)	414 (28.5%)
Yes	214 (14.7%)	Day (6am - 8pm)	1037 (71.5%)
Missing	104 (7.2%)		
Atrial Fibrillation:		Screening Time:	
No	1026 (70.7%)	Night (8pm - 6am)	233 (16.1%)
Yes	319 (22.0%)	Day (6am - 8pm)	1218 (83.9%)
Missing	106 (7.3%)		
mRS:			
0	829 (57.1%)		
1	118 (8.1%)		
2	125 (8.6%)		
3	121 (8.3%)		
4	141 (9.7%)		
5	8 (0.6%)		
Missing	109 (7.5%)		
Dysphagic:			
No	812 (56.0%)		
Yes	559 (38.5%)		
Missing	80 (5.5%)		

Table 6.6. Characteristics of covariates considered in the multiple regression analysis
mRS modified Rankin Scale

6.4.4.1 Onset to Admission Delay

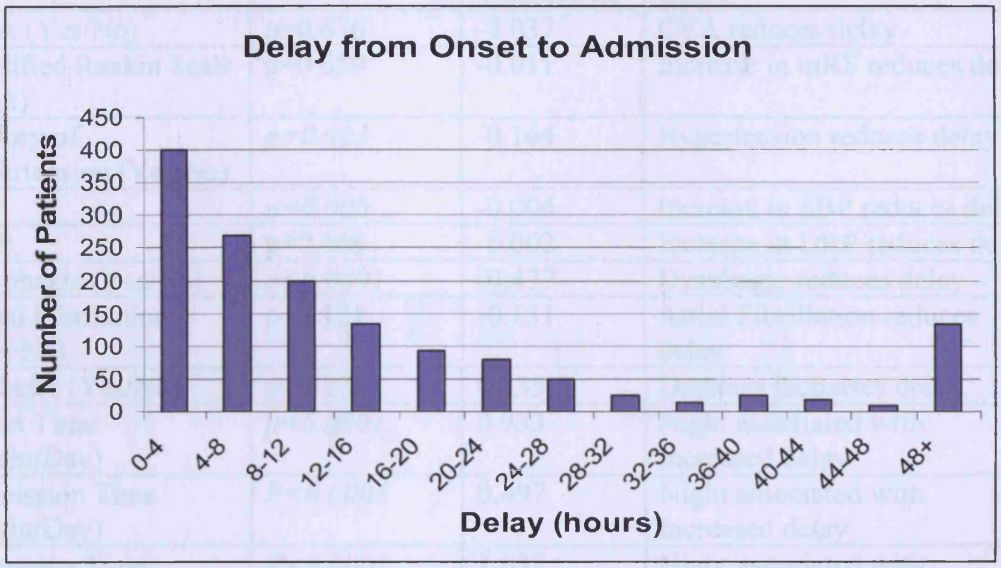

Figure 6.5: Profile of onset-admission delay

On univariate analysis, stroke onset at night (8pm to 6am), hospital admission at night, and screening at night were significantly associated with increased delay, while higher SBP, a history of hypertension, and presence of dysphagia were significantly associated with reduced delay. (Non-significant associations included higher dependency (mRS) and reduced delay, presence of atrial fibrillation and reduced delay, and a history of diabetes and increased delay). Following multivariate analysis, factors that retained their significant association with delay from stroke onset to admission were SBP ($p=0.025$), dysphagia ($p<0.0001$), onset time ($p<0.0001$) and screening time ($p<0.0001$).

Factor	Significance	Regression Coefficient	Direction of Influence Upon Delay
CVA (Yes/No)	p=0.676	-0.037	CVA reduces delay
Modified Rankin Scale (rank)	p=0.659	-0.011	Increase in mRS reduces delay
History of hypertension (Yes/No)	*p=0.023*	-0.164	Hypertension reduces delay
SBP	*p=0.006*	-0.004	Increase in SBP reduces delay
DBP	p=0.466	-0.002	Increase in DBP reduces delay
Dysphagic (Yes/No)	*p<0.0001*	-0.477	Dysphagic reduces delay
Atrial Fibrillation (Yes/No)	p=0.121	-0.131	Atrial Fibrillation reduces delay
Diabetes (Yes/No)	p=0.171	0.135	Diabetes increases delay
Onset Time (Night/Day)	*p<0.0001*	0.933	Night associated with increased delay
Admission Time (Night/Day)	*P<0.0001*	0.497	Night associated with increased delay
Screening Time (Night/Day)	*P<0.0001*	1.037	Night associated with increased delay

SBP systolic blood pressure; DBP diastolic blood pressure; Day 0800 – 2000; night 2000 - 0800

Table 6.7: Delay from onset to admission (log-transformed) – Univariate analysis

Variable	Parameter Estimate	Standard Error	95% Confidence Intervals	P-value
Intercept	2.28651	0.18975	1.91425 to 2.65877	P < 0.0001
SBP	-0.00262	0.00117	-0.00492 to -0.00033	P = 0.025
Dysphagic	-0.44520	0.06764	-0.57790 to -0.31250	P < 0.0001
Screening Time	0.62229	0.10005	0.42601 to 0.81857	P < 0.0001
Onset Time	0.77891	0.07280	0.63610 to 0.92173	P < 0.0001

Log Delay stroke onset to admission = 2.287 - 0.0026 (SBP) - 0.445 (Dysphagic) + 0.622 (Screening Time) + 0.779 (Onset Time)

Table 6.8: Delay from onset to admission (log-transformed) – Final Model (log-minutes)

If a patient was dysphagic then their delay was reduced by 36% compared to non-dysphagic patients. If a patient had an onset of stoke during the night (2000-0600 hours), then their delay was increased by 118%, compared to patients who have stroke onset during day hours. If a patient was screened during the night (2000-0600 hours), then their delay was increased by 86% compared to patients who were screened during day hours (however this is merely an association, and not clinically relevant, since screening was carried out after admission). For every one unit increase in SBP the delay was reduced by 0.3%.

6.4.4.2 Onset to Screening Delay

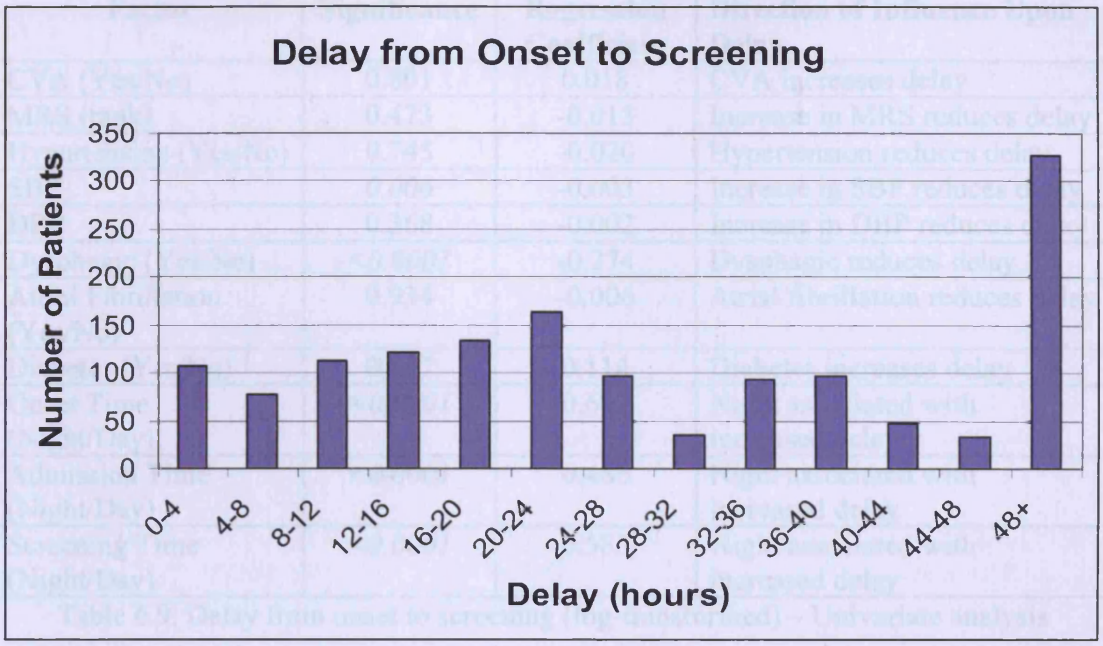

Figure 6.6. Profile of onset-screening delay

The profile of onset-screening display is depicted above. On univariate analysis, stroke onset at night, hospital admission at night, and screening at night were significantly associated with increased delay, while higher SBP and presence of dysphagia were significantly associated with reduced delay. Following multivariate analysis, factors that retained their significant association with delay from stroke onset to screening were SBP ($p=0.023$), dysphagia ($p<0.0001$), admission time ($p<0.0001$) and onset time ($p<0.0001$).

Factor	Significance	Regression Coefficient	Direction of Influence Upon Delay
CVA (Yes/No)	0.801	0.018	CVA increases delay
MRS (rank)	0.473	-0.015	Increase in MRS reduces delay
Hypertension (Yes/No)	0.745	-0.020	Hypertension reduces delay
SBP	*0.006*	-0.003	Increase in SBP reduces delay
DBP	0.368	-0.002	Increase in DBP reduces delay
Dysphagic (Yes/No)	*<0.0001*	-0.274	Dysphagic reduces delay
Atrial Fibrillation (Yes/No)	0.934	-0.006	Atrial fibrillation reduces delay
Diabetes (Yes/No)	0.167	0.114	Diabetes increases delay
Onset Time (Night/Day)	*<0.0001*	0.612	Night associated with increased delay
Admission Time (Night/Day)	*<0.0001*	0.486	Night associated with increased delay
Screening Time (Night/Day)	*<0.0001*	0.585	Night associated with increased delay

Table 6.9. Delay from onset to screening (log-transformed) – Univariate analysis

Variable	Parameter Estimate	Standard Error	95% Confidence Intervals	P-value
Intercept	3.30003	0.16871	2.96905 to 3.63101	<.0001
SBP	-0.00237	0.00104	-0.00441 to -0.00033	0.0226
Dysphagic	-0.27271	0.05982	-0.39007 to -0.15536	<.0001
Admission Time	0.34858	0.06724	0.21668 to 0.48049	<.0001
Onset Time	0.54591	0.06087	0.42650 to 0.66532	<.0001

Log delay stroke onset to screening = 3.000 - 0.002 (SBP) - 0.273 (Dysphagic) + 0.349 (Admission Time) + 0.546 (Onset Time)

Table 6.10. Delay from onset to screening (log-transformed) – Final Model (log-minutes)

If a patient was dysphagic then their delay was reduced by 24% compared to non-dysphagic patients. If a patient had onset of stoke overnight, then their delay was increased by 73% compared to patients who developed their stroke during day hours. If a patient was admitted during night hours then their delay was increased by 42% compared to patients who were admitted during day hours. For every one unit increase in SBP the delay was reduced by 0.2%.

6.4.5 Delay by OCSP

Descriptive analysis of delay was done based on the OCSP classification, which was available in 1155 patients (79.77%) – as depicted in Table 6.11. No statistical calculations were carried out as this classification is not ordinal.

OCSP	Median delay (range) hours		
	Onset to Admission	Admission to Screening	Onset to Screening
TACS (333)	6.67 (0-168.00)	11.91 (0-708.30)	20.50 (0.50-710.00)
PACS (406)	9.00 (0.40-501.00)	14.79 (0-692.50)	24.13 (0.80-513.00)
LACS (294)	13.34 (0-724.00)	15.00 (0-762.60) 2 missing values	33.00 (1.08-803.00) 1 missing value
POCS (65)	18.25 (0.8-178.3)	15.00 (0-177.80)	31.50 (3.00-254.00)
PICH (57)	5.75 (0.25-352.50)	13.50 (0-91.00)	18.50 (0.80-369.00)
OCSP Oxfordshire Classification of Stroke Project; TACS total anterior circulation stroke; PACS partial anterior circulation stroke; LACS lacunar stroke; POCS posterior circulation stroke; PICH primary intracerebral haemorrhage (CT confirmed haemorrhage at review)			

Table 6.11. Median delay times by OCSP classification of stroke.

Those presenting with PICH and TACS tended to present earlier, reflected in a shorter median onset to admission delay, and they tended to be reviewed earlier also, i.e. shorter onset to screening delay. On the other hand, those presenting with a lacunar syndrome (LACS) or a posterior circulation syndrome presented to hospital later, and consequently were reviewed later by a specialist. Admission to screening delay was similar in all groups (median delay: 11.91 – 15.00 hours). A quarter of the patients presented within 4 hours of onset, with two thirds presenting within 24h hours of symptom onset. On the other hand, delay to screening peaked at around 24 hours from onset, mostly due to delays in hospital admission. Also a significant number were seen beyond 48 hours of onset, due to delays in hospital admission, and lack of weekend research staff cover.

6.5 DISCUSSION

This analysis confirms that only a small minority of patients screened are eligible for participation in acute stroke blood pressure trials with criteria used for the COSSACS and CHHIPS studies. Successful randomisation took place in 8.75%, compared to previous trials of thrombolysis in acute ischaemic stroke (~4%). A higher figure of 12.8% was quoted in the FASTER trial, a study recruiting patients with minor strokes and transient ischaemic attacks, where communication is unlikely to be impaired thus facilitating consent, and subjects are likely to have had less disabling strokes, compared to the current studies[117]. The differences are likely

to be a reflection of varying patient characteristics, trial inclusion criteria (mainly window of eligibility from symptom onset), and the presence or absence of rapid admission protocols in participating centres.

As stroke research moves out from smaller-sized pilot trials to larger phase III trials, the applicability of trial interventions in the clinical scenario must be an important consideration when designing clinical trials. Potential changes in trial design that may enable the enrolment of a larger fraction of the population thereby reducing the time and resources required to recruit adequate sample sizes, and extending the applicability of results, should be considered seriously before commencement of a trial. Lessons learnt from one trial must be translated to other trials to optimise trial design.

The major reasons for exclusion of patients presenting with a clinical stroke syndrome were: CHHIPS depressor arm – stroke mimics, SBP ≤160 mmHg, non-dysphagic patients on pre-stroke anti-hypertensives, time from symptom onset >36 hours, and baseline dependency (mRS>3); CHHIPS pressor arm – stroke mimic, pre-stroke anti-hypertensive therapy, SBP>140 mmHg, and time from symptom onset >12 hours; COSSACS – stroke mimic, either dysphagic or not on anti-hypertensives, and time from symptom onset >48 hours.

Potential avenues to better recruitment in future trials would include:

i. Improvement in trial design, including use of disability-adjusted endpoints (i.e. an improvement on the modified Rankin Scale, as opposed to dichotomised outcomes – mRS ≤3 and >3, allowing inclusion of patients with the full spectrum of dependency) and stratification based on baseline severity allowing a smaller sample size;
ii. Simpler trial protocol employing only one active agent; and use of agents which do not require intensive monitoring;
iii. Reviewing the eligibility criteria to consider whether certain excluded groups should in fact be included: e.g. those with SBP in the middle zone (140-160 mmHg), following thrombolysis, those with higher baseline dependency (mRS 4-5);
iv. Adequate number of centres, with established rapid admission protocols for stroke;
v. Adequate number of researchers to allow round-the-clock screening;
vi. Nurse-led screening, initiation and monitoring, once safety of intervention regime has been established;

vii. Involvement of front-line clinicians in recruitment strategies;

viii. Encouraging an ethos of research, so that clinicians and patients have a greater understanding of the benefits of research and impact on clinical care.

In the analysis of time delay, more severe strokes tended to arrive in hospital earlier, suggesting a selection bias by patients and/or their carers, and this could be explained by the significant association of delay to admission and to screening with dysphagia (in itself a marker of stroke severity). Patients suffering their stroke overnight were either unaware of their symptoms, or tended to wait till the morning before contacting medical services, and this is an important point for health education, if thrombolysis services are to run "round-the-clock". Interestingly, higher SBP was associated with a small, but significant reduction in delay to admission, and to screening, the cause of which remains unclear.

Pre-hospital delay was the larger component of delay, largely due to factors outside the control of secondary care physicians. Intra-hospital delays were significant also, and importantly are more amenable to remedy as they lie within the bounds of secondary care. A comprehensive approach with multiple interventions along the pathway of the patient to hospital and to a stroke specialist unit is required to minimise delays to reaching an appropriate area of care, where patients may be considered for thrombolysis, if appropriate, and also for participation in trials investigating the optimal management of patients with acute stroke. Involvement of front-line clinicians in research should improve recruitment to clinical trials.

A significant proportion of patients who were diagnosed to have a stroke by the general practitioner or in the emergency department were deemed not to have had a definite acute cerebrovascular event on clinical grounds (31.8%). This highlights the need for access to, and early review by a trained physician/ specialist to prioritise those patients who would benefit from early management in an acute stroke unit and to identify those who would be suitable for acute intervention (both as treatment and as part of a trial).

6.5.1 Strengths of the Study

Data collection was prospective, incorporated into the routine screening that was performed to seek patients for the two stroke-BP trials. This should have minimised any bias with regards to recording of timings e.g. recall bias. This study is unique in that it studies patients outside the context of a thrombolysis trial. Three of the four centres provided intravenous thrombolysis for

acute ischaemic stroke, two only during the second half of data collection. Few patients (n=21) were excluded from the two studies having received intravenous thrombolysis.

The screening program was individually designed in each of the centres in an effort to maximise recruitment to ongoing clinical trials for acute stroke. All patients with a possible stroke were screened by suitably trained researchers at all potential admission points, at the four centres, though admittedly a minority may have been missed or reviewed with a larger intra-hospital delay e.g. weekends, non-specific presentation, and onset in-hospital. Case ascertainment for patients presenting to hospital with a stroke syndrome is likely to be near-complete. Thus this study, in my opinion, reflects the experience in most National Health Service secondary care organisations in the United Kingdom. The admission profile of patients with acute stroke is expected to change following the increasing application of intravenous thrombolysis for acute ischaemic stroke.

6.5.2 Weaknesses of the Study

Only 63.9% of patients had reliable timing available for all 3 time points studied. Timing was difficult to ascertain for those who had communication difficulties or reduced consciousness, and subject to recall bias in those with delayed presentation e.g. beyond the 1st 24 to 48 hours from symptom onset. Estimation of timing of stroke onset by patients and carers is subject to recall bias, though these are accepted when considering appropriateness of thrombolysis. More reliable timings were available from the notes for admission time, and screening time was recorded immediately. Additionally all information was collected at one visit, further visits being considered unethical once a patient was considered ineligible for the proposed studies. A repeat visit may have reduced the amount of missing data. Though missing data were assumed to be at random, this is unlikely to be the case, and missing values may be skewed towards more severe strokes, due to reduced consciousness and impaired communication. Future work will involve imputations methods to correct for this possible source of bias. No patient related demography was collected that may enable comparison with other studies looking at reasons for delay in hospital admission or reasons for exclusion from clinical trials.

6.6 SUMMARY

- This is the first analysis to report a detailed screening log (onset, admission and screening times) for an acute stroke trial.
- Profiling the time course from symptom onset to specialist review has highlighted points of delay (e.g. potential increase in recruitment by ~50%, if specialist review could be made available at initial hospital contact).
- Identification of factors associated with delay should enable focussed resource use, and allow comparison between trial participants and the population screened.
- Future trials must incorporate formal screening into their protocols.

7 CONCLUSIONS

The work in this thesis describes the feasibility and safety of blood pressure manipulation immediately following acute ischaemic or haemorrhagic stroke. Both high and low blood pressure are common following acute stroke, and associated with a worse prognosis. Whether optimisation of these blood pressure changes is associated with improved outcomes is not known. While previous studies have shown that BP modification is feasible, no significant benefit in terms of clinical outcomes has been demonstrated, due to inadequate sample size and limited duration, and most trials excluded patients with impaired swallowing.

7.1 SUMMARY OF RESULTS

In chapter 1, I reviewed the epidemiology of stroke, risk factors for deterioration after stroke, and current therapy for acute stroke. I also reviewed blood pressure changes post-stroke, effects on outcome, and interactions with other treatments. Established interventions immediately following acute ischaemic stroke include: intravenous thrombolysis for acute ischaemic stroke within 3 hours of symptom onset; aspirin for non-haemorrhagic stroke; and organised care in a dedicated unit. Carotid endarterectomy for significant carotid artery stenosis should be carried out within two weeks of an event. To date, the benefits of neuroprotective agents have been restricted to pre-clinical animal models. Various studies are looking at extending the applicability of thrombolysis, including: intra-arterial thrombolysis; and combination of intravenous thrombolysis with adjuvant therapy e.g. intra-arterial thrombolysis, sonolysis and endovascular mechanical thrombolysis. While physiological derangements are common in the acute post-stroke scenario, and associated with worse outcome, intervention to correct these derangements has not been associated with clinical improvements to date.

The complex relationship between BP and stroke is also elaborated. Consistent with the association of high BP with increased risk of stroke, BP reduction is beneficial for primary and secondary prevention of stroke. While there remains lack of agreement between individual studies with regards to the prognostic value of BP in the immediate post-stroke situation, two systematic reviews reported worse outcomes in those with higher BP[307,235]. Studies investigating early anti-hypertensive therapy have been undertaken only recently, and preliminary results have been encouraging (ACCESS[357] and INTERACT[361]).

On the other hand, low BP post-stroke is also associated with a worse prognosis. This has prompted a few studies investigating BP elevation ("pressor therapy") following acute stroke, which were reviewed in Chapter 2. Interpretation of published literature was complicated by differences in trial methodology, and the small sample sizes of individual studies. While small studies have shown that BP elevation can be carried out safely in acute stroke (with close monitoring), no definite evidence of impact on clinical outcomes, including overall mortality and adverse events was noted. Also applicability of pressor therapy to the general acute stroke population was not reported. Through the course of the CHHIPS study, only one patient was randomised to the pressor arm of the current study over 14 months, and therefore this arm was abandoned. Obstacles to recruitment included: delay to hospital admission; increasing prevalence of pre-stroke anti-hypertensive use (contraindication for the study); need for urgent neuroradiology input; practical difficulties with pressor agent availability, and contraindications; and the need for intensive monitoring, in costly high-dependency environments.

The balance of benefit versus harm with induced hypertension in acute stroke remains to be demonstrated in a well-structured RCT. While BP elevation is potentially beneficial, possible contributing causes should be treated first, in line with existing guidelines e.g. sepsis, hypovolaemia. If considered, therapy must be initiated early, before irreversible damage to the ischaemic penumbra, which may be demonstrable on specialized imaging.

Chapter 4 summarised the BP effects noted in this study, the first to compare different routes of administration as well as different anti-hypertensive agents in acute stroke. The spontaneous fall of BP following stroke reported in observational studies[229,352] was seen in the placebo group. Active treatment (labetalol and lisinopril) was more effective than placebo at reducing post-stroke SBP within 24 hours of randomisation, and this difference was statistically significant for the treatment groups combined, and for lisinopril, but not labetalol, compared to placebo. The SBP changes at 24 hours for the active group combined are similar to those obtained in previous studies (using intravenous nimodipine[324] or transdermal glyceryl trinitrate[323]). At 2 weeks, SBP, but not DBP, was significantly lower in the active treatment groups combined, by a mean of 8 mmHg compared to placebo. There was no significant change in the primary outcome of death and dependency at 2 weeks. There was a beneficial effect of active BP lowering intervention compared to placebo on the secondary outcome of mortality at three months (borderline statistical significance).

Using an incremental dose approach, 77% and 60% of subjects achieved target SBP reduction in the labetalol and lisinopril groups at 4 hours, but this had fallen to just under half by 24 hours. While rate of target achievement was maintained for lisinopril at above two-thirds, there was a decline in target achievement in the labetalol group to about 50%, reflecting its short duration of action.

In the dysphagic group, sublingual lisinopril appeared to be an effective and well-tolerated alternative to the intravenous route of administrating anti-hypertensive agents in acute stroke, opening up the possibility of acute administration by paramedics on initial patient contact or by nurses in the Accident & Emergency department on patient arrival before a formal swallow assessment has taken place. Intravenous labetalol has a more rapid onset and shorter duration of BP lowering effect, indicating the need for frequent dosing or a continuous infusion to maintain target BP levels, with consequent intensive monitoring requirements.

Safety issues of depressor therapy were considered in Chapter 5. Early neurological deterioration at 72 hours (a marker of subsequent poor outcome) was not significantly different between groups. The number of events was too small to establish any association between stroke subtype and effect of intervention. Intervention did not result in a significant change in the primary outcome (2-week death and dependency), which is unsurprising, given that recruitment was far short of the sample size predicted by power calculation. Given the actual recruitment of 179, the study had 80% power at the 0.05 significance level to detect a minimum relative risk reduction of 23.6% in the primary outcome of death and dependency at two weeks (active versus placebo). Thus a type II error is possible, and smaller relative risk reductions which may be clinically relevant have not been excluded.

Labetalol resulted in early BP drops (significant at 4 hours); as compared to the sustained BP drop seen with lisinopril (significant at 24 hours). However, there was no difference in the rate of adverse events. Whether early rapid lowering is beneficial or harmful is unclear at present. It is tempting to hypothesise that an earlier BP drop may be cerebroprotective, reducing the known complications of cerebral oedema and haemorrhagic transformation. There was no significant difference in the number of serious adverse events reported by group, or the number of patients reported to have a serious adverse event. Also, no significant difference between groups was

seen in the other safety parameters, including drug-related adverse events, treatment discontinuation rates and trial withdrawals. Overall rate of adverse events was low, and almost three-quarters of subjects completed the protocol-specified intervention (compared to nearly two-thirds in a previous trial of BP lowering in acute stroke[251]).

Chapter 6 studied the reasons for patient exclusion from trials studying the management of BP in acute stroke (CHHIPS and COSSACS). Only 8.75% of all stroke patients were randomised to one of the two studies. This figure is in line with trials investigating more acute therapies like thrombolysis (~4%) and those recruiting patients with TIA or minor ischaemic stroke (12.8%). The major reasons for exclusion were: CHHIPS depressor arm – stroke mimic (33%), SBP ≤160 mmHg (26%), non-dysphagic patients on pre-stroke antihypertensives (22%), time from symptom onset >36 hours (7%), and baseline dependency (mRS>3: 4%); CHHIPS pressor arm – stroke mimic (32%), pre-stroke antihypertensive therapy (44%), SBP>140 mmHg (16%), and time from symptom onset >12 hours (8%); COSSACS – stroke mimic (32%), either dysphagic or not on antihypertensives (45%), and time from symptom onset > 48 hours (6%).

In the analysis of time delays, more severe strokes including those with dysphagia; and those with higher SBP tended to arrive in hospital earlier. Patients suffering their stroke in the night or whilst asleep did not seek medical attention until the morning, which may limit the applicability of overnight thrombolysis services. While pre-hospital delay was the larger component of delay, there were significant intra-hospital delays also, which are more amenable to remedy as they lie within the bounds of secondary care. A comprehensive approach with multiple interventions along the pathway of the patient to hospital and to a stroke specialist unit is required to minimise delays precluding intravenous thrombolysis and clinical trial participation. Public education and involvement of front-line clinicians in research could improve recruitment to clinical trials.

7.2 STUDY LIMITATIONS

Inadequate recruitment was the most important limiting factor in this study. While a simpler protocol with a single anti-hypertensive agent may have improved the number recruited in the depressor arm, a definitive trial is likely to require more resources in terms of participating centres, personnel and funds. Analyses were carried out between active therapy (combining both groups with active intervention) and placebo, due to the small sample size, and no conclusions can be drawn about the effects of the individual agents.

Only one patient was recruited to the pressor arm in this study. An acute study of pressor therapy will only be feasible once rapid admission, assessment and neuroimaging becomes the norm, and adequate trained personnel and monitoring facilities are available.

In Chapter 6, only 63.9% of patients had reliable timing available for stroke onset. Timing was difficult to ascertain for those who had communication difficulties or reduced consciousness. Estimation of timing of stroke onset by patients and carers is subject to recall bias especially with delayed admission, though these are accepted when considering appropriateness of thrombolysis. More reliable timings were available from the notes for admission time, and screening time was recorded immediately. Additionally all information was collected at one visit, further visits being considered unethical once a patient was considered ineligible for the proposed studies. A repeat visit may have reduced the amount of missing data. Missing data were assumed to be at random, but may be skewed towards more severe strokes, due to reduced consciousness and impaired communication. Future work will involve imputations methods to correct for this possible source of bias. No patient related demography was collected that may enable comparison with other studies looking at reasons for delay in hospital admission or reasons for exclusion from clinical trials.

7.3 CLINICAL IMPLICATIONS

Elevated BP following stroke may represent a therapeutic target following acute stroke. BP lowering following acute stroke to 145-155 mmHg, or reduction by 15 mmHg in this study was not associated with demonstrable harm. This is in agreement with the results from the INTERACT study, which reported no significant difference between two groups comparing aggressive versus standardized BP lowering following haemorrhagic stroke (while intensive treatment significantly lowered the occurrence of the primary outcome: mean proportional haematoma growth at 24 hours, the difference was not significant after adjusting for baseline haematoma volume and delay from onset to CT scan)[361]. While BP lowering is carried out frequently in the acute stroke situation, and preliminary data suggest no harm[267,266,268], more evidence is required before BP lowering immediately following acute stroke can be accepted in routine clinical practice. Since only a minority of patients presenting with acute stroke were eligible for one of two major multi-centre acute stroke trials investigating the management of blood pressure following stroke, clinical applicability of the results would be restricted.

7.4 PROSPECTS FOR FUTURE STUDIES

This study has produced important preliminary safety information to encourage further definitive studies of titrated-BP lowering in acute stroke. Both labetalol and lisinopril are promising agents for use in the immediate post-stroke phase. Sublingual lisinopril is an attractive option for those with dysphagia. Future studies are required to confirm these results, and to ascertain the impact of BP lowering on clinically relevant outcomes.

Recommendations for future studies include the need for optimising recruitment with the following measures: simple protocol using only one anti-hypertensive agent; less intensive monitoring, lower BP cut-off; ensuring eligibility of a larger subset of patient presenting to hospitals with stroke (including those on pre-stroke antihypertensive therapy), and enabling direct applicability of trial results to the clinical scenario; adequate number of centres, likely to require international collaboration; centres with rapid admission protocols for stroke patients, and partnership between front-line clinicians and researchers to promote a high rate of ongoing recruitment.

Additionally, the issue of BP-lowering in the context of thrombolysis in acute ischaemic stroke has not been studied. While the association of intracranial haemorrhage with elevated BP was noted in trials of thrombolysis for acute myocardial infarction, this has not been consistently reported in trials of thrombolysis for acute ischaemic stroke. Despite strict BP eligibility criteria for thrombolysis in acute ischaemic stroke, and for initiation of antihypertensive therapy following thrombolysis, there is no direct evidence of benefit. However, it is unlikely that such a trial would be carried out in view of the prevailing guidelines advocating antihypertensive therapy. There remains a place for a randomised controlled trial of antihypertensive therapy for those receiving thrombolysis for acute ischaemic stroke, and not advised BP-lowering treatment based on current guidelines i.e. SBP <180 mmHg.

A number of ongoing studies seek to clarify the management of elevated BP in the early post-stroke situation, including the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS)[294]; the Efficacy of Nitric Oxide in Stroke (ENOS) Study - continue or stop pre-stroke anti-hypertensives, and transdermal glyceryl trinitrate versus placebo[378]; the Scandinavian Acute Stroke Trial (SCAST) - candesartan versus placebo (www.scast.no); the

Anti-hypertensive Treatment in Acute Cerebral Haemorrhage (ATACH) study – nicardipine infusion in acute haemorrhagic stroke, data analysis ongoing: ClinicalTrials.gov identifier: NCT00415610); the ATACH2 study (planned); the ongoing IntraCerebral Haemorrhage - Acutely Decreasing Arterial Pressure Trial (ICH-ADAPT) – labetalol infusion in acute haemorrhagic stroke; and the INTERACT2 study (intensive: SBP <140 mmHg versus standard: SBP <180 mmHg BP lowering within 6 hours of acute haemorrhagic stroke). While these studies are extremely important as they will clarify the management of blood pressure in acute stroke, most of them suffer from difficulties in recruitment. The SCAST study, on the other hand, is recruiting rapidly due to a large number of sites and commercial funding support. It may be that academic-commercial partnership is inevitable for the success of trials in the setting of acute stroke, which are resource-intensive, and face many practical and ethical dilemmas.

The results described in this thesis are encouraging, with no obvious evidence of harm from early BP manipulation. A logical step would be to take the work further using one antihypertensive compared to placebo, within the context of an international trial, ensuring that adequate numbers are recruited to address effects on clinically relevant outcomes. Stratification by ischaemic versus haemorrhagic subtype will allow clarification of the trend towards worse outcome noted in this study for patients with ICH as their qualifying event, this being in contrast to existing data e.g. INTERACT[359], where early BP lowering was safe and well tolerated. Lisinopril is attractive since it can be administered in a crushed form sublingually (as shown in this study) with no obvious evidence of harm, comparable BP lowering effect, and the possibility of early administration by first responders without significant BP monitoring requirements. All stroke studies must include data on number of potential subjects excluded during screening, to allow comparison between included and excluded subjects, and an understanding of the clinical relevance of trial results.

7.5 SUMMARY

- This thesis has shown that BP lowering can be achieved in hypertensive acute stroke patients, with both lisinopril and labetalol, with no significant increase in early neurological deterioration or adverse events at 72 hours, and death and dependency at 2 weeks. Interestingly, three month mortality was reduced in those receiving active BP-lowering therapy, with borderline significance.
- Significant problems with recruitment related to inadequate number of participating centres, lower than anticipated numbers of patients conforming to eligibility criteria, need for intensive monitoring inherent in pilot studies, and lack of round-the-clock cover for recruitment, due to funding limitations.
- A study of pressor therapy in acute stroke was not feasible using the current CHHIPS criteria, due to lack of eligible patients.
- There is an urgent need for further studies of BP lowering in acute stroke. The criteria for an ideal trial of BP lowering in acute stroke are: inclusion of all stroke patients with the full spectrum of baseline disability, irrespective of co-morbidity and prior medications; use of an established drug, having multiple routes of administration, and not requiring intensive monitoring; a large number of recruiting centres (with established rapid admission protocols), having adequate researchers, thus ensuring maximal recruitment of eligible subjects and sufficient numbers to categorically demonstrate effects on clinically relevant outcomes; and a partnership between researchers, front-line clinicians and patients, where research is considered part of the ethos of clinical care.

8 APPENDICES

8.1 APPENDIX I: Stroke Classification and Stroke Scales

8.1.1 Oxfordshire Community Stroke Project (OCSP) Classification

Patients presenting with a stroke can be classified according to their constellation of symptoms and signs, into 4 groups, prior to any formal neuro-imaging:

1. TACS – "total anterior circulation stroke"
2. PACS – "partial anterior circulation stroke"
3. LACS – "lacunar stroke"
4. POCS – "posterior circulation stroke"

Classification depends on 3 main features –

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

All three features indicate TACS. The presence of two out of three features, restricted sensory and/or motor involvement of only one of three body areas (face, arm, leg), isolated higher cerebral dysfunction indicate PACS. Sensory and/or motor involvement of more than one of the three body areas, and ataxic hemiparesis indicate LACS. Brainstem, cerebellar or occipital lobe signs indicate a POCS.

8.1.2 National Institutes of Health Stroke Scale (NIHSS)

1a. Level of Consciousness	0 = Alert; keenly responsive. 1 = Not alert; but rousable by minor stimulation 2 = Not alert; requires repeated, strong or painful stimulation to attend 3 = Only reflex motor or autonomic response, or totally unresponsive, flaccid, and areflexic.
1b. LOC Questions	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best Gaze	0 = Normal. 1 = Partial gaze palsy; gaze abnormality, but no forced deviation or total gaze paresis. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic manoeuvre.
3. Visual	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial Palsy	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides
5a. Motor Arm: Left 5b. Motor Arm: Right	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. 99 = Amputation or joint fusion, explain:
6a. Motor Leg: Left 6b. Motor Leg: Right	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. 99 = Amputation or joint fusion, explain:
7. Limb Ataxia	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. 99 = Amputation or joint fusion, explain: _____
8. Sensory	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
9. Best Language	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. 2 = Severe aphasia; all communication through fragmentary expression 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; unintelligible out of proportion to dysphasia, or mute/anarthric. UN = Intubated or other physical barrier, explain: _____
11. Extinction and Inattention	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

8.1.3 Modified Rankin Scale (mRS)

0	**No symptoms** The patient is unaware of any new limitation or symptom caused by the stroke, however minor.
1	**Minor symptoms** The patient has some symptoms as a result of their stroke, whether physical or cognitive – e.g. affecting speech, reading or writing; or physical movement; or sensation; or vision; or swallowing; or mood – but can continue in all previous work, social and leisure activities. If the patient is unable to perform an activity that they previously performed at least monthly, then they should be graded 2.
2	**Minor handicap** The patient is unable to undertake an activity that was possible before the stroke – e.g. driving a car, dancing, reading or working – but can still look after him/ herself without help from others on a day-to-day basis. Therefore, the patient can manage dressing, moving around, feeding, toileting, preparing simple meals, shopping, and travelling locally without needing assistance from anyone else. Supervision is not necessary. The patient could be left alone for a week or more without concern.
3	**Moderate handicap** The patient is independently mobile (with aids if necessary) and can manage dressing, toileting, feeding, etc, but may need help from someone for more complex tasks – e.g. shopping, cooking or cleaning. This help will be required more often than weekly to ensure that these activities are completed, though the assistance may be advisory rather than physical – e.g. financial affairs.
4	**Moderately severe handicap** The patient requires someone else to help with some daily tasks – e.g. walking, dressing, toileting or eating. The patient is visited at least once (or twice) daily, or lives in close proximity to a carer. If the patient cannot be left alone for moderate periods of the day, then they should be graded 5.
5	**Severe handicap** Someone else is always available during the day and at times during the night, though this need not be a trained nurse.

8.1.4 Barthel Index

Eating	0 1 2	Unable to feed themselves Needs help Independent
Bathing	0 1	Dependent Independent
Washing	0 1	Needs help Independent
Dressing	0 1 2	Unable to dress Needs help Independent
Bladder	0 1 2	Incontinent Occasional accident Continent
Bowel	0 1 2	Incontinent Occasional accident Continent
Toilet	0 1 2	Dependent Needs some help Independent
Transfers	0 1 2 3	Unable Major help Minor help Independent
Mobility	0 1 2 3	Immobile Wheelchair independent Walks with help Independent
Stairs	0 1 2	Unable Needs help Independent up & down

8.2 APPENDIX II

8.2.1 Publications arising from the thesis

Peer-reviewed articles

Potter JF, Robinson TG, Ford GA, **Mistri A**, James M, Chernova J, Jagger C. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. Lancet Neurology 2009; 8: 48-56

Potter JF, **Mistri A**, Brodie F, Chernova J, Wilson E, Jagger C, James M, Ford G, Robinson T for the CHHIPS Trial Group. Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) Pilot Trial Report (HTA Project 01/73/03)

Mistri AK, Robinson TG, Potter JF. Pressor Therapy in Acute Ischaemic Stroke: Systematic Review. Stroke 2006; 37: 1565-1571

Eames PJ, **Mistri AK**, Shah N, Robinson TG. Acute stroke hypertension: current and future management. Expert Review of Cardiovascular Therapy. 2005 3; 3: 405-412

The CHHIPS Trial Group (Trial Coordinator: **A Mistri**). CHHIPS (Controlling Hypertension and Hypotension Immediately Post-Stroke) Pilot Trial: rationale and design. Journal of Hypertension. 23; 3: 649-655

Mistri AK, Fotherby M. Treatment of hypertension as Secondary Prevention of Stroke. Geriatric Medicine 2006 October.

Mistri AK, Potter JF. How low to go? Treatment of Hypertension Post-stroke. Geriatric Medicine – Care of the Elderly Heart Supplement 2006 September.

Abstracts/Posters/Platform presentations

Mistri A, Potter J, Robinson T. for the CHHIPS Trial Group.
Controlling Hypertension And Hypotension Immediately Post Stroke (CHHIPS) - Ongoing Clinical Trial.

British Association of Stroke Physicians Annual Scientific Meeting 2005
Association of British Neurologists Meeting 2005
Stroke Association Scientific Meeting 2005
European Society of Hypertension 2006
International Stroke Conference 2006

Mistri A, Robinson T, Potter J.
Pressor Therapy in Acute Stroke – Systematic Review.

British Association of Stroke Physicians Annual Scientific Meeting 2006.

Mistri AK, Robinson TG, Potter JF.
Pressor Therapy in Acute Ischaemic Stroke – A Systematic Review of Benefits and Harms.

European Stroke Conference 2006

Mistri A, Robinson T, Potter J.
Improving Recruitment To Acute Stroke Blood Pressure Trials, By Analysing Screening Data
UK Stroke Forum 2006

Amit Mistri, Toby Black, Anand Dixit, Penny Eames, Nainal Shah, Martin Holt, Suzanne Stevens, Gary Ford, Martin James, Damian Jenkinson, Tom Robinson, John Potter, for the CHHIPS & COSSACS Trial Groups
Factors influencing recruitment to blood pressure trials in acute stroke
UK Stroke Forum 2007 - Platform

Mistri A, Robinson T, Potter J.
Delays to hospitalisation following stroke.
European Stroke Conference 2008

Mistri A, Robinson T, Potter J. for the CHHIPS Trial Group
BP lowering in acute stroke – the CHHIPS Pilot Study
European Stroke Conference 2008 - Platform

Mistri A, Robinson T, Potter J. for the CHHIPS Trial Group
Lowering Blood Pressure in Dysphagic Acute Stroke Patients - CHHIPS Pilot Study
European Stroke Conference 2008 - Platform

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