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# Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial

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# Abstract

## Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial

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**Objectives:** To assess the effects of acute pressor and depressor blood pressure (BP) manipulation on 2-week death and dependency following acute stroke and investigate the safety and efficacy of such treatments.
**Design:** A multicentre, prospective, randomised, double-blind, placebo-controlled titrated-dose trial.
**Setting:** Five hospitals in England.
**Participants:** Patients over 18 years admitted to hospital with a clinical diagnosis of suspected stroke and either (1) symptom onset < 36 hours and hypertension, defined as systolic BP (SBP) > 160 mmHg (depressor arm), or (2) symptom onset < 12 hours and hypotension, defined as SBP ≤ 140 mmHg (pressor arm).
**Interventions:** Patients were allocated to either the pressor or the depressor arm depending on blood pressure at randomisation. The ratio of allocation to active intervention versus matched placebo was 2:1 for the depressor arm and 1:1 for the pressor arm.
**Main outcome measures:** The primary end point was death and dependency at 2 weeks, with dependency defined as a modified Rankin score > 3. Secondary end points were the safety of acute pressor (0–12 hours post stroke) and depressor (0–36 hours post stroke) BP manipulation in stroke patients; whether effects of BP reduction are influenced by stroke type (ischaemic versus haemorrhagic); whether alternative routes for administration of antihypertensive therapy (including sublingual and intravenous) are effective in dysphagic stroke patients; whether effects of BP manipulation are influenced by the time to treatment; and the short- and medium-term cost-effectiveness of such therapy in the acute post-stroke period on subsequent disability or death.
**Results:** 180 patients were recruited over the 36-month trial period, 179 in the depressor arm and one in the pressor arm (who received placebo). No significant difference was found in death or dependency at 2 weeks between those receiving active depressor treatment with lisinopril or labetalol and those receiving placebo, although numbers recruited to the trial were lower than projected. Active treatment was not associated with an increase in early neurological deterioration despite significantly greater reductions in BP at 24 hours and 2 weeks with active therapy compared with placebo. Active treatment was generally well tolerated and treatment discontinuation rates were similar in active and placebo groups. Survival analysis showed that the active treatment group had a lower mortality at 3 months than the placebo group ($p = 0.05$). The pressor arm was closed early because of problems with recruitment, so no conclusions can be drawn regarding this therapy.
**Conclusions:** Oral and sublingual lisinopril and oral and intravenous labetalol are effective BP-lowering agents in acute cerebral infarction and haemorrhage and do not increase the likelihood of early neurological deterioration. The study was not sufficiently powered to detect a difference in disability or death at 2 weeks. However, the 3-month difference in mortality in favour of active treatment is of interest, although care must be taken in interpretation of the results. Further work is needed to confirm this and to assess whether there are differences in the effectiveness of labetalol compared with lisinopril in terms of reducing death or dependency after acute stroke, and whether the introduction of treatment post stroke earlier than was achieved here would be of greater benefit.

# Contents

# List of abbreviations

| | |
|---|---|
| ACCESS | Acute Candesartan Cilexetil Therapy in Stroke Survivors study |
| ACEI | angiotensin-converting enzyme inhibitor |
| ANOVA | analysis of variance |
| anti-HT | antihypertensive therapy |
| BEST | low-dose beta blockade in acute stroke trial |
| BP | blood pressure |
| CEAC | cost-effectiveness acceptability curve |
| CI | confidence interval |
| CHHIPS | Controlling Hypertension and Hypotension Immediately Post Stroke (trial) |
| COSSACS | Continue or Stop post-Stroke Antihypertensives Collaborative Study |
| CPI | Consumer Prices Index |
| CT | computerised tomography |
| DBP | diastolic blood pressure |
| DHP | DHP pharmaceuticals |
| ECG | electrocardiogram |
| ENOS | Efficacy of Nitric Oxide in Stroke trial |
| EQ-5D | EuroQol 5-dimensional generic health-related quality of life instrument |
| GEE | generalised estimating equations |
| GIST | Glucose Insulin in Stroke Trial |
| HTA | health technology assessment |
| ICER | incremental cost-effectiveness ratio |
| IMAGES | Intravenous Magnesium in Acute Stroke trial |
| INB | incremental net benefit |
| IST | International Stroke Trial |
| LoS | length of stay |
| MREC | multicentre research ethics committee |
| mRS | modified Rankin Scale |
| NIHSS | National Institutes of Health Stroke Scale |
| OCSP | Oxfordshire Community Stroke Project |
| OR | odds ratio |
| PEG | percutaneous endoscopic gastrostomy |
| PICH | primary intracerebral haemorrhage |

| | |
|---|---|
| QALY | quality-adjusted life-year |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SCAST | Scandinavian Candesartan Acute Stroke Trial |
| TIA | transient ischaemic attack |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

# Executive summary

## Background

Elevated blood pressure (BP) levels are common following acute stroke and may have an adverse prognostic effect. Observational data, however, suggest that both high and low BP levels in the acute stroke period are associated with a poor short- and long-term prognosis.

The limited data available from randomised controlled trials of BP reduction following acute stroke suggest that beta-blockers and calcium channel blockers commenced within 24–48 hours of stroke onset are unlikely to have benefit in terms of reducing short- or long-term disability or death. Other trials suggest that labetalol and the angiotensin receptor blockers may be effective post stroke, with one trial showing that candesartan nearly halved the number of subsequent fatal and non-fatal vascular events in severely hypertensive, non-dysphagic, acute ischaemic stroke patients. Conversely, an induced BP increase is a standard treatment for cerebral ischaemia in patients with vasospasm after subarachnoid haemorrhage, but few data exist to support this therapy in acute ischaemic stroke.

In view of the equivocal evidence and marked variations in clinical practice, the placebo-controlled Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) pilot trial was established to assess the safety and efficacy of therapeutically reducing BP with labetalol or lisinopril (depressor arm) in patients with hypertension (systolic BP > 160 mmHg) and acute cerebral infarction or haemorrhage and of therapeutically raising BP with phenylephrine (pressor arm) in ischaemic stroke patients with 'low' BP.

## Objectives

The primary outcome measure was death and dependency at 2 weeks following pressor or depressor therapy compared with placebo. The secondary objectives were: (1) to determine the safety of acute pressor or depressor therapy post stroke assessed by early neurological deterioration; (2) to assess if stroke type (ischaemic versus haemorrhagic) affected the BP changes due to depressor therapy; (3) to evaluate the BP effects of sublingual lisinopril and intravenous labetalol; (4) to study whether the effects of therapy on BP manipulation were influenced by the time to treatment; (5) to assess the short-term (2 week) cost-effectiveness of active treatment in relation to death and dependency and the medium-term (3-month) cost-effectiveness in relation to mortality.

## Methods

Inclusion criteria included age over 18 years with a clinical diagnosis of suspected stroke and either (1) symptom onset < 36 hours and hypertension, defined as systolic BP (SBP) > 160 mmHg (depressor arm), or (2) symptom onset < 12 hours and hypotension, defined as SBP ≤ 140 mmHg (pressor arm).

Exclusion criteria included being on antihypertensive therapy on admission and having an indication for urgent BP lowering, a contraindication to trial therapy, significant co-morbidity or a life expectancy of less than or equal to 6 months. Patients who were dysphagic and on antihypertensive treatment were included after a trial protocol amendment.

SBP levels, time of stroke onset, swallowing status and functional assessments including the modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) were determined before central randomisation in a ratio of 2:1 between active treatment and placebo for the depressor arm and 1:1 between active treatment and placebo for the pressor arm. The depressor non-dysphagic patients were assigned to stepped doses of oral lisinopril 5 mg, labetalol 50 mg or matching placebo with a target SBP of 145–155 mmHg or a SBP fall of ≥ 15 mmHg, with patients receiving additional doses at 4 and 8 hours post randomisation if target BP levels were not met. The established treatment regime was continued for 14 days post randomisation. Dysphagic patients underwent a similar titrated dose regime, receiving either sublingual lisinopril 5 mg, intravenous

labetalol 50 mg or matching placebo for 72 hours and then therapy orally if able to swallow or via a nasogastric tube if not until day 14.

Hypotensive (SBP < 140 mmHg) patients recruited within 12 hours of ischaemic stroke and who were euvolaemic could be randomised to normal saline infusion and either intravenous phenylephrine or matching placebo, to be continued up to 24 hours after stroke onset, after which normal BP management was allowed.

At 72 hours the NIHSS was repeated to assess early stroke deterioration and at day 14 functional assessments including mRS and NIHSS were measured again. At 3 months the cause and date of death, length of hospital stay and discharge destination were recorded by the co-ordinating centre.

The primary analysis was on an intention to treat basis, comparing the numbers of subjects who were dead or dependent (mRS > 3) at 2 weeks post randomisation. Analyses were first undertaken of active treatment compared with placebo, followed by comparisons across the three treatment groups where indicated. Logistic regression analysis was used to assess the effect of depressor or pressor treatment separately on death and dependency at 2 weeks. Repeated measures analysis of BP at baseline and at 4, 8 and 24 hours was performed using a generalised estimating equations (GEE) model. Differences in 3-month mortality and cost-effectiveness data were also assessed. Significance levels were set at 5%.

## Results

A total of 180 patients were recruited over the 36-month trial period, 179 in the depressor arm and one in the pressor arm (who received placebo). Study recruitment was less than anticipated (being 11% in the depressor arm), primarily related to the number of centres enrolled and the presence of study exclusion criteria in the majority of patients screened for study eligibility. Thus, there was limited statistical power for many of the study end points. The labetalol, lisinopril and placebo depressor groups were well matched for age, baseline BP, stroke type, time to treatment, NIHSS score and prevalence of dysphagia. In the depressor group the primary outcome measure of death and dependency at 2 weeks was assessed in 172 patients (seven patients being excluded because of non-stroke diagnosis, protocol violation or withdrawal of consent) and occurred in 61% of the active depressor treatment group and 59% of the placebo group ($p = 0.82$). There was no evidence of early neurological deterioration with labetalol or lisinopril compared with placebo and study numbers were too small to detect any differences by stroke subtype. The active depressor treatment group (lisinopril and labetalol combined) had a significantly greater fall in SBP within the first 24 hours than the placebo group [21 mmHg, 95% confidence interval (CI) 17–25, vs 11 mmHg, 95% CI 5–17; $p = 0.004$ at 24 hours], although time effects of BP lowering differed between the labetalol, lisinopril and placebo groups. Sublingual lisinopril and intravenous labetalol also significantly reduced BP within the first 24 hours compared with placebo. Patients on active treatment also had a significantly greater fall in SBP at 2 weeks than patients in the placebo group (31 mmHg, 95% CI 27–36, vs 24 mmHg, 95% CI 17–30; $p = 0.045$) although there was no significant difference in fall in diastolic BP (DBP; 13 mmHg, 95% CI 8–15, vs 9 mmHg, 95% CI 5–13; $p = 0.10$). No major safety problems were observed with labetalol or lisinopril treatment, no significant differences were seen in serious adverse events between active treatment and placebo, and no differences were found in discontinuation rates between those randomised to active treatment and those randomised to placebo. The study was too small to detect any differences in the response to hypotensive therapy between patients with cerebral infarction and those with cerebral haemorrhage. Survival analysis showed that the active treatment group had a lower mortality at 3 months ($p = 0.05$) with a hazard ratio of 2.2 (95% CI 1.0–5.0) for increased risk of death in the placebo group. Economic evaluation suggested that, on average, active treatment is both more effective and less expensive than placebo at 3 months.

## Conclusion

Both labetalol and lisinopril lowered BP to a greater degree than placebo in acute stroke patients within 24 hours of symptom onset without causing serious adverse effects or an early increase in stroke severity. However, depressor therapy did not reduce death and dependency at 2 weeks, but because of the reduced numbers recruited to the trial (only 11% of the target numbers were randomised) the study was underpowered to answer this primary outcome measure. Both sublingual lisinopril and intravenous labetalol were effective hypotensive agents in the immediate post-stroke period in dysphagic patients. Of interest was the reduction in stroke mortality at 3 months with

active therapy, a finding in keeping with one other acute BP-lowering stroke trial with a 12-month follow-up period, although care must be taken in interpretation of the CHHIPS results in view of the sample size. Further work is now needed to confirm these results and to assess if there are differences in the effectiveness of labetalol compared with lisinopril in terms of reducing death or dependency after acute stroke, and whether the introduction of earlier BP lowering post stroke than was achieved in CHHIPS would be of greater benefit. That we are still uncertain as to the best management of BP in the acute stroke situation is a matter of serious concern. However, the CHHIPS pilot trial indicates that BP can be safely reduced with labetalol or lisinopril after acute stroke and that this may translate into a decrease in mortality at 3 months. These findings need to be acted on by formulating the definitive trial of BP lowering in acute stroke. The role of increasing BP in acute stroke remains unresolved, although the numbers in whom this therapy could be applied are very small based on the CHHIPS trial entry criteria.

# Chapter 1
# Background

Stroke is the most common life-threatening neurological condition, affecting 110,000 patients per annum in the UK,[1] and the third most common cause of death and the most important single cause of severe adult disability.[2,3] Not surprisingly, stroke represents a significant cost to society, costing £7 billion a year in England alone, with stroke patients occupying 13% of all NHS beds. Accordingly, the National Service Framework for Older People calls for the establishment of specialist stroke services supported by the implementation of the Royal College of Physicians national clinical guidelines for the management of common post-stroke problems.[4]

A disturbance of cardiovascular autonomic regulation is a well-recognised complication of acute stroke[5,6] and is in part reflected in changes in absolute BP levels[7] and BP variability.[8] Elevated BP levels are common following acute stroke, the International Stroke Trial[9] and the Chinese Acute Stroke Trial[10] reporting that 54% and 48% of patients, respectively, had SBP levels > 160 mmHg within the first 48 hours following acute stroke, with 28% and 25% of patients, respectively, having markedly raised SBP levels >180 mmHg. Sustained increases in BP may be harmful by increasing the risk of cerebral oedema, haemorrhagic transformation of the infarct[11] and an increase in size of cerebral haemorrhage.[12] Data from a number of studies suggest that high BP levels in the acute stroke period are associated with poor short-[7,13–23] and long-term[24,25] prognosis. Utilising 24-hour BP monitoring within 24 hours of stroke onset we have shown that the odds ratio (OR) for 30-day death and dependency associated with each 10 mmHg increase in 24-hour SBP is 1.88 (95% CI 1.27–2.78),[7] and that acute 24-hour SBP levels > 160 mmHg are independently associated with an increased hazard ratio of 2.41 (95% CI 1.24–4.67) over a median follow-up period of 3 years compared with a reference SBP value of < 140 mmHg.[26] It has also been shown that increased acute stroke beat-to-beat BP levels and variability are associated with adverse prognosis; the OR for 30-day death and disability was 1.38 (95% CI 1.1–1.9) for every 10 mmHg increase in mean arterial BP and 1.32 (95% CI 1.1–1.7) for every 1 mmHg increase in mean arterial BP variability.[8]

However, the natural history is for a spontaneous reduction in BP levels over a period of 4–10 days post ictus.[27–30] Furthermore, there are well-documented abnormalities in cerebrovascular reactivity following acute stroke,[31–33] particularly an impairment of dynamic cerebrovascular autoregulation.[34] Cerebral blood flow is thus dependent on systemic BP levels, and further reductions may risk penumbral viability. Studies have shown that low BP in the acute stroke period is also associated with poor short-[35] and long-term[36–38] prognosis, although relative systolic hypotension (< 140 mmHg) is a rare complication, occurring in fewer than 18% of all stroke patients.[39] Most recently, an analysis of 17,398 patients recruited to the International Stroke Trial (IST) found a U-shaped relation between baseline casual SBP and both early (2-week) death and late (6-month) death and dependency; early death increased by 17.9% for every 10 mmHg decrease in SBP below 150 mmHg and by 3.8% for every 10 mmHg rise in SBP above 150 mmHg.[39] A U-shaped relationship between BP on admission and outcome was also seen in a prospective study of 304 patients with a first hemispheric ischemic stroke after adjusting for risk factors. Relative risk of death at 1 month and 1 year rose by 28.2% (95% CI 8.6–51.3%) and 17.5% (95% CI 3.1–34.0%), respectively, for every 10 mmHg decrease in SBP below 130 mmHg, and by 10.2% (95% CI 4.2–16.6%) and 7.2% (95% CI 2.2–12.3%), respectively, for every 10 mmHg increase in SBP above 130 mmHg.[40] Similarly, in a retrospective analysis of patients with acute stroke, those with admission SBP of between 121 and 140 mmHg had the lowest stroke mortality rates at 1 month and 1 year post stroke.[41] However, this U-shaped relationship has not been confirmed by studies of 24-hour BP monitoring in acute stroke,[7,14] which overcomes the problems of multisite, multiobserver BP measurements.[42] This may be due to the fact that BP levels measured over a longer period of time (beyond the hyperacute stage) may not have a significant influence on prognosis.

At present the acute management of post-stroke BP changes is a matter of some debate, as reflected in surveys of clinical practice.[43–45] The Stroke Association reported that 6% of physicians would start antihypertensive therapy on admission, 21%

would wait a few hours and the rest would wait for anything from a few days to a few weeks.[43] A similar picture exists in the USA, where the University Health Consortium Stroke Benchmarking Project reported that 57% of stroke patients received antihypertensive therapy following admission; of these, 54.5% continued preadmission drugs and 45.5% had therapy introduced de novo. Furthermore, there was significant variability in the thresholds used to intervene, 67% using SBP > 180 mmHg and 33% using values < 180 mmHg.[44] With respect to hypotensive BP levels, up to 12% of patients were reported to receive inotropic support in a European survey of acute physiological stroke management.[46]

Until recently the therapeutic management of BP in the acute stroke period has largely been based on anecdotal reports in the medical literature, which have highlighted the potential benefits of pressor agents[47–49] and the potential adverse effects of depressor therapy.[50,51] However, limited data are now available from randomised, placebo-controlled trials regarding the therapeutic management of acute stroke BP, as recently reviewed in the Cochrane Blood Pressure in Acute Stroke Collaboration.[52] Beta-blockers may theoretically be of benefit by limiting catecholamine-induced cardiac and neurological damage and by reducing the metabolic demands of ischaemic brain; however, they were associated with a non-significant change in 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).[53] Calcium channel antagonists may have a cerebroprotective effect by limiting post-ischaemic intracellular calcium influx. In addition, these agents may be beneficial in acute stroke because of a preferential vasodilatory action on cerebral blood vessels with an increase in cerebral blood flow. These agents have been assessed orally and intravenously in acute ischaemic stroke[54–57] and, although effective in reducing early BP, there was no significant effect on early or end-of-trial mortality.[52] We have recently shown in a randomised placebo-controlled trial[58] that bendroflumethiazide has no hypotensive effect following acute stroke. Transdermal nitrates in a small study of acute ischaemic stroke patients caused a small BP reduction compared with placebo,[59] and may improve regional cerebral blood flow;[60] however, the use of a transdermal nitrate preparation does not result in a sustained hypotensive effect, even with incremental dose titration.[61] Furthermore, the clinical usefulness of nitrates may be limited by tachyphylaxis and lack of 24-hour BP control.[62]

However, there is good evidence to support the use of an angiotensin-converting enzyme inhibitor (ACEI) in acute stroke to reduce BP. Captopril[63] and perindopril[64] have been shown to reduce systemic BP without adverse effects on cerebral blood flow, even in the presence of significant carotid artery disease,[65] in patients treated within 7 days of acute ischaemic stroke. Oral lisinopril has been shown to be safe and effective in treating hypertension in the acute post-stroke period when commenced within 24 hours of ictus.[66] Perindopril[67] and ramipril[68] have also been shown to provide secondary prevention by reducing stroke recurrence and other cardiovascular events in both ischaemic and haemorrhagic stroke patients, although therapy was not introduced in the majority of patients until at least 2 months after index stroke. Other drugs acting on the renin–angiotensin system have also been studied acutely. Candesartan, an angiotensin type 2 receptor antagonist, has been assessed in severely hypertensive (> 180/105 mmHg) acute ischaemic stroke patients, comparing acute (< 72 hours) and delayed (> 7 days) intervention.[69] Results were significantly in favour of the candesartan group, with an OR of 0.475 (95% CI 0.252–0.895) for cumulative 12-month mortality and vascular events.[70] There is some preliminary evidence to support the use of labetalol, a combined alpha- and beta-blocker, in both haemorrhagic[71] and ischaemic[72] stroke patients. A small pilot study of bolus intravenous labetalol following intracerebral or subarachnoid haemorrhage showed a 6–19% fall in SBP from baseline, without adverse haemodynamic effects. In the National Institute of Neurological Disorders and Stroke (NINDS) trial of thrombolysis for acute ischaemic stroke, 9% of patients in the placebo arm were hypertensive (> 185/110 mmHg) and received intravenous labetalol therapy. The OR for death at 3 months was significantly reduced compared with hypertensive patients in the placebo group who did not receive labetalol therapy (0.1, 95% CI 0.1–0.7). Interpretation of this post hoc analysis is difficult because use of labetalol was not randomised.

Although induced hypertension is a standard treatment for cerebral ischaemia in patients with vasospasm after subarachnoid haemorrhage, there are few experimental data or human data to support this practice following acute ischaemic stroke. Increasing BP levels in patients with low systemic BP values could reduce focal cerebral injury by increasing intraluminal hydrostatic pressure, opening collateral channels and improving perfusion to penumbral ischaemic tissue.[73,74] Hypervolaemia has been used in isolation[75] and with dobutamine[76] and is associated

with neurological recovery in stroke patients with middle cerebral artery occlusion, albeit in series of five and one patients respectively. Inotropes have also been used in larger patient series.[77,78] Rordorf and colleagues[77] infused phenylephrine in a series of 13 acute stroke patients at a rate of 40–300 µg/minute to maintain a 20% increase from baseline systolic BP over a period of at least 60 minutes. The infusion was maintained for a period of up to 6 days in responders, of whom there were seven, who maintained an improvement in their National Institutes of Health Stroke Scale (NIHSS, see Appendix 4d) score of > 2 until discharge.[77] Noradrenaline infusion has also been used to induce hypertension in a group of 19 acute complete or subtotal middle cerebral artery territory stroke patients and is associated with enhanced cerebral perfusion without detrimental increases in intracranial pressure.[78] Two recent reviews[79,80] concluded that pressor therapy in acute stroke is feasible and safe but increases resource utilisation. In summary, evidence in support of pressor therapy/induced hypertension is largely anecdotal, and its effects on clinically relevant outcomes have not been clarified.

In conclusion, hypertension and marked hypotension following acute stroke may be associated with a significant, but potentially reversible, increase in morbidity and mortality. The therapeutic management of BP in the acute stroke phase is thus associated with great uncertainty. Preliminary experience with both depressor and pressor agents has demonstrated that BP manipulation is potentially achievable in acute stroke. However, the effects of acute BP manipulation on short- and long-term outcomes are unclear, as are the ideal choice of agents, the timing, dose and route of administration, and the safety and efficacy of such therapy. Whether all stroke types benefit from such interventions and whether outcomes are dependent on initial stroke severity are also uncertain.

The Controlling Hypertension and Hypotension Immediately Post stroke (CHHIPS) study was designed to try and answer these questions. The primary study objective was to assess the effects of acute pressor and depressor BP manipulation on 2-week death and dependency following acute stroke. The secondary objectives were to establish the safety of acute pressor (0–12 hours post stroke) and depressor (0–36 hours post stroke) BP manipulation in stroke patients as assessed by the absence of early (< 72 hours) neurological deterioration; to investigate if beneficial or detrimental effects of BP manipulation are influenced by stroke type (ischaemic versus haemorrhagic); to determine if alternative therapeutic routes (including sublingual and intravenous) are effective in dysphagic stroke patients; to investigate if beneficial or detrimental effects of BP manipulation are influenced by the time to treatment; and to determine the short- and medium-term cost-effectiveness of the acute pressor and depressor therapy in relation to mortality.

# Chapter 2
# Methods

## Study design

The study was a prospective, randomised, double-blind, matching, placebo-controlled design. Patients were allocated to either the pressor or depressor arm depending upon their blood pressure at randomisation.

## Recruitment

Of the 10 centres originally expressing an interest in participating in the trial, only five initially took up the offer of funding. Reasons for non-participation included level of intensity of work involved in the trial, lack of adequate acute monitoring facilities and trained staff, competing commercial clinical trials, and perceived inability to recruit patients or research staff. Four sites participating in the trial, Leicester (Leicester General Hospital, Leicester Royal Infirmary, The Glenfield Hospital), Newcastle-upon-Tyne (Freeman Hospital), Bournemouth (Royal Bournemouth Hospital) and Exeter (Royal Devon and Exeter Hospital), were allocated funding for clinical research fellows and agreed to undertake all aspects of the trial. The fifth site, Aintree University Hospital, Liverpool, was funded for a research nurse and undertook only the non-dysphagic depressor limb of the trial. Recruitment began in January 2004 for an initial proposed period of 30 months, although because of low numbers this was extended to 36 months in three of the centres – Leicester, Newcastle and Aintree. This difference in duration of recruitment occurred because two centres could not retain or recruit further research fellows within the time frame of trial recruitment when the initial personnel returned to their clinical training. As recruitment was lower than proposed, and with multicentre research ethics committee (MREC) approval, an additional centre was subsequently enrolled at Ashington (Wansbeck Hospital) in October 2005, a research nurse working with support from the research fellow at Newcastle.

## Participants

Patients admitted with a fixed neurological deficit of over 60 minutes duration and a potential diagnosis of an acute stroke were identified by researchers at each of the six participating sites from A&E departments, medical admission and stroke units and general inpatient beds. Stroke was defined as a rapid onset of symptoms and/or signs involving a focal or global loss of function with no other apparent cause. The following inclusion and exclusion criteria were applied:

### Inclusion criteria

- Age > 18 years.
- Stroke onset < 36 hours; initially 24 hours (< 12 hours for pressor arm). For patients waking with suspected stroke, time of onset was taken as the last time the patient was documented to be free of stroke symptoms.
- Clinical diagnosis of suspected stroke, with neuroimaging before (for all pressor arm patients) or following study entry to exclude non-stroke diagnoses and to define ischaemic and haemorrhagic stroke.
- Hypertension was defined as an SBP > 160 mmHg from the mean of six supine BP recordings (using a validated BP monitor and cuff of suitable size) taken over a 10-minute period. Relative hypotension was defined as an SBP ≤ 140 mmHg, again using the mean of six BP recordings.
- Informed patient consent or relative/independent clinician assent.

### Exclusion criteria

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

- Pre-existing antihypertensive therapy in non-dysphagic patients [who were entered into the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS)].
- Impaired consciousness level (NIHSS[81] Section 1a score ≥2; see Appendix 4d).
- Intracerebral haemorrhage (pressor arm) diagnosed by neuroimaging before trial entry.
- Contraindications to trial therapy:
  - lisinopril, e.g. history of angio-oedema related to ACEI therapy, impaired renal function (serum creatinine > 200 µmol/l)
  - labetalol, e.g. asthma, second- or third-degree heart block, uncontrolled heart failure
  - phenylephrine, e.g. uncontrolled angina, past medical history of arrhythmias or occlusive vascular disease.
- Premorbid dependence [modified Rankin Scale (mRS) score > 3].[82]
- Co-existing life-threatening condition with life expectancy < 6 months.
- Females of child-bearing potential.
- Non-stroke diagnoses (on subsequent neuroimaging).

## Consent

Eligible patients interested in the study were invited to read a patient information leaflet detailing the nature of the study along with the potential risks and benefits of participating. After obtaining written and witnessed consent, subjects were randomised. If subjects were unable to give written informed consent, relative assent was accepted or, if this was not feasible, independent clinician assent could be obtained until a relative was available or the patient recovered enough to give consent.

## Randomisation

Consenting patients fulfilling the trial entry criteria were randomised by secure internet central randomisation (block size six) to receive either active treatment or matching placebo in a ratio of 2:1 between active treatment and matching placebo (depressor arm) and 1:1 between active treatment and matching placebo (pressor arm). Each researcher had a unique username and password allowing an audit trail of data entry. Researchers were blinded to patients' treatment randomisation until the end of the trial in April 2007. During the trial each site was asked to maintain a log of patients who were screened detailing whether they were eligible for the study or, if ineligible, giving the reasons for exclusion. Specific baseline neurological assessments performed at randomisation included NIHSS, mRS and Oxfordshire Community Stroke Project (OCSP)[83] classification (see Appendix 4e).

## Usual care

All routine management of patients with suspected stroke with respect to investigation [including haematology, biochemistry, chest radiology and electrocardiography (ECG)], acute management and rehabilitation were continued as standard local practice, including casual BP observations and the timing of introduction of antithrombotic therapy. Neuroimaging was not a requirement before randomisation in the depressor arm but was necessary before randomisation in the pressor arm to exclude cerebral haemorrhage. Standard secondary preventative treatment was initiated by the local investigators, although decisions regarding future antihypertensives were delayed until the end of the trial intervention (2 weeks); however, no protocol for this was specified by the co-ordinating centre.

## Blood pressure measurement and stroke onset

Before randomisation BP was taken as the mean of six supine recordings made over 10 minutes using a validated BP monitor (UA-767 monitor and cuff of the appropriate size) conducted by suitably trained research staff. Hypertension was defined as a mean SBP level of > 160 mmHg and relative hypotension as a mean SBP level of ≤ 140 mmHg. Time of stroke onset required clear definition; for those patients waking with suspected stroke, time of onset was taken as the last time the patient was documented to be free of stroke symptoms.

## Time window

Patients were eligible for pressor therapy within 0–12 hours of stroke onset, whereas those eligible for depressor therapy could be treated up to 36 hours from onset. The initial protocol allowed recruitment into the depressor arm only up to 24 hours from onset, but this was amended in May 2005 to increase recruitment of patients who would potentially benefit from intervention. Although BP reduction may have differential time effects related to the ischaemic penumbra and reducing stroke

recurrence it was anticipated that BP elevation would be important only when the penumbra was viable, and therefore patients eligible for pressor therapy were only randomised during the hyperacute time window (0–12 hours) when salvageable penumbra was likely to be present.

## Dysphagia

Patients were defined as dysphagic or non-dysphagic on the basis of a standardised bedside swallow assessment by appropriately trained staff, performed as part of the routine clinical assessment of a patient with suspected stroke in all participating centres. It was anticipated that 25% of patients would initially be dysphagic, affecting the ability to take medication orally. To ensure inclusion of this important subgroup, patients were stratified by the presence of dysphagia; such patients were independently randomised to sublingual or intravenous therapy.

## Trial medication supplies

All drugs were centrally manufactured by the pharmaceutical company (DHP) and shipped directly to the individual centres. The local production of suspension at the time of drug administration was necessary because of the short shelf life of suspension preparations.

## Depressor arm

Hypertensive, non-dysphagic patients were randomly assigned to receive either oral lisinopril 5 mg or oral labetalol 50 mg or oral matching placebo. Hypertensive, dysphagic patients received either sublingual lisinopril 5 mg and intravenous placebo, or intravenous labetalol 50 mg bolus injection (over a period of at least 1 minute) and sublingual placebo, or sublingual and intravenous placebo. All patients were asked to remain supine for a 30-minute period following each intravenous bolus injection. Placebo and active tablets were matched for size, shape and colour; similarly, labetalol and phenylephrine and placebo vials for intravenous administration were matched for size, shape and colour.

Brachial artery BP was monitored at 30-minute intervals for 4 hours post dose; patients developing symptomatic or asymptomatic hypotension (SBP < 140 mmHg) during this period had study medication discontinued. At 4 hours in those patients not achieving the target SBP of 145–155 mmHg or a 15 mmHg reduction in SBP from levels at randomisation, further treatment doses were given: non-dysphagic patients received oral lisinopril 5 mg or oral labetalol 50 mg or oral matching placebo; dysphagic patients received sublingual lisinopril 5 mg and intravenous placebo, or intravenous labetalol 50 mg bolus injection (over a period of at least 1 minute) and sublingual placebo, or sublingual and intravenous matching placebo.

BP was monitored for a further 4 hours post dose (i.e. until 8 hours post randomisation). Again, in those patients not achieving the target SBP of 145–155 mmHg or a 15 mmHg reduction from baseline SBP at 8 hours, a further treatment dose was given: non-dysphagic patients received further oral lisinopril 5 mg or oral labetalol 50 mg or matching placebo; dysphagic patients received further sublingual lisinopril 5 mg (and intravenous placebo) or intravenous labetalol 50 mg bolus injection (over a period of at least 1 minute) (and sublingual placebo) or sublingual and intravenous matching placebo. No further trial medication was give after 8 hours until 24 hours after the initial dose following randomisation.

The established treatment regimes for non-dysphagic patients were then continued for a 2-week period as follows: oral lisinopril 5, 10 or 15 mg once daily in the morning with matching placebo in the evening to give a twice-daily dosage regime or oral labetalol 50, 100 or 150 mg twice daily or oral matching placebo twice daily. Dysphagic patients received the established treatment regimes for 72 hours as follows: sublingual lisinopril 5, 10 or 15 mg once daily and intravenous placebo, or intravenous labetalol 50, 100 or 150 mg bolus injection (over a period of at least 1 minute) twice daily and sublingual placebo, or sublingual and intravenous matching placebo.

At 72 hours the dysphagic patients had their swallow reassessed, and those patients remaining dysphagic at 72 hours received treatment with lisinopril or labetalol or matching placebo suspension via nasogastric or percutaneous endoscopic gastrostomy (PEG) feeding tube. Those patients who regained their swallow received lisinopril or labetalol or matching placebo suspension orally. Therefore, all dysphagic patients received two trial treatment packages. The first trial treatment pack enabled sublingual and intravenous active treatment and/or matched placebo treatment for 72–96 hours. The second trial treatment pack contained lisinopril or labetalol or placebo tablets

to be crushed locally and made into a suspension to be administered via nasogastric/PEG tube or orally according to the patient's swallow until 2 weeks.

## Pressor arm

Hypotensive patients with or without dysphagia were recruited within 12 hours of stroke onset to the pressor arm of the study. Before study treatment all patients were required to have neuroimaging to exclude primary intracerebral haemorrhage (PICH) or other non-ischaemic stroke pathology. As induced hypertension may be associated with haemorrhage or oedema[11] it was not considered safe to expose patients with PICH to pressor therapy. The patient's hydration status was also assessed by clinical examination and laboratory estimation of urea and creatinine before study treatment to ensure that patients were euvolaemic. To reduce the risk of potential hypovolaemia, normal saline was infused at a rate of 100 ml/hour throughout the treatment period in all patients. BP monitoring and treatment were carried out in an acute stroke or high-dependency unit (dictated by a nurse–patient ratio of 1:2) during the medication infusion period. Patients were fitted with chest leads for continuous ECG recording and an appropriately sized cuff of the Finapres/Portapres non-invasive beat-to-beat BP monitor. The cuff was fitted to the middle finger or thumb of the hemiparetic arm and maintained at heart level. After achievement of a satisfactory BP signal and the stabilisation of BP (mean 2-minute BP levels not varying by $> 10$ mmHg over $\geq 10$ minutes), patients received either intravenous phenylephrine at a rate of 60 µg/minute (1 ml/minute) or matching intravenous placebo. Phenylephrine 30 mg (10 mg/ml)/placebo was diluted in 500 ml of 0.9% sodium chloride. Pressor therapy was continued for up to 24 hours after stroke onset (minimum pressor stimulus 12 hours). As it was considered unlikely that the benefits of pressor therapy would extend beyond the period of penumbral viability, it was not considered ethical to expose patients to the potential risks of pressor therapy beyond this time. Furthermore, the costs and inconveniences of continuous non-invasive BP monitoring did not justify the continuation of therapy for longer. The infusion rate was adjusted by 30 µg/minute (0.5 ml/minute) increments at 30-minute intervals to maintain an increase in SBP to the target SBP of 150 mmHg (range 145–155 mmHg) or a 15 mmHg increase above baseline values. A maximum infusion rate of intravenous phenylephrine of 180 µg/minute (3 ml/minute) or of intravenous matching placebo was allowed.

## Changes to protocol

The following changes were made to the original trial protocol (all dates quoted are those of MREC amendment approval):

1. Protocol amendments 1 and 2 were approved in February 2004 to incorporate the dosing regime for use of intravenous labetalol and to add on the baroreceptor sensitivity/blood pressure variability substudy respectively. The results of this substudy will not be reported here.
2. Protocol amendment 3, approved in May 2004, permitted the use of transcranial ultrasound to monitor cerebral blood flow and autoregulation in the cerebral blood flow/cerebrovascular autoregulation substudy (this substudy was funded by the Stroke Association and the results are not considered in this report).
3. Protocol amendments 4 and 5 were initially submitted for further substudies; however, following the introduction of the European Clinical Trials Directive these were subsequently approved as separate studies in their own right.
4. Protocol amendment 6 in July 2004 permitted the inclusion of dysphagic patients on previous antihypertensive therapy to improve recruitment. Patients receiving previous antihypertensive therapy who were *not* dysphagic were considered for the COSSACS study. This protocol amendment also allowed inclusion of those with a pre-stroke mRS score of 3 or less (having previously been 2 or less).
5. Protocol amendment 7 in February 2005 allowed the collection of health economic data, which was described in the initial trial protocol as a cost-effectiveness analysis. The protocol was amended to specify inclusion of health economics and the use of a patient diary, the EuroQoL 5-dimensional questionnaire (EQ-5D), at 2 weeks and 3 months, along with a structured telephone interview at 3 months if patients were willing (see Appendix 4c). Non-consent to this phase of the study did not exclude patients from the main study.
6. Protocol amendment 8, approved in June 2005, extended the window of recruitment for the depressor arm from 24 to 36 hours post stroke. As it was felt that any effect of pressor therapy would occur only whilst the penumbra remained viable, the time window for the pressor arm remained 12 hours from stroke for the duration of the study. In addition, the original trial was scheduled to recruit until the end of June 2006, and this was extended to the

end of December 2006 to recruit a sufficient number of patients into each arm.

Because of limited recruitment to the pressor phase of the study this limb of the trial was terminated after consultation with the Health Technology Assessment (HTA) Programme and MREC in April 2005.

## Study objectives

The primary objective was to assess the effects of acute pressor and depressor BP manipulation on 2-week death and dependency following acute stroke.

The secondary objectives were to:

- establish the safety of acute pressor (0–12 hours post stroke) and depressor (0–36 hours post stroke) BP manipulation in stroke patients as assessed by the absence of early (72 hours) neurological deterioration
- investigate if beneficial or detrimental effects of BP manipulation are influenced by stroke type (ischaemic versus haemorrhagic)
- determine if alternative therapeutic routes (sublingual, intravenous) for administering depressor therapy are effective at lowering BP in dysphagic stroke patients
- investigate if beneficial or detrimental effects of BP manipulation are influenced by time to treatment
- assess the cost-effectiveness and cost–utility of active treatment in relation to death and dependency, mortality and quality-adjusted life-years (QALYs) gained over a period of 2 weeks and 3 months.

## Outcome measures

Data were collected on time and cause of death up to 3 months following the index event. Dependency was measured at baseline and at 2 weeks using the Barthel Index and the mRS) (see Appendices 4a and 4b). Neurological deficit was assessed using the NIHSS, which was recorded at baseline and at 24, 48 and 72 hours and again after 2 weeks. BP was recorded at baseline, at 4, 8 and 24 hours and at 2 weeks by taking the average of six readings using the UA-767 BP machine. Information was collected regarding routine haematological and biochemical parameters (full blood count, urea and electrolytes, glucose, cholesterol), ECG findings and the results of neuroimaging. An EQ-5D questionnaire was performed at 2 weeks and again at 3 months (if patients were willing to undergo this) following the approval of protocol amendment 7. Baseline and 2-week assessments were performed by trained research staff in the participating centres, whereas 3-month follow-up was performed centrally by telephone from the coordinating centre.

## Serious adverse events

Reporting of all serious adverse events (SAEs) was required for all patients up to 2 weeks (i.e. the intended duration of study medication). Information was collected regarding severity (mild, moderate, severe or fatal), causality in terms of relation to treatment (definite, uncertain or no causality) and system affected (e.g. neurological, respiratory). All expected SAEs were reported to the Trial Steering Committee and the Data Safety Monitoring Committee on a 6-monthly basis. Reporting of sudden unexpected serious adverse events (SUSARs) was mandatory, as per the European Clinical Trials Directive (fatal or life-threatening events reported within 7 days, non-life-threatening events reported within 15 days to the sponsor).

## Sample size

It was postulated that there would be a 60% death or dependency rate at 2 weeks in the placebo arm of the trial[39] with a dropout rate of 15%. Therefore, in the depressor arm of the trial 1650 patients (550 in each group) would need to be recruited to have an 80% power at the 5% significance level to detect a relative reduction of 15% (or absolute risk reduction of 9%) in death and dependency between either of the two treatment groups and the placebo group. Assuming a standard deviation of 30 mmHg in casual SBP measurements in each group, the minimum detectable BP difference between the active treatment and placebo groups with 500 patients in each group and an 80% power at the 5% significance level is 5.1 mmHg.

It was anticipated that approximately 20% of patients would have an admission SBP of ≤ 140 mmHg.[39] Therefore, recruiting 400 patients (200 in each group) to the pressor arm of the trial would have an 80% power at the 5% significance level to detect a relative reduction of 25% in death and dependency between the active treatment and placebo groups, assuming a patient dropout rate of 15%.

Therefore, if both depressor and pressor arms of the trial were undertaken, a total of 2050 patients would have to be recruited to the trial, at a rate of approximately seven patients per centre per month during a 30-month recruitment period, assuming that 10 centres were actively recruiting. Stroke registers maintained by the acute stroke units prior to participating in the CHHIPS trial confirmed that between 500 and 800 patients were admitted per annum at each centre, 91% within 24 hours.

After the trial began, significant problems were encountered with the screening and identification of eligible patients, and these are addressed in Chapter 4. After discussion with the Trial Steering Committee, various amendments were made to the original protocol to try and improve recruitment (see Changes to protocol); these are also considered in Chapter 3 (Recruitment).

There were initial difficulties in obtaining phenylephrine in 2004 because of manufacturing problems, there being no supplies in the UK for 2 months, which delayed the start of the pressor arm until March 2004. Subsequently, in line with the recommendation of the Trial Steering Committee and HTA, following significant problems recruiting hypotensive patients in the hyperacute post-stroke period amongst all centres it was agreed to close the pressor arm to recruitment in April 2005. This allowed time and resources to be concentrated on improving recruitment into the depressor arm and ensuring complete data collection.

## Statistical analysis

Systolic and diastolic blood pressure levels at randomisation were calculated as the average of six readings. Stroke was classified as ischaemic (evidence of an infarct or haemorrhagic transformation of infarct in keeping with the physical signs at presentation), PICH or no relevant abnormality on neuroimaging [standard computerised tomography (CT) scanning in all centres]. Patients were excluded from the intention to treat analysis if imaging confirmed a diagnosis other than acute stroke. The primary end point was death and dependency at 2 weeks, with dependency defined as an mRS score of greater than 3.

All continuous measures are approximately normally distributed. Binary outcomes – death and dependency at 2 weeks, or change in NIHSS score at 72 hours greater than 3 points – were analysed by logistic regression. Regression analysis was used to compare continuous outcomes by and across treatment groups. Repeated measures analysis of SBP at baseline and at 4, 8 and 24 hours was carried out using generalised estimating equations (GEE) modelling with unstructured correlation. The model included time, treatment and time by treatment interaction terms. Analyses were first undertaken of active treatment compared with placebo, followed by comparisons across the three treatment groups when appropriate. To protect the results from multiple tests, Fisher's protected least square difference (LSD) method was used. Statistical significance was set at 5% and, if no significant difference was found across the three groups for a particular outcome measure, no further subgroup analysis was performed. Survival data were analysed by Cox's proportional hazards model with non-parametric Kaplan–Meier plots. Significance levels were set at 5%.

## Health economic analysis

Economic analyses of the CHHIPS study data were carried out to determine the cost-effectiveness of active treatment versus placebo.

The primary outcomes were incremental cost per incremental survivor at 3 months of active treatment versus placebo, and incremental cost per incremental QALY gained at 14 days and 3 months. Additional analyses comparing death and dependency at 14 days and death at 14 days were performed. Date of death was collected for each patient. An mRS score of 6 was given to those patients who had died.

As baseline EQ-5D data were not available and limited observations were available at 3 months, it was not possible to directly calculate QALYs gained from EQ-5D scores. Therefore, utilities were mapped to mRS scores calculated from a previous study.[84] In this study, 459 individuals completed a number of outcome measures at 6 months post stroke, and the utility of the mRS scores was estimated using the time trade-off approach (*Table 1*).

These utility scores were compared with utility scores estimated by converting the EQ-5D profiles reported in the trial using the standard UK valuation set.[85] QALYs gained were subsequently estimated based on the mRS-based utilities.

Our original intention was to perform the analyses from a societal perspective. However, because of small sample sizes, the perspective was limited

***TABLE 1*** *Time trade-off health state valuations*

| | mRS score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 (dead) |
| Years in current state | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Years at full health | 9.27 | 8.77 | 7.3 | 6.86 | 5.43 | 3.36 | 0 |
| Utility | 0.927 | 0.877 | 0.73 | 0.686 | 0.543 | 0.336 | 0 |

Figures show mean point of indifference between the number of years spent with a given mRS score and the number of years spent in full health, e.g. subjects were indifferent between 10 years at an mRS score of 5 and 3.36 years at full health. The utility is the ratio between the two.
From Duncan *et al.*[84]

to that of the acute hospital admitting the stroke patient. Drug acquisition costs were used to represent the cost of study drugs. Intravenous labetalol was administered as a bolus over 1 minute and so any additional cost incurred by this route of administration would be small. All patients who received intravenous agents were hospital inpatients and therefore no additional cost was incurred for home administration or district nurse or GP time. The number of tablets or vials used was averaged over the intervention period of 14 days. Hospital length of stay (LoS) was used to measure the hospitalisation cost.

The price year was 2006. Sources other than 2006 were converted to 2006 prices using the Consumer Prices Index (CPI). LoS was calculated as (date of discharge or date of death) – date of randomisation. For patients not yet discharged, LoS was truncated at 14 or 84 days as follows. When date of discharge was recorded as more than 3 months post randomisation, LoS was set to a maximum of 84 days. When date of discharge was not recorded, but it was known that patients were still in hospital at day 14, the observations were used in the 14-day analysis but counted as missing in the 3-month analysis.

To calculate the cost of a hospital admission the *National Schedule of Reference Costs*[86] was used, which calculated the mean cost of a stroke admission to be £2462, based on a mean LoS of 11 days. The daily cost of excess bed-days is £176. Inpatient costs tend to be skewed towards the first few days of admission. Therefore, to allow for this, cost of admission is calculated as £2462+(LoS−11) × 176.

The results are presented as quantities of resource use and total cost by treatment group [labetalol, lisinopril, active treatment (labetalol and lisinopril combined) and placebo]. Quantities of resource use and costs are compared using *t*-tests and analysis of variance (ANOVA) as appropriate. Incremental cost-effectiveness ratios (ICERs) are calculated as:

$$\text{ICER} = (C_2 - C_1)/(E_2 - E_1)$$

where $C_2$ and $E_2$ are the cost of and QALYs gained from active treatment respectively and $C_1$ and $E_1$ are the cost of and QALYs gained from placebo. This expresses the extra cost to generate one extra unit of outcome (e.g. extra survivor).

Confidence intervals around incremental costs and outcomes, and cost-effectiveness acceptability curves (CEACs) are generated using a non-parametric bootstrap with 1000 replications. The CEAC shows the strategy with the highest probability of being cost-effective at varying thresholds of willingness to pay for a unit of outcome. We also present results as incremental net benefit (INB) curves, in which:

$$\text{INB} = \lambda(E_2 - E_1) - (C_2 - C_1)$$

where λ is the willingness to pay for a unit of outcome and INB can be interpreted as the monetary value of the benefits less the value of the costs. A value greater than zero implies that the added benefits are valued more highly than the added costs; therefore the intervention would be deemed cost-effective. As the value of λ is unknown, the curve plots for a range of values (a value of λ of between £20,000 and £30,000 per QALY gained or £1m per premature death averted is thought to be a 'reasonable' willingness to pay for a unit of health outcome). As baseline characteristics of treatment groups are similar, no adjustment for baseline differences was carried out.

# Chapter 3
# Results

## Screening data

Local trial co-ordinators at the four centres participating in both the pressor and the depressor limbs of the CHHIPS study kept a record of patients screened during set periods of the trial. It was not possible to keep a complete 24-hour analysis of all stroke admissions for the whole trial period because of staffing levels. In total, 2361 patients were screened during periods lasting between 14 and 19 months in the four centres; 94 had been discharged or had died before the researcher could review them, leaving a total of 2267 patients with a clinical presentation of stroke (*Table 2*). Non-stroke patients (i.e. those with stroke mimics) and those with transient ischaemic attacks (TIAs; symptoms and signs having resolved by the time the patient was reviewed by a researcher) have been excluded from this analysis as they were ineligible for the trial.

Those who were on antihypertensive medication and able to swallow were excluded as per protocol and considered for another clinical trial. The remaining patients were split into three groups based on systolic blood pressure: SBP > 160 mmHg (depressor group); SBP 141–160 mmHg (excluded from CHHIPS); and SBP ≤ 140 mmHg (pressor group). A schematic breakdown of the patients is depicted in the flowchart in *Figure 1*.

## Depressor arm

Of the patients with a SBP of > 160 mmHg, i.e. 'potential CHHIPS depressor group' ($n = 578$), 396 had exclusion criteria, specified in the protocol, and 182 (8.1%) were eligible at the time of hospital presentation. A total of 66 (2.9% of all screened but 36.3% of all eligible patients at hospital presentation) were randomised to the CHHIPS depressor arm. The reasons for ineligibility of patients at hospital admission screening are given in *Figure 2* and *Table 3*, and the reasons for non-recruitment of patients initially eligible are given in *Figure 3* and *Table 4*.

## Pressor arm

The reasons for patient ineligibility at hospital admission for the revised CHHIPS pressor protocol are given in *Figure 4* and *Table 5*. In total, 11.4% 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). Patients presenting with a SBP of ≤ 140 mmHg and not on antihypertensive medication were categorised as 'potential CHHIPS pressor group'. The outcomes of potentially suitable CHHIPS pressor patients are presented in *Table 6*; among the 10 patients who were potentially suitable at hospital admission (0.4% of all screened), in three cases no clear reason for non-recruitment was found. The one patient recruited into the pressor arm was not recruited during the screening period.

## Recruitment

The CHHIPS study recruited 180 patients who had persistent neurological symptoms lasting more than 60 minutes from the six active recruiting

***TABLE 2*** *Breakdown of site contributions to screening register and resulting recruitment to CHHIPS*

| Site | Months | From | To | Number screened | Number recruited to CHHIPS | % recruited to CHHIPS |
|---|---|---|---|---|---|---|
| Bournemouth | 19 | Jan 2005 | Jul 2006 | 470 | 26 | 5.5% |
| Exeter | 15 | Jan 2005 | Mar 2006 | 282 | 13 | 4.6% |
| Leicester | 16 | Jan 2005 | Apr 2006 | 1104 | 18 | 1.6% |
| Newcastle | 14 | Apr 2005 | Jun 2005 | 411 | 9 | 2.2% |
| | | Jan 2006 | Nov 2006 | | | |
| Total | 64 | Months inclusive | | 2267 | 66 | 2.9% |

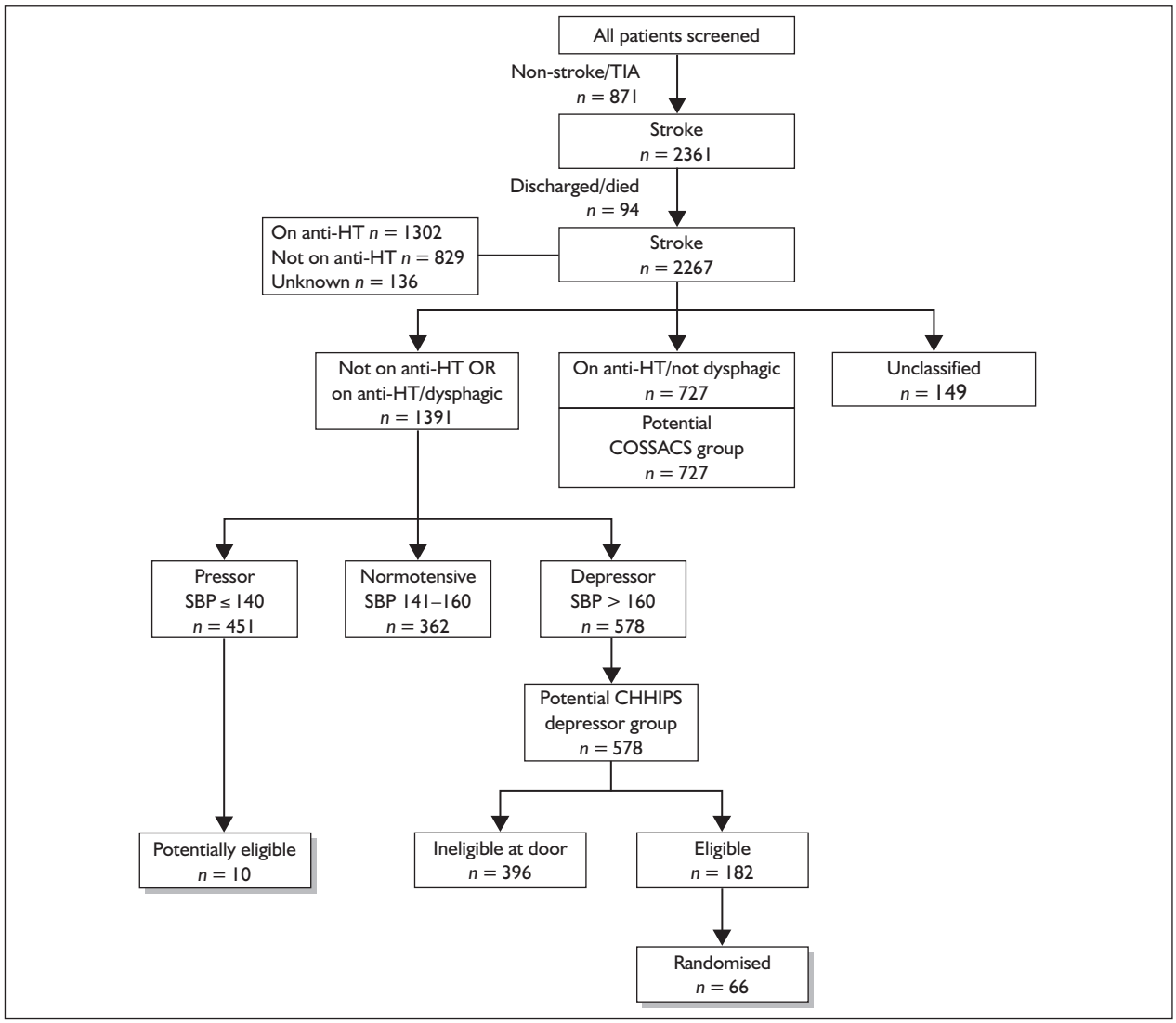


***FIGURE 1*** *Schematic breakdown of patients screened and randomised for the CHHIPS study from the log. Anti-HT, antihypertensive treatment; COSSACS, Continue Or Stop post-Stroke Antihypertensives Collaborative Study; SBP, systolic blood pressure; TIA, transient ischaemic attack.*

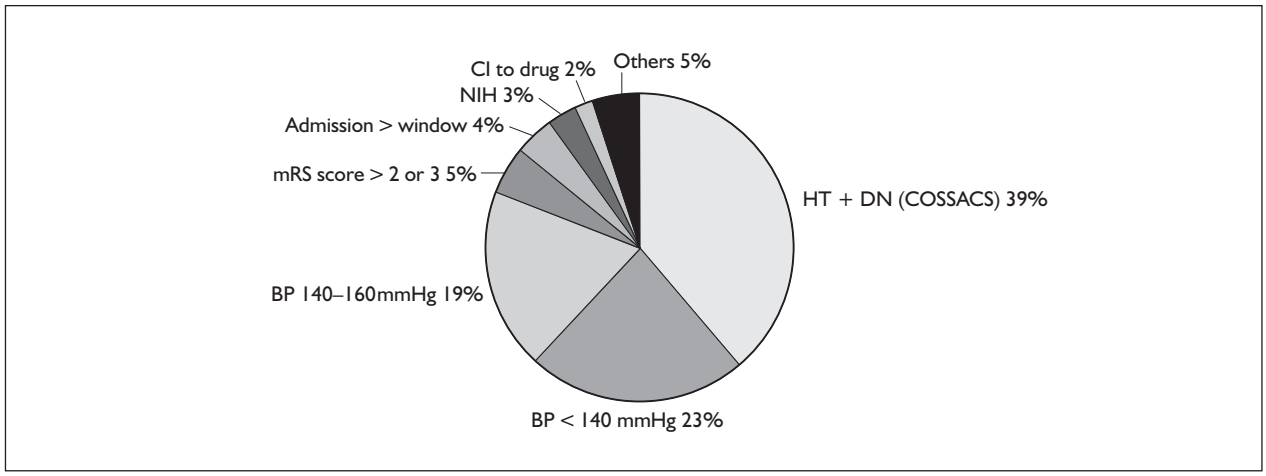


***FIGURE 2*** *Pie chart illustrating reasons for patient ineligibility (n = 1936) at hospital admission for revised CHHIPS depressor protocol. CI, contraindication; DN, not dysphagic; HT, on antihypertensives; NIH, NIHSS Section 1a score of > 1, i.e. depressed consciousness level.*

***TABLE 3*** *Reasons for patient ineligibility at hospital admission for revised CHHIPS depressor protocol*

| Exclusion criterion | Number |
|---|---|
| On antihypertensive therapy | 727 |
| BP ≤ 140 mmHg | 451 |
| BP 140–160 mmHg | 362 |
| mRS score > 2/3 (too dependent) | 104 |
| Admission > trial window | 80 |
| NIHSS Section 1a score > 1 (too drowsy) | 67 |
| Contraindication to drug | 43 |
| Others | 102 |
| Total | 1936 |
| Unclassified[a] | 149 |

BP, blood pressure; mRS, modified Rankin Scale.
a Unclear about antihypertensive drug therapy at time of admission and/or dysphagia status, but with other exclusion criteria for the depressor arm of the study.

***TABLE 4*** *Reasons for entry or non-entry of eligible patients at the time of hospital admission to revised CHHIPS depressor protocol*

| Outcome | Number |
|---|---|
| Randomised | 66 |
| Within time window at presentation but outside by the time reviewed by researcher | 64 |
| Declined participation/unable to consent/no relative assent feasible | 26 |
| SBP > 160 mmHg documented at admission but lower (< 160 mmHg) when reviewed by researcher, therefore not eligible | 25 |
| Reason for exclusion unknown | 1 |
| Total eligible | 182 |

SBP, systolic blood pressure.

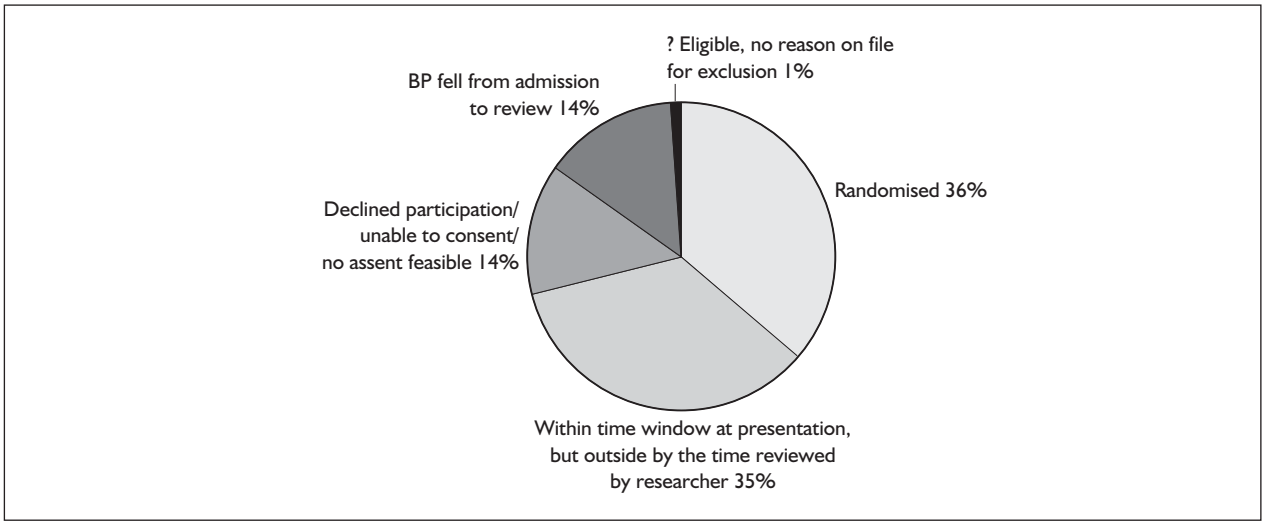


***FIGURE 3*** *Pie chart illustrating reasons for entry or non-entry of eligible patients (n = 182) at the time of hospital admission to revised CHHIPS depressor protocol. BP, blood pressure.*

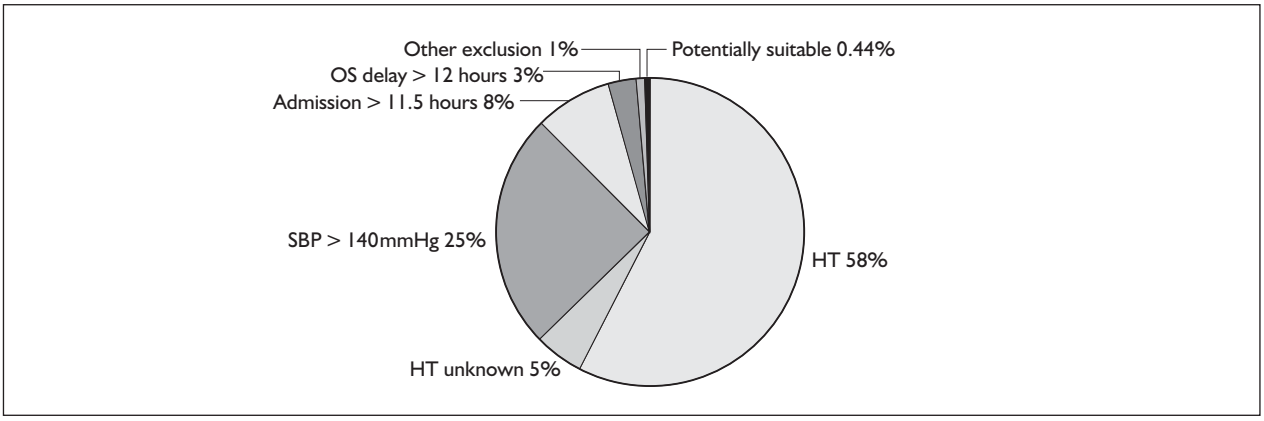


***FIGURE 4*** *Pie chart illustrating reasons for patient ineligibility at hospital admission (n=226) for revised CHHIPS pressor protocol. HT, antihypertensive therapy; OS, onset to screening time; SBP, systolic blood pressure.*

***TABLE 5*** *Reasons for patient ineligibility at hospital admission for revised CHHIPS pressor protocol*

| Reason for exclusion | Number |
|---|---|
| On antihypertensive treatment | 1302 |
| Antihypertensive status not known | 112 |
| SBP > 140 mmHg | 570 |
| OA delay unknown or > 12 hours | 180 |
| Screened > 12 hours from symptom onset[a] | 77 |
| mRS score> 2/3 (too dependent) | 5 |
| Thrombolysed (exclusion) | 3 |
| Uncertain diagnosis (exclusion) | 3 |
| Contraindication to drug | 2 |
| Non-consent | 2 |
| CT not performed | 1 |
| Potentially eligible | 10 (0.4%) |
| Total | 2267 |

CT, computerised tomography; mRS, modified Rankin Scale; OA, onset to admission.
a Assumes that unknown onset to admission delay equates to > 12 hours, i.e. ineligible.

***TABLE 6*** *Outcome of potentially suitable CHHIPS pressor patients*

| Outcome | Number | Location |
|---|---|---|
| No clear reason for non-recruitment | 3 | Exeter, Leicester, Newcastle (one each) |
| Presented after pressor arm of trial discontinued | 7 | |
| Total | 10 | |

centres over the course of the study, with 179 in the depressor arm and one in the pressor arm. Reasons why centres did not recruit to the numbers originally proposed included concerns about the intensity of monitoring required and suitable facilities, patients receiving thrombolysis and thus requiring open-label blood pressure control, decreasing numbers of potentially eligible patients (this was particularly true in terms of increasing numbers of patients being on antihypertensive medication on admission), and ongoing conflicting trials at the time that CHHIPS started recruiting. In addition to these considerations, each site had a dedicated research fellow or nurse and there was no provision for cover during periods of absence for study or annual leave (statutory holiday leave of 30 working days per annum) and weekend cover was ad hoc.

Seven patients were entered into the study but were subsequently withdrawn because of non-stroke diagnoses [one Bell's palsy, one subdural haematoma, one subarachnoid haemorrhage, one unspecified, one withdrawal of consent and two protocol violations (one on antihypertensive therapy and dysphagic before approval of protocol amendment 6 allowing inclusion of these patients and one intracerebral haemorrhage with systolic blood pressure > 200 mmHg)]. The primary end point was recorded for all 172 patients; thus, the retention rate was 96.7%. The patient in the pressor arm is not included in the analysis below as he or she was randomised to placebo.

The protocol amendments were effective at increasing recruitment. Of the total of 180 patients recruited, six (3%) had an mRS score of 3, 10 (5%) were receiving prior antihypertensive therapy but were dysphagic at entry, and 25 were recruited between 24 and 36 hours from stroke onset (13.9%).

## Compliance with randomised treatment

Out of 179 patients randomised in the depressor arm, seven were withdrawn for non-stroke diagnosis and 126 (73%) completed the full 14-day trial treatment as specified in the CHHIPS protocol; one patient was withdrawn before receiving any allocated treatment and a further 45 discontinued study medication at some point during the first 2 weeks. *Figure 5a* and *b*

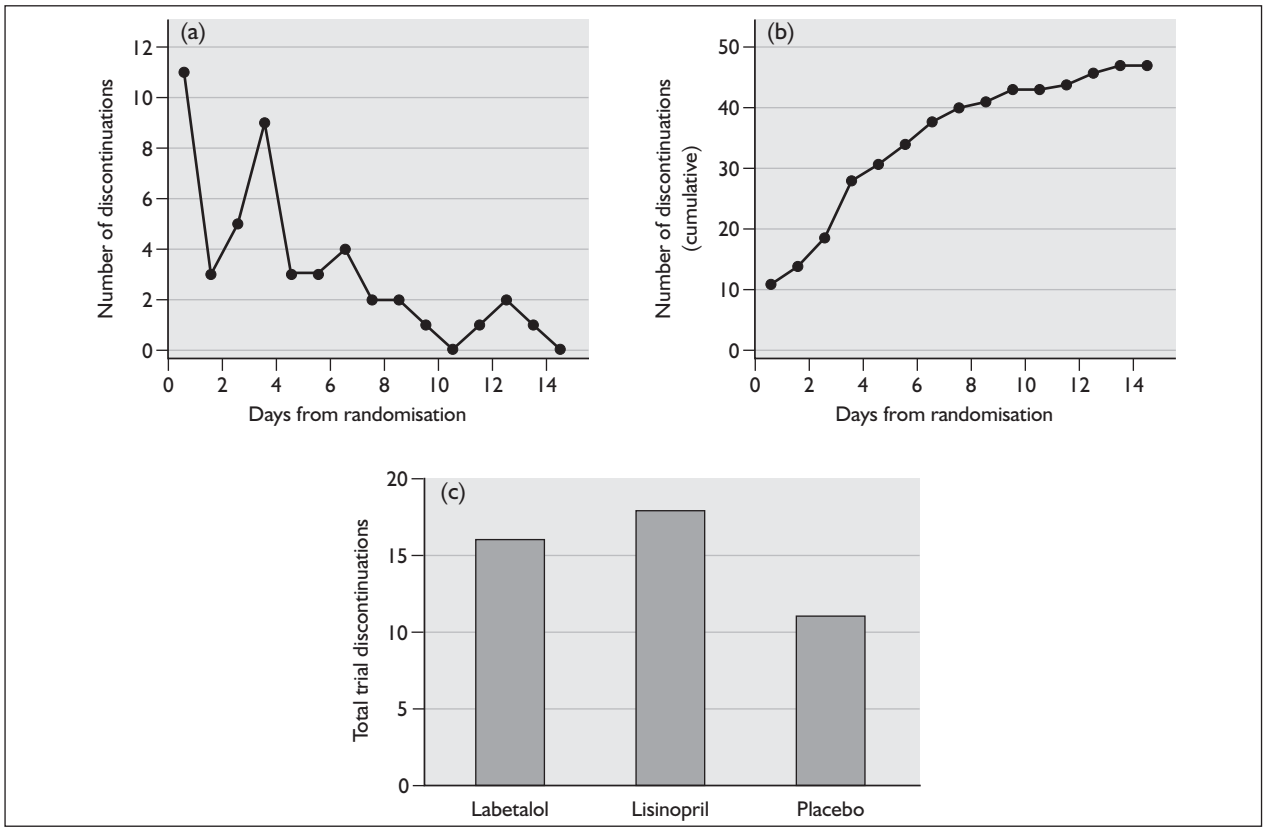


***FIGURE 5*** *(a) Trial medication discontinuations by time for active and placebo groups combined. (b) Cumulative trial medication discontinuations for active and placebo groups combined. (c) Total medication discontinuations by group.*

shows the timing of treatment discontinuation in days from randomisation. The total number of discontinuations by group [16 (28%) in the labetalol group, 18 (32%) in the lisinopril group and 11 (21%) in the placebo group] are shown in *Figure 5c*, and discontinuations by treatment group and dysphagia status are illustrated in *Figure 6a–e*. There was no significant difference between labetalol, lisinopril and placebo in the number of discontinuations ($p = 0.44$). Discontinuations because of SAEs are considered in more detail in the section on causality. A full list of medication discontinuations can be found in Appendix 1. The allocation of patients randomised in the depressor arm and the distribution of trial withdrawals is shown in the CONSORT diagram in *Figure* 7.

## Baseline characteristics

The labetalol, lisinopril and placebo groups were well matched for gender, age, systolic and diastolic

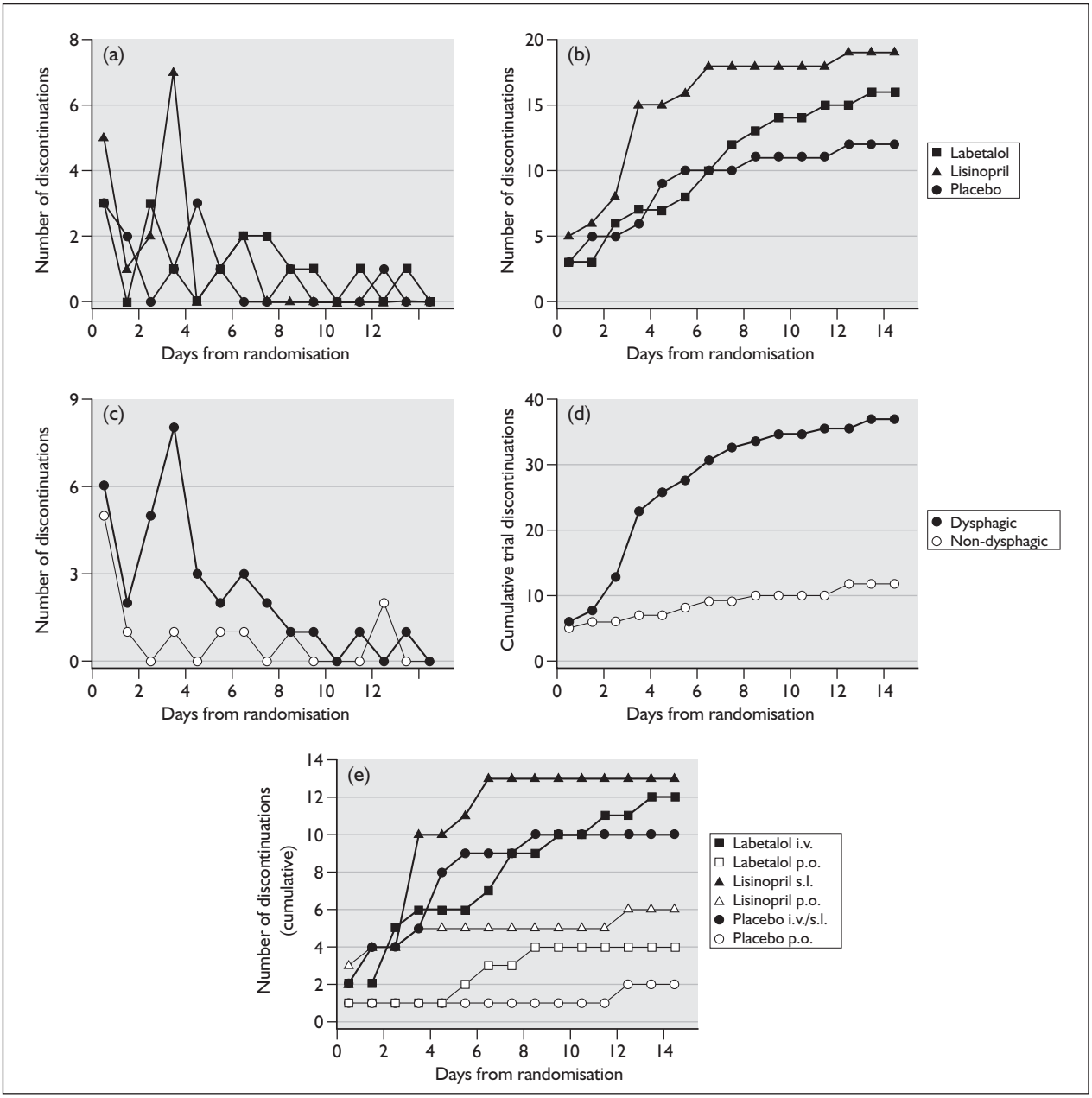


***FIGURE 6*** *(a) Trial medication discontinuations by treatment group by time. (b) Cumulative trial medication discontinuations by treatment group. (c) Trial medication discontinuations by dysphagia status. (d) Cumulative trial medication discontinuations by dysphagia status. (e) Cumulative trial medication discontinuations by group and dysphagia status. i.v., intravenous; p.o., oral; s.l., sublingual.*

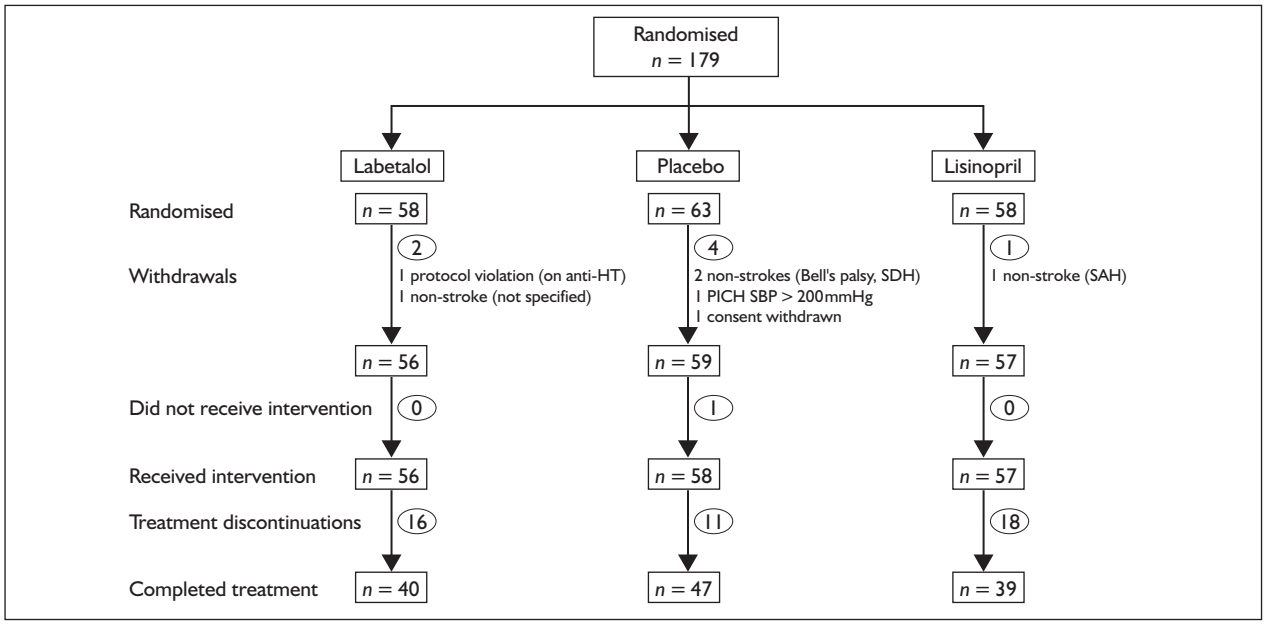


***FIGURE 7*** *Randomisation and intention to treat groups. Anti-HT, antihypertensive therapy; PICH, primary intracerebral haemorrhage; SAH, subarachnoid haemorrhage; SBP, systolic blood pressure; SDH, subdural haemorrhage.*

BP, mRS score, NIHSS score and dysphagia at randomisation (*Table 7*). Mean age (SD) for all of the trial patients was 74 (11) years, mean SBP and DBP were 181 (16) mmHg and 95 (13) mmHg, respectively, and mean NIHSS score was 11 (7).

# Outcomes

All analyses were on an intention to treat basis.

## Primary outcome – death and dependency

The primary end point of the study was death or dependency (dependency defined as mRS score > 3) at 2 weeks. There was no significant difference in death and dependency at 2 weeks between the active treatment and the placebo groups [relative risk (RR) 1.03, 95% CI 0.80–1.33; $p = 0.82$] or between the three groups ($p = 0.97$) even after adjusting for time to treatment (data not shown). The data for each group are presented in *Table 8*. There was one death by 2 weeks in the labetalol group (related to initial stroke), five deaths in the lisinopril group (four related to initial stroke, one to respiratory causes) and six in the placebo group (two neurological and four respiratory). The study had the statistical power to detect a 22% absolute risk difference between the active treatment and the placebo limbs (assuming 60% death/disability in the placebo group) with a power of 80% at the 5% alpha error level.

## Secondary outcomes

### *Safety: early neurological deterioration*

Early neurological deterioration at 72 hours, defined as an increase in NIHSS score of more than 3 points from baseline, occurred in seven (6%) people in the active treatment group and three (5%) in the placebo group (RR 1.22, 95% CI 0.33–4.54; $p = 0.76$; *Table 9*). There was one death at 72 hours in the active treatment group compared with three in the placebo group.

### *Stroke subtype*

The effect of stroke subtype [classified as CT-/magnetic resonance imaging-confirmed relevant infarct including haemorrhagic transformation of infarct, PICH or other (this group includes those whose neuroimaging was reported as normal)] on outcome was also studied. Two patients randomised to the placebo arm died before neuroimaging and therefore are not included in the figures as stroke subtype was classified as 'unknown'. The numbers in each group were too small to allow further useful analysis (*Table 10*).

### *Change in blood pressure*

Blood pressure values fell from randomisation to 24 hours in each of the three groups and remained lower at 2 weeks (*Tables 11 and 12; Figure 8*). There was a statistically significant reduction in SBP from baseline to 24 hours in the combined active treatment group compared with the placebo group (mean reduction 10 mmHg, 95% CI 17–3; $p = 0.004$) (*Table 11*). Analysis across the three treatment groups showed the presence of an

***TABLE 7*** *Baseline characteristics of CHHIPS depressor patients at randomisation*

| Patients' characteristics at randomisation[a] | Treatment group | | | |
|---|---|---|---|---|
| | Labetalol ($n = 56$) | Lisinopril ($n = 57$) | Active (lisinopril + labetalol) ($n = 113$) | Placebo ($n = 59$) |
| Male gender, *n* (%) | 34 (61) | 30 (53) | 64 (57) | 31 (53) |
| Age (years) | 74 (11) | 75 (11) | 74 (11) | 74 (11) |
| SBP (mmHg) | 181 (16) | 182 (17) | 182 (17) | 181 (16) |
| DBP (mmHg) | 93 (14) | 96 (12) | 95 (13) | 96 (12) |
| OCSP, *n* (%) | | | | |
| Total anterior | 19 (35) | 20 (34) | 39 (35) | 22 (37) |
| Partial anterior | 15 (27) | 21 (36) | 36 (32) | 18 (31) |
| Lacunar | 17 (31) | 11 (19) | 28 (25) | 16 (27) |
| Posterior | 4 (7) | 5 (9) | 9 (8) | 3 (5) |
| Unknown | 1 (2) | 0 (0) | 1 (1) | 0 (0) |
| mRS score, *n* (%)[b] | | | | |
| 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, median (IQR) | 9 (6–16) | 10 (5–16) | 9 (5–16) | 9 (5–17) |
| Dysphagic, *n* (%) | 27 (48) | 28 (49) | 55 (49) | 28 (47) |
| No history of stroke, *n* (%) | 53 (95) | 50 (88) | 103 (91) | 56 (95) |
| Unknown, *n* | 1 | 0 | 1 | 0 |
| No history of TIA, *n* (%) | 51 (91) | 52 (91) | 103 (91) | 55 (93) |
| No diabetes, *n* (%) | 52 (93) | 53 (93) | 105 (95) | 55 (95) |
| Unknown, *n* | 3 | 1 | 4 | 1 |
| Smoking, *n* (%) | | | | |
| No | 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) |
| No hypercholesterolaemia, *n* (%) | 39 (71) | 43 (75) | 82 (73) | 37 (63) |
| Unknown, *n* | 2 | 0 | 2 | 0 |
| No history of IHD, *n* (%) | 47 (84) | 53 (91) | 100 (88) | 54 (92) |
| Unknown, *n* | 1 | 0 | 1 | 0 |
| Time to treatment (hours) | 19.2 (6.6) | 20.5 (8.5) | 19.8 (7.6) | 17.4 (6.6) |
| Type of stroke, *n* (%) | | | | |
| Ischaemic | 33 (59) | 31 (54) | 64 (57) | 35 (61) |
| PICH | 9 (16) | 9 (16) | 18 (16) | 7 (12) |
| No relevant abnormality on CT scan, *n* (%) | 14 (25) | 17 (30) | 31 (27) | 15 (26) |
| Died before CT carried out, *n* | 0 | 0 | 0 | 2 |

CT, computerised tomography; DBP, diastolic blood pressure; IHD, ischaemic heart disease; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project; PICH, primary intracerebral haemorrhage; SBP, systolic blood pressure; TIA, transient ischaemic attack.
a Data presented as mean (SD) for normally distributed variables if not stated otherwise.
b Increasing dependency.

***TABLE 8*** *Death and dependency (modified Rankin Scale score > 3 at 2 weeks) by treatment arms*

| | Treatment group | | | |
|---|---|---|---|---|
| | **Labetalol (*n* = 56)** | **Lisinopril (*n* = 57)** | **Active (labetalol + lisinopril) (*n* = 113)** | **Placebo (*n* = 59)** |
| Dead or dependent | | | | |
| Yes, *n* (%) | 34 (61) | 35 (61) | 69 (61) | 35 (59) |
| No, *n* (%) | 22 (39) | 22 (39) | 44 (39) | 24 (41) |
| Active vs placebo | $p = 0.82$ | | | |
| Across three treatment groups | $p = 0.97$ | | | |

***TABLE 9*** *Change in neurological status at 72 hours*

| | Treatment group | | | |
|---|---|---|---|---|
| | **Labetalol (*n* = 56)** | **Lisinopril (*n* = 57)** | **Active (labetalol + lisinopril) (*n* = 113)** | **Placebo (*n* = 59)** |
| An increase in NIHSS score of ≥4 or dead at 72 hours, *n* (%) | 1 (2) | 7 (12) | 8 (7) | 6 (10) |
| Active vs placebo | $p = 0.56$ | | | |
| Across three groups | $p = 0.09$ | | | |
| An increase in NIHSS score of ≥4 at 72 hours, *n* (%) | 1 (2) | 6 (10) | 7 (6) | 3 (5) |
| A decrease in NIHSS score of ≥4 at 72 hours, *n* (%) | 51 (91) | 48 (84) | 99 (88) | 52 (88) |
| NIHSS score not significantly changed (change ≤3 from baseline) at 72 hours, *n* (%) | 4 (7) | 2 (4) | 6 (5) | 1 (2) |
| Dead at 72 hours, *n* (%) | 0 (0) | 1 (2) | 1 (1) | 3 (5) |

NIHSS, National Institutes of Health Stroke Scale.

overall difference between the groups ($p = 0.005$). This difference could be seen to arise from the significant reduction in SBP with lisinopril compared with placebo (mean reduction 14 mmHg, 95% CI 22–5; $p = 0.001$) but not with labetalol compared with placebo (mean reduction 7 mmHg, 95% CI 15 to –1; $p = 0.096$).

SBP change at 2 weeks showed a difference in the combined active treatment arm compared with the placebo group (mean reduction 8 mmHg, 95% CI 16–0.2; $p = 0.045$). When analysed across the three groups, no statistically significant difference in SBP change at 2 weeks between groups was found. DBP change at 2 weeks did not show any statistically significant differences either in the combined active group compared with the placebo group (mean reduction 4 mmHg, 95% CI 9 to –0.8; $p = 0.10$) or across the three groups ($p = 0.12$) (*Table 12*).

### *Dysphagic group*

Mean SBP changes over the first 24 hours and 2 weeks and mean DBP changes at 2 weeks in dysphagic and non-dysphagic patients by treatment group are shown in *Table 14*. Repeated measures analysis for SBP at 4, 8 and 24 hours in the dysphagic group for the three treatment arms (*Table 15*) showed an overall significant difference between treatments with time ($p = 0.0001$; *Figure 9*). There was a borderline significant reduction in SBP in the lisinopril group compared with 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

***TABLE 10*** *Neurological deterioration, systolic and diastolic blood pressure change and death and dependency at 2 weeks by stroke subtype*

| Treatment group (*n*) | Increase in NIHSS score ≥4 at 72 hours, *n* (%) | SBP change at 24 hours (mmHg), mean (SE)[a] | SBP change at 2 weeks (mmHg), mean (SE)[a] | DBP change at 2 weeks (mmHg), mean (SE)[a] | Death and dependency at 2 weeks (mRS score> 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 (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 (0) | –17 (5) | –15 (7) | –5 (4) | 11 (73) |

DBP, diastolic blood pressure; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure.
a Minus sign indicates a fall from baseline.

***TABLE 11*** *Change in systolic blood pressure (SBP) from randomisation by time and by group (dysphagic and non-dysphagic groups combined)*

| | Treatment group | | | |
|---|---|---|---|---|
| | Labetalol | Lisinopril | Active (labetalol + lisinopril) | Placebo |
| SBP change at 4 hours (mmHg), mean (SE)[a] | –22 (2) | –16 (2) | –19 (2) | –9 (2) |
| SBP change at 8 hours (mmHg), mean (SE)[a] | –20 (3) | –29 (3) | –25 (3) | –14 (3) |
| SBP change at 24 hours (mmHg), mean (SE)[a] | –18 (3) | –25 (3) | –21 (2) | –11 (3) |
| Active vs placebo | $p = 0.004$ | | | |
| Across three groups | $p = 0.005$ | | | |
| Labetalol vs placebo | $p = 0.096$ | | | |
| Lisinopril vs placebo | $p = 0.001$ | | | |
| SBP change at 2 weeks (mmHg), mean (SE)[a] | –31 (3) | –32 (3) | –31 (2) | –24 (3) |
| Active vs placebo | $p = 0.045$ | | | |
| Across three groups | $p = 0.13$ | | | |

a Minus sign indicates a fall from baseline.

***TABLE 12*** *Change in diastolic blood pressure (DBP) from randomisation by time and by group (dysphagic and non-dysphagic groups combined)*

| | Treatment group | | | |
|---|---|---|---|---|
| | **Labetalol** | **Lisinopril** | **Active (labetalol + lisinopril)** | **Placebo** |
| DBP change at 4 hours (mmHg), mean (SE)[a] | –10 (1.3) | –9 (1.4) | –5 (1.7) | –5 (1.4) |
| DBP change at 8 hours (mmHg), mean (SE)[a] | –13 (2.2) | –18 (2.3) | –10 (2.7) | –6 (2.2) |
| DBP change at 24 hours (mmHg), mean (SE)[a] | –6 (2.1) | –13 (2.1) | –3 (2.6) | –6 (2.1) |
| Active vs placebo | $p = 0.189$ | | | |
| Across three groups | $p = 0.021$ | | | |
| Labetalol vs placebo | $p = 0.909$ | | | |
| Lisinopril vs placebo | $p = 0.019$ | | | |
| DBP change at 2 weeks (mmHg), mean (SE)[a] | –11 (2) | –15 (2) | –13 (1) | –9 (2) |
| Active vs placebo | $p = 0.10$ | | | |
| Across three groups | $p = 0.12$ | | | |

DBP, diastolic blood pressure.
a Minus sign indicates a fall from baseline.

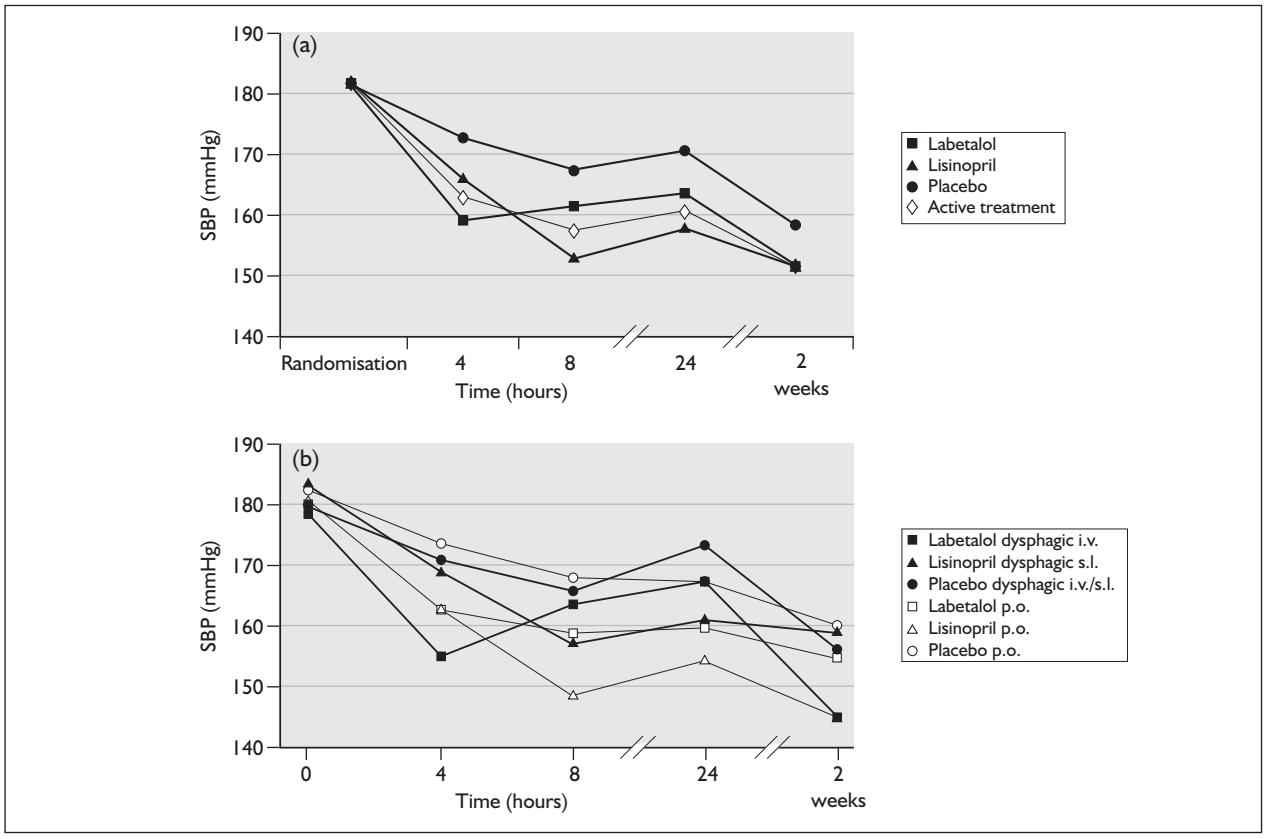


***FIGURE 8*** *(a) Systolic blood pressure (SBP) changes for the active treatment group (labetalol and lisinopril groups combined) and the labetalol and lisinopril groups separately vs placebo following randomisation. Standard error bars are omitted for clarity. (b) SBP changes by group following randomisation. Standard error bars are omitted for clarity. The sample sizes for the blood pressure trends shown in (b) are shown in Table 13. i.v., intravenous; p.o., oral; s.l., sublingual.*

***TABLE 13*** *Sample sizes for the blood pressure trends shown in Figure 8b*

| | 0 hours | 4 hours | 8 hours | 24 hours | 2 weeks |
|---|---|---|---|---|---|
| ***Systolic blood pressure*** | | | | | |
| Labetalol i.v. | 27 | 27 | 27 | 27 | 26 |
| Labetalol p.o. | 29 | 29 | 29 | 29 | 29 |
| Lisinopril s.l. | 28 | 28 | 27 | 28 | 23 |
| Lisinopril p.o. | 29 | 29 | 28 | 29 | 28 |
| Placebo i.v./s.l. | 28 | 28 | 27 | 28 | 23 |
| Placebo p.o. | 31 | 29 | 30 | 30 | 30 |
| ***Diastolic blood pressure*** | | | | | |
| Labetalol i.v. | 27 | 23 | 18 | 19 | 26 |
| Labetalol p.o. | 29 | 26 | 23 | 21 | 29 |
| Lisinopril s.l. | 28 | 21 | 17 | 21 | 23 |
| Lisinopril p.o. | 29 | 26 | 22 | 22 | 28 |
| Placebo i.v./s.l. | 28 | 22 | 22 | 18 | 23 |
| Placebo p.o. | 31 | 25 | 21 | 23 | 30 |

i.v., intravenous; p.o., oral; s.l., sublingual.

***TABLE 14*** *Changes in systolic blood pressure (SBP) at 24 hours and 2 weeks and diastolic blood pressure (DBP) at 2 weeks (dysphagic and non-dysphagic groups)*

| Treatment group (*n*) | Baseline SBP (mmHg), mean (SD) | Baseline DBP (mmHg), mean (SD) | SBP change at 24 hours (mmHg), mean (SE) | SBP change at 2 weeks (mmHg), mean (SE) | DBP change at 2 weeks (mmHg), mean (SE) |
|---|---|---|---|---|---|
| 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) |

23–2; $p = 0.024$), but not at 4 hours. In contrast, the labetalol dysphagic group had a significant reduction in SBP compared with placebo at 4 hours (mean reduction 16 mmHg, 95% CI 26–5; $p = 0.005$), but not at 8 hours and 24 hours (*Table 15*).

### *Achievement of target blood pressure*

As per protocol, patients not achieving the target SBP at 4 hours (a fall of 15 mmHg from baseline or SBP 145–155 mmHg) received a second test dose of medication. If the BP target was not achieved at 8 hours, a further dose was given, up to a maximum of three doses (i.e. three doses of lisinopril 5 mg or labetalol 50 mg or equivalent placebo, up to a maximum of 15 mg lisinopril or 150 mg labetalol).

The numbers of patients who reached the SBP reduction target at 4, 8 and 24 hours are shown in *Table 16* and the numbers of patients who reached the SBP reduction target at 4 hours and maintained it at 8 hours are shown in *Table 17*. The percentages of patients who received additional doses at 4 hours were labetalol 23%, lisinopril 39% and placebo 63%; the percentages who received additional doses again at 8 hours were 7%, 12% and 39% respectively.

***TABLE 15*** *Repeated measures analysis for systolic blood pressure (SBP) changes in the dysphagic group*

| Treatment group (*n*) | SBP at randomisation (mmHg), mean (SD), | SBP at 4 hours (mmHg), mean (95% CI) | SBP at 8 hours (mmHg), mean (95% CI) | SBP at 24 hours (mmHg), mean (95% CI) |
|---|---|---|---|---|
| Labetalol (27) | 179 (15) | 155 (148–163) | 164 (156–171) | 167 (159–175) |
| *p*-Value[a] | | 0.005 | 0.62 | 0.26 |
| Lisinopril (28) | 184 (18) | 169 (162–177) | 156 (149–164) | 161 (153–169) |
| *p*-Value[a] | | 0.77 | 0.07 | 0.024 |
| Placebo (28) | 180 (18) | 171 (163–178) | 166 (159–174) | 173 (166–181) |

a *p*-Value is given for active treatment at each time point compared with placebo, adjusted for baseline values. Overall for the model, $p < 0.0001$.

***TABLE 16*** *Numbers and percentages of patients in whom SBP targets were achieved at various time points by treatment arm for dysphagic and non-dysphagic groups combined*

| | Treatment group | | | |
|---|---|---|---|---|
| | Labetalol (*n* = 56) | Lisinopril (*n* = 57) | Active (labetalol + lisinopril) (*n* = 113) | Placebo (*n* = 59) |
| Target achieved at | | | | |
| 4 hours, *n* (%) | 43 (77) | 35 (61) | 78 (69) | 22 (37) |
| 8 hours, *n* (%) | 37 (66) | 47 (82) | 84 (74) | 27 (46) |
| 24 hours, *n* (%) | 32 (57) | 37 (65) | 69 (61) | 27 (46) |

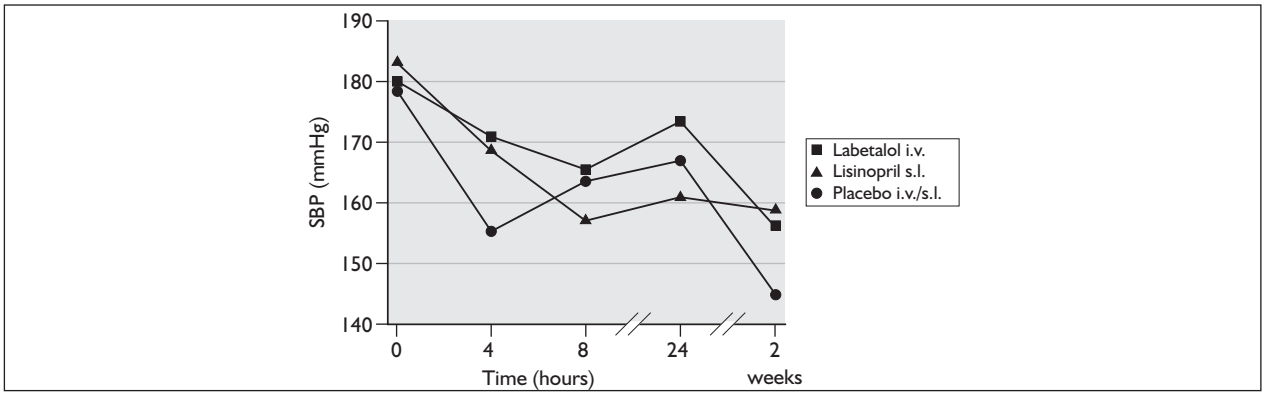


***FIGURE 9*** *Mean systolic blood pressure (SBP) values by treatment group over the 2-week period in dysphagic patients. Standard error bars omitted for clarity. i.v., intravenous; s.l., sublingual.*

Those reaching and not reaching the target BP were further split by treatment type and group to assess whether any differences found were an effect of the route of administration (*Table 18*). In total, 50% of those receiving intravenous labetalol had reached the target SBP at 4 hours, but by 8 hours 50% of this group were again above the target SBP level and did not receive further treatment until 24 hours after the initial test dose. In contrast, 87% of those receiving sublingual lisinopril who had achieved the target SBP at 4 hours had maintained the target SBP at 8 hours.

### *Time to treat*

The minimum time to treatment was 6.8 hours in the labetalol group,7.0 hours in the lisinopril group and 5.5 hours in the placebo group (*Figure 10a–c*). No difference was found in the primary outcome of death and dependency at 2 weeks when adjusted for time to treatment. All patients were randomised within 36 hours of stroke onset, although for a few patients there was a further delay between randomisation and first treatment dose, explaining the observed differences in time to treatment (*Figure 10a–c*). None of the patients received treatment within 5 hours of stroke onset.

### *Serious adverse events*

#### Description

SAEs were categorised as advised by the Medicines and Healthcare Products Regulatory Agency (MHRA) in terms of commonly occurring adverse events following a stroke (Appendix 2 of this report contains the SAE reporting form used). In total, 96 SAEs were reported in 58 patients. Twenty-three patients had multiple SAEs: 17 patients had 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 in the three intervention groups, with 28 SAEs being reported in the labetalol group, 33 in the lisinopril group and 35 in the placebo group. In each group there were more SAEs reported in the dysphagic than in the non-dysphagic arm labetalol group: 18 dysphagic versus 10 non-dysphagic; placebo group: 25 dysphagic versus 10 non-dysphagic; lisinopril group: 17 dysphagic versus 16 non-dysphagic) (*Figure 11*).

#### Severity

There were fatal SAEs in each of the treatment groups: one in the labetalol group, six in the placebo group and five in the lisinopril group. One

***TABLE 17*** *Numbers and percentages of patients in whom SBP targets were maintained at 4 and 8 hours by treatment arm for dysphagic and non-dysphagic groups combined*

| Treatment group (*n*) | 4 hours, *n* (%) | 8 hours, *n* (%) |
|---|---|---|
| Labetalol (56) | Yes: 43 (77) | Yes: 28 (50) |
| | | No: 15 (27) |
| | No: 13 (23) | Yes: 9 (16) |
| | | No: 4 (7) |
| Lisinopril (57) | Yes: 35 (61) | Yes: 32 (56) |
| | | No: 1 (2) |
| | No: 22 (39) | Yes: 15 (26) |
| | | No: 7 (12) |
| Labetalol + lisinopril (113) | Yes: 78 (69) | Yes: 60 (53) |
| | | No: 16 (14) |
| | No: 35 (31) | Yes: 24 (21) |
| | | No: 11 (10) |
| Placebo (59) | Yes: 22 (37) | Yes: 15 (25) |
| | | No: 7 (12) |
| | No: 36 (63) | Yes: 12 (20) |
| | | No: 23 (39) |

Note: Because of death or missing values, numbers presented in the total column may not add up to 100%.

***TABLE 18*** *Numbers and percentages of patients reaching and maintaining the systolic blood pressure (SBP) target in the dysphagic and non-dysphagic groups*

| Treatment group (*n*) | 4 hours, *n* (%) | 8 hours, *n* (%) |
|---|---|---|
| Labetalol dysphagic (27) | Yes: 22 (81) | Yes: 11 (41) |
| | | No: 11 (41) |
| | No: 5 (19) | Yes: 3 (11) |
| | | No: 2 (7) |
| Labetalol non-dysphagic (29) | Yes: 21 (72) | Yes: 17 (58) |
| | | No: 4 (14) |
| | No: 8 (28) | Yes: 6 (21) |
| | | No: 2 (7) |
| Lisinopril dysphagic (28) | Yes: 16 (57) | Yes: 14 (50) |
| | | No: 2 (7) |
| | No: 12 (43) | Yes: 9 (32) |
| | | No: 3 (11) |
| Lisinopril non-dysphagic (29) | Yes: 19 (66) | Yes: 19 (65) |
| | | No: 0 (0) |
| | No: 10 (34) | Yes: 6 (21) |
| | | No: 4 (14) |
| Labetalol + lisinopril dysphagic (55) | Yes: 38 (69) | Yes: 25 (45) |
| | | No: 13 (24) |
| | No: 17 (31) | Yes: 12 (22) |
| | | No: 5 (9) |
| Labetalol + lisinopril non-dysphagic (58) | Yes: 40 (69) | Yes: 36 (62) |
| | | No: 4 (7) |
| | No: 18 (31) | Yes: 12 (21) |
| | | No: 6 (10) |
| Placebo dysphagic (28) | Yes: 9 (32) | Yes: 6 (21) |
| | | No: 3 (11) |
| | No: 19 (68) | Yes: 6 (22) |
| | | No: 13 (46) |
| Placebo non-dysphagic (30) | Yes: 13 (43) | Yes: 9 (31) |
| | | No: 4 (13) |
| | No: 17 (57) | Yes: 7 (23) |
| | | No: 10 (33) |

patient in the placebo group had two fatal events reported. The cause of death as reported by local investigators is presented in *Table 19*. All fatal SAEs up to 2 weeks were classified as either respiratory or neurological. The numbers are too small to identify any statistically significant trends. *Figure 12* illustrates the severity of the SAEs by treatment group for the non-dysphagic and dysphagic groups combined, and *Figure 13* shows the severity of the SAEs by treatment group in the dysphagic versus the non-dysphagic groups.

### Causality

There was thought to be a causal relationship between study medication and SAE by the local investigators in two patients in the labetalol group and two patients in the lisinopril group (*Figure 14*); these are described below. There was no unblinding

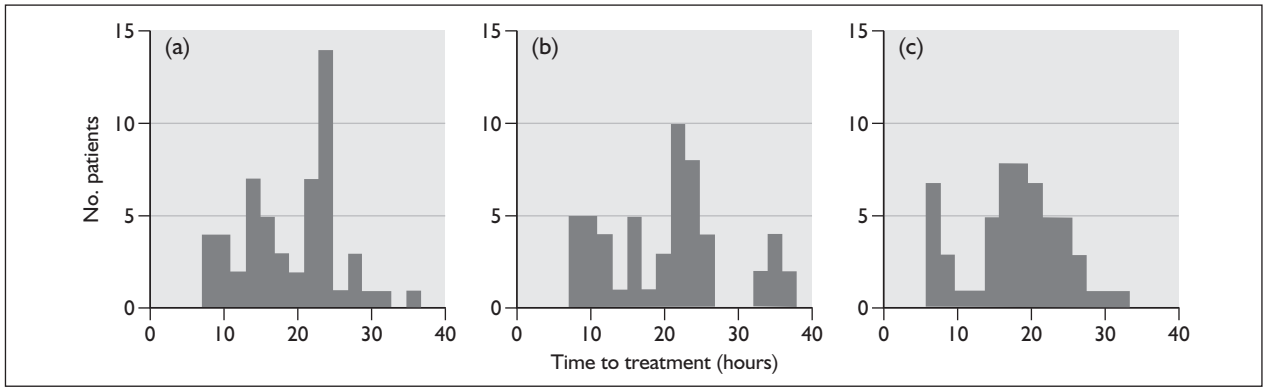


***FIGURE 10*** *(a) Time to treatment (labetalol). (b) Time to treatment (lisinopril). (c) Time to treatment (placebo).*

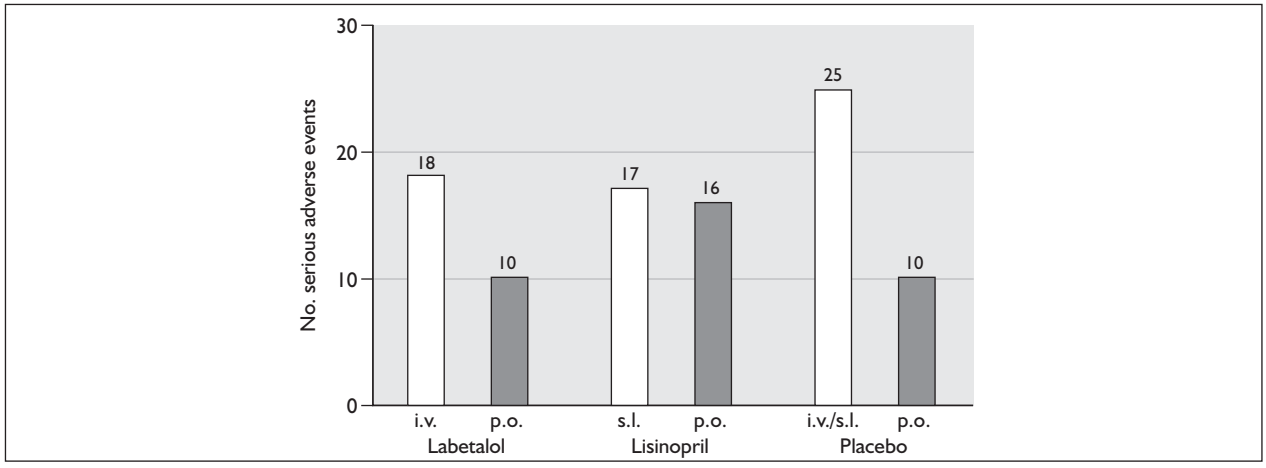


***FIGURE 11*** *Serious adverse events by treatment group and method of drug administration. i.v., intravenous; s.l., sublingual.*

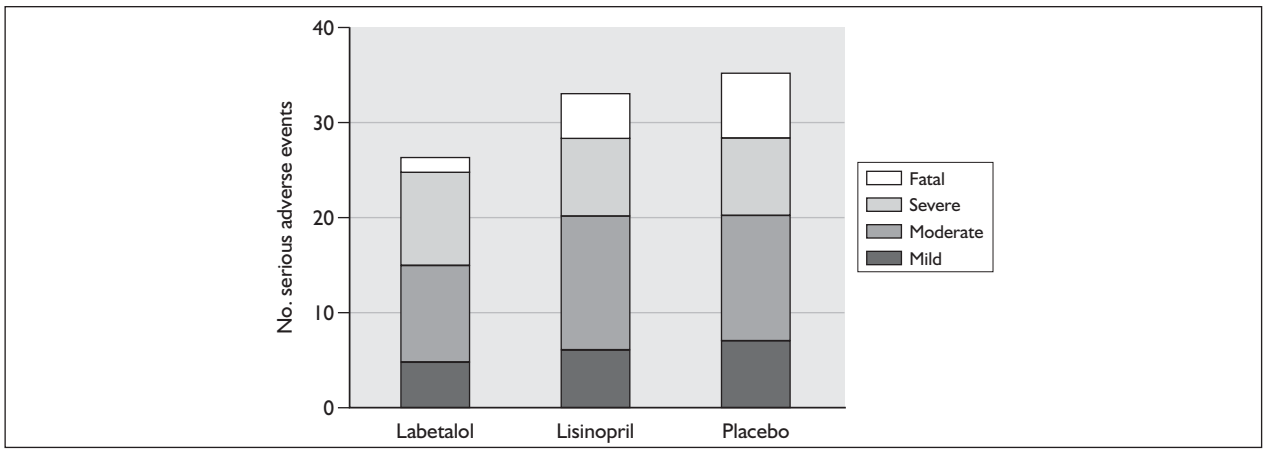


***FIGURE 12*** *Severity of the serious adverse events (SAEs) by treatment group for the dysphagic and non-dysphagic groups combined.*

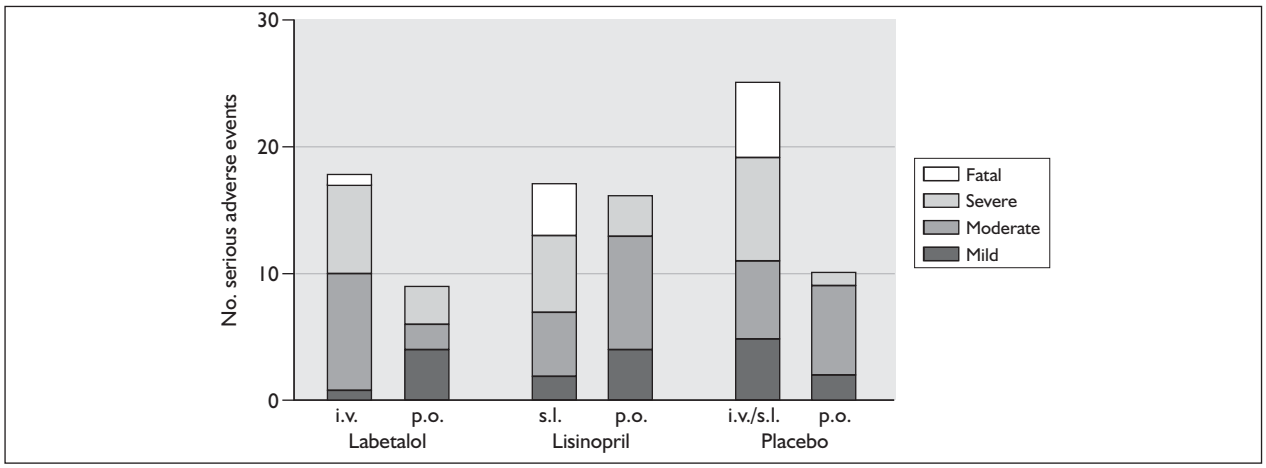


***FIGURE 13*** *Severity of the serious adverse events by treatment group in the dysphagic vs the non-dysphagic groups. Note: Includes two fatal SAEs for one patient in the dysphagic placebo group.*

***TABLE 19*** *Cause of death by treatment group at 2 weeks for dysphagic and non-dysphagic groups combined*

| | Treatment group | | |
|---|---|---|---|
| **Cause of death** | **Labetalol, *n*** | **Lisinopril, *n*** | **Placebo, *n*** |
| Neurological (stroke) | 1 | 4 | 2 |
| Respiratory (pneumonia) | 0 | 1 | 4 |
| Total | 1 | 5 | 6 |

of treatment allocation in these patients until the end of the trial.

Of those in whom a causal relationship was reported, one patient in the labetalol group and one in the lisinopril group developed bronchospasm, requiring nebulised bronchodilators; both events were reported to be of moderate severity. The patient in the labetalol group continued with the study medication; the patient in the lisinopril group did not at the discretion of the local investigators. One patient in the labetalol group had an extension of the presenting intracerebral haemorrhage, evidenced on repeat CT scan, without further neurological deterioration; this was graded as a severe SAE and led to interruption of study medication. One patient in the lisinopril group became hypotensive (BP 82/42 mmHg); this was again felt to be caused by the study drug and led to discontinuation.

There was uncertainty regarding causality in nine patients in the labetalol group, four in the lisinopril group and four in the placebo group.

### Discontinuations

There were 18 discontinuations of study medication because of SAEs (six labetalol, eight lisinopril, four placebo), and five of these patients (one labetalol, two lisinopril, two placebo) subsequently suffered a fatal event.

### System affected

The majority of SAEs and deaths recorded within the first 14 days of treatment were related to the neurological and respiratory systems. There were 32 neurological SAEs, of which seven were fatal; these events included deterioration in NIHSS score, recurrent stroke and seizure. There were 28 respiratory SAEs, of which five were fatal; events in this group included bronchopneumonia,

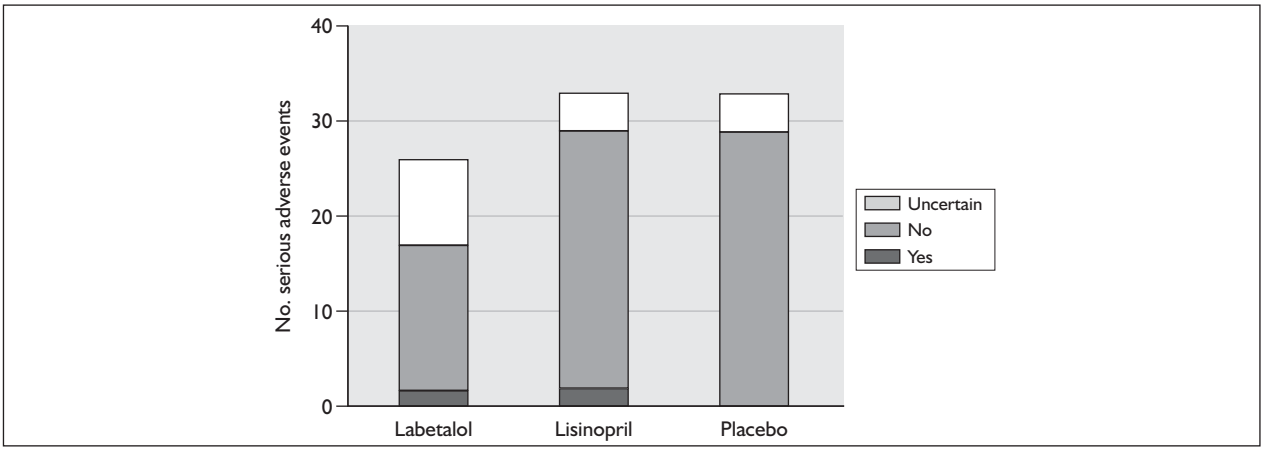


***FIGURE 14*** *Causality of serious adverse events according to treatment type as assessed by investigators.*

bronchospasm and low oxygen saturations. One patient was reported as having two fatal SAEs, one of which was neurological (deterioration in NIHSS score ≥4) and the other respiratory (bronchopneumonia) – both are included. The cause of death is that recorded by the local investigator. *Figure 15* illustrates the SAEs by system affected.

#### *Three-month mortality*

The co-ordinating centre established patient survival at 3 months after randomisation, and deaths were recorded from the NHS register, cause of death being taken from death certificates (*Table 20*). Mortality at 3 months was reduced in the active treatment group compared with the placebo group [11/113 (9.7%) vs 12/59 (20.3%); $p = 0.05$; *Figure 16, Table 21*] with a hazard ratio of 2.2, (95% CI 1.0–5.0) for death in the placebo group compared with the active treatment group. No comparative analysis between the labetalol and lisinopril groups was undertaken because of the small numbers involved and insufficient data were available on disability at 3 months for adequate analysis of the combined end point of death or disability.

#### *Utility and quality-adjusted life-years*

Comparison of point estimate utilities derived from the EQ-5D and mRS scores[84] shows utility scores based on the mRS to be significantly higher than those based on the EQ-5D ($p = 0.002$) (*Figure 17*). For consistency, mRS-based utilities were used to estimate utility and QALYs.

On average, patients on active treatment gained 0.043 QALYs over 3 months compared with those on placebo, although we were unable to detect any statistically significant difference ($p = 0.074$; *Table 22*). These results must be interpreted with caution as they are based on small sample sizes and are likely to suffer from selection bias because of the mortality rate (23 of 33 observations).

#### *Resource use and cost*

Length of stay (LoS) and hospitalisation costs at 14 days and 3 months are presented in *Tables 23* and *24*. There was no difference in median LoS between active treatment and placebo at 14 days, and very little at 3 months. Drug costs were negligible for each of the three groups. There was no difference in the mean cost per patient for the first 14 days following stroke for active treatment versus placebo. At 3 months active treatment patients cost £1071 less on average than placebo patients, although this difference was not statistically significant. For details of costings used see Appendix 3.

## Cost-effectiveness

The primary analysis was incremental cost per incremental survivor at 3 months. Active treatment was compared with placebo (*Table 25*).

On average, active treatment was £1071 cheaper than placebo and resulted in a higher survival probability than placebo at 3 months, although these differences were not statistically significant. However, the scatter plot of bootstrapped cost and outcome pairs (*Figure 18*) suggests that there is a preponderance of points in the southeast quadrant of the cost-effectiveness plane, implying that, in the majority of cases, active treatment is likely to be both more effective and less costly than placebo.

The CEAC shows the proportion of the 1000 bootstrapped points with an ICER below a given threshold willingness to pay for a unit of outcome

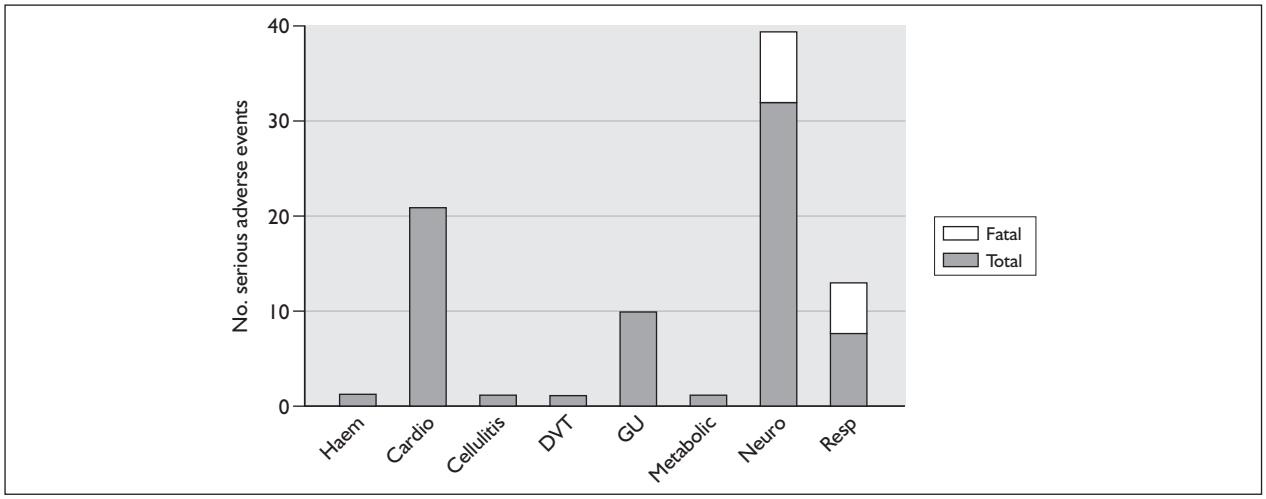


***FIGURE 15*** *Fatal and non-fatal serious adverse events during the 14-day treatment period by system affected. Includes two fatal events for one patient (one respiratory and one neurological). Cardio, cardiological; DVT, deep vein thrombosis; GU, genitourinary; haem, haematological; neuro, neurological; resp, respiratory.*

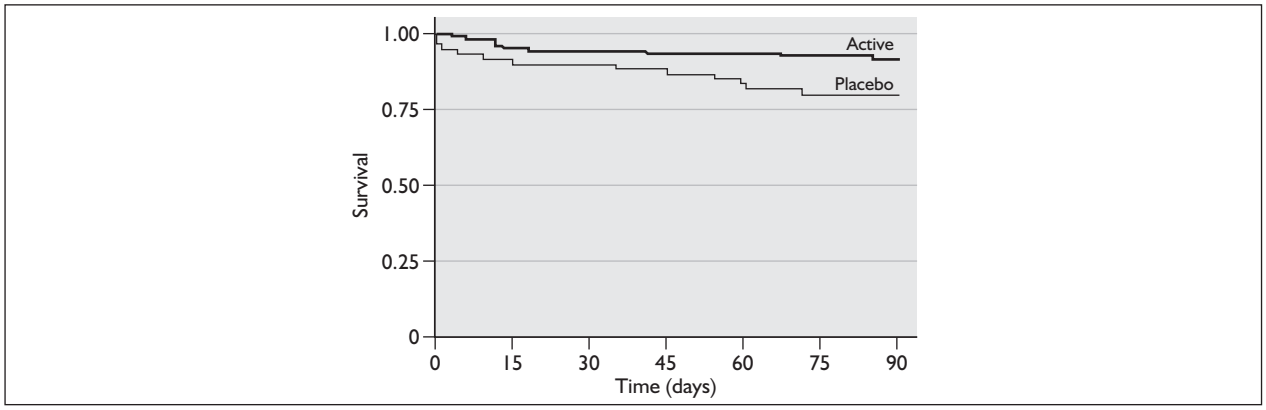


***FIGURE 16*** *Kaplan–Meier plot for 90-day survival estimates for active treatment versus placebo.*

***TABLE 20*** *Recorded cause of death by treatment group at 3 months*

| | Treatment group | | |
|---|---|---|---|
| **Cause of death** | **Labetalol** | **Lisinopril** | **Placebo** |
| Cardiac | 1 (heart failure) | 1 (myocardial infarction) | 0 |
| Neurological | 3 (stroke) | 5 (stroke) | 6 (stroke) |
| Respiratory | 0 | 1 | 6 (pneumonia) |
| Total | 4 | 7 | 12 |

***TABLE 21*** *Mortality at 3 months' follow-up*

| | Treatment group | | |
|---|---|---|---|
| | **Active** | **Placebo** | **Total** |
| Dead, *n* | 11 | 12 | 23 |
| Alive, *n* | 102 | 47 | 149 |
| Total, *n* | 113 | 59 | 172 |

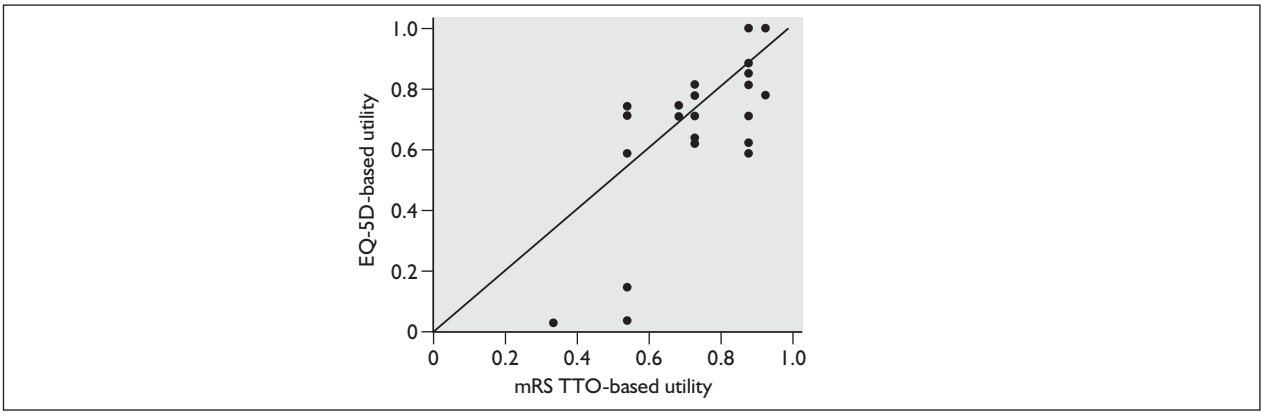


***FIGURE 17*** *Modifed Rankin Scale (mRS) vs EQ-5D utility estimates.*

***TABLE 22*** *Mean (SD) modified Rankin Scale (mRS)-based utility at baseline, 14 days and 3 months*

| | ***n* (labetalol, lisinopril, placebo)** | **Labetalol** | **Lisinopril** | **Active (labetalol + lisinopril)** | **Placebo** | ***p*-Value (active vs placebo)** |
|---|---|---|---|---|---|---|
| Baseline | (56, 57, 59) | 0.895 (0.070) | 0.890 (0.071) | 0.892 (0.070) | 0.899 (0.063) | |
| 14 days | (56, 57, 59) | 0.576 (0.216) | 0.517 (0.255) | 0.546 (0.237) | 0.526 (0.271) | |
| 3 months | (8, 11, 14) | 0.403 (0.437) | 0.306 (0.426) | 0.346 (0.421) | 0.088 (0.225) | |
| QALYs gained (14 days) | (56, 59, 57) | 0.028 (0.004) | 0.027 (0.005) | 0.028 (0.005) | 0.027 (0.005) | 0.732 |
| QALYs gained (3 months) | (8, 14, 11) | 0.111 (0.074) | 0.087 (0.084) | 0.097 (0.079) | 0.054 (0.044) | 0.074 |

***TABLE 23*** *Resource use and costs at 14 days by treatment type (intention to treat analysis)*

| | ***n* (labetalol, lisinopril, placebo)** | **Labetalol** | **Lisinopril** | **Active (labetalol + lisinopril)** | **Placebo** |
|---|---|---|---|---|---|
| Mean (SD) LoS (days) | (56, 57, 59) | 11.57 (4.263) | 11.23 (4.464) | 11.40 (4.35) | 11.36 (4.429) |
| Median (IQR) LoS (days) | (56, 57, 59) | 14 (11.25–14) | 14 (8–14) | 14 (9–14) | 14 (10–14) |
| Patients still hospitalised, *n* (%) | (56, 57, 59) | 40 (71) | 36 (63) | 76 (67) | 36 (61) |
| Cost of hospitalisation (£), mean (SD) | (56, 57, 59) | 2563 (750) | 2502 (786) | 2532 (766) | 2525 (779) |
| Cost of study drugs (£), mean (SD) | (56, 57, 59) | 7 (8) | 1 (1) | 4 (6) | 0 (0) |
| Total cost (£), mean (SD) | (56, 57, 59) | 2569 (752) | 2504 (786) | 2536 (767) | 2525 (779) |
| Student's *t*-test of total cost (active vs placebo) | | $t = 0.093$, $p = 0.92$ | | | |
| Mann–Whitney test of median LoS (active vs placebo) | | $p = 0.88$ | | | |

IQR, interquartile range; LoS, length of stay.

***TABLE 24*** *Resource use and costs at 3 months by treatment type (intention to treat analysis)*

| | ***n* (labetalol, lisinopril, placebo)** | **Labetalol** | **Lisinopril** | **Active (labetalol + lisinopril)** | **Placebo** |
|---|---|---|---|---|---|
| Mean (SD) LoS (days) | (53, 57, 53) | 45.75 (34.66) | 40.98 (34.87) | 43.37 (34.68) | 49.47 (54.98) |
| Median (IQR) LoS (days) | (56, 57, 59) | 38 (7–84) | 30 (7–84) | 36.5 (7–84) | 36 (10–84) |
| Patients still hospitalised, *n* (%) | (55, 59, 57) | 17 (31) | 12 (20) | 29 (25) | 16 (28) |
| Cost of hospitalisation (£), mean (SD) | (53, 57, 53) | 8579 (6100) | 7739 (6137) | 8159 (6104) | 9233 (9676) |
| Cost of study drugs (£), mean (SD) | (56, 57, 59) | 7 (8) | 1 (1) | 4 (6) | 0 (0) |
| Total cost (£), mean (SD) | (53, 57, 53) | 8586 (6103) | 7740 (6137) | 8163 (6106) | 9233 (9676) |
| Student's *t*-test of total cost (active vs placebo) | | $t = 0.864$, $p = 0.38$ | | | |
| Mann–Whitney test of median LoS (active vs placebo) | | $p = 0.84$ | | | |

IQR, interquartile range; LoS, length of stay.

***TABLE 25*** *Cost-effectiveness, active treatment vs placebo, based on mortality at 3 months*

| **Treatment group (*n*)** | **£ per patient** | **Survival (proportion)** |
|---|---|---|
| Active treatment (106) | 8163 | 0.896 |
| Placebo (57) | 9233 | 0.789 |
| Increment (95% CI) | –1071 (–3817 to 1633) | 0.107 (–0.015 to 0.239) |
| ICER | (active treatment dominates) | |

ICER, incremental cost-effectiveness ratio.

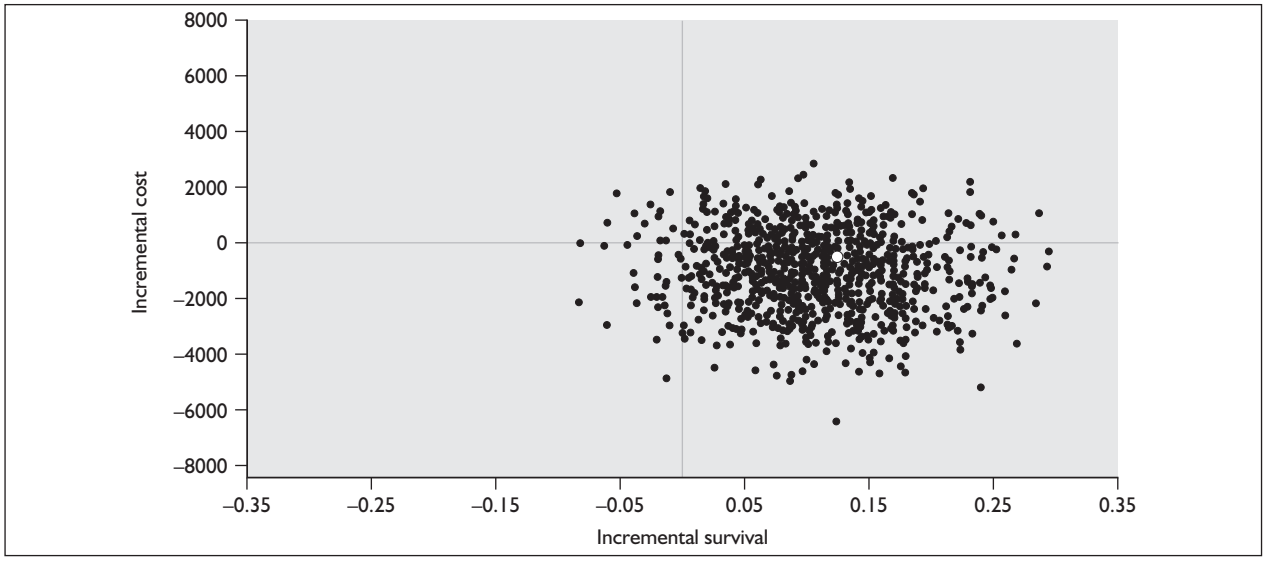


***FIGURE 18*** *Scatter plot of cost and outcome pairs.*

(*Figure 19*). A typical willingness to pay for a life saved is approximately £1m (*Green Book*,[87] paragraph 31, HM Treasury). In total, 96.3% of the bootstrapped re-samples resulted in an ICER of below £1m per life saved. This is interpreted as a 96.3% probability that the incremental cost per life saved from active treatment compared with placebo is less than £1m. Even if the willingness to pay for a fatality avoided is £0, there is a 75.5% probability that active treatment is the 'cost-effective' treatment.

An alternative presentation of these data is in the form of an incremental net benefit chart, and this is illustrated in *Figure 20*. At a willingness to pay of £1m the mean incremental net benefit is £110,000 (95% CI –£12,500 to £238,000). This means that, given a willingness to pay for a life saved of £1m, on average the added benefits of active treatment are valued more highly than any added costs. However, we did not detect a statistically significant result.

## Cost–utility analysis

We present here cost–utility ratios evaluated at 14 days and 3 months. Over 14 days there is very little difference in costs or outcomes, and mean figures suggest a point estimate ICER of £41,500, with only a 48% probability that the ICER is under £30,000 per QALY gained (*Table 26*, *Figure 21*). At the same £30,000 threshold this corresponds to a mean incremental net monetary benefit of –£8 (not statistically significant). Mean results over 3 months suggest that active treatment results in lower costs (–£5768, or 47% less than placebo; not statistically significant) and a better quality of life (0.039 QALYs, 95% CI 0.001–0.081). This results in active treatment dominating placebo, with a 97.5% probability of the ICER being below £30,000 per QALY gained. These results must be interpreted with caution because of the high risk of selection bias as stated in the section on utility and quality-adjusted life-years.

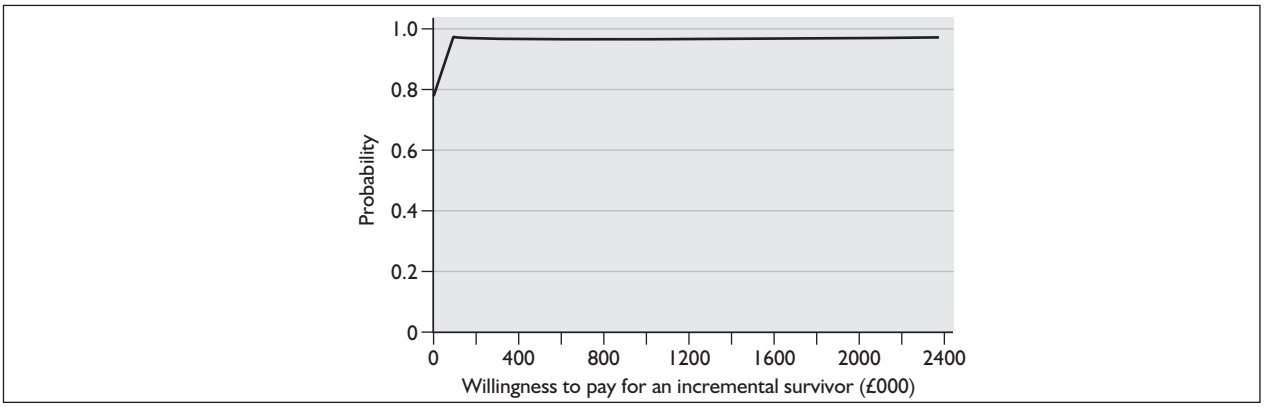


***FIGURE 19*** *Cost-effectiveness acceptability curve.*

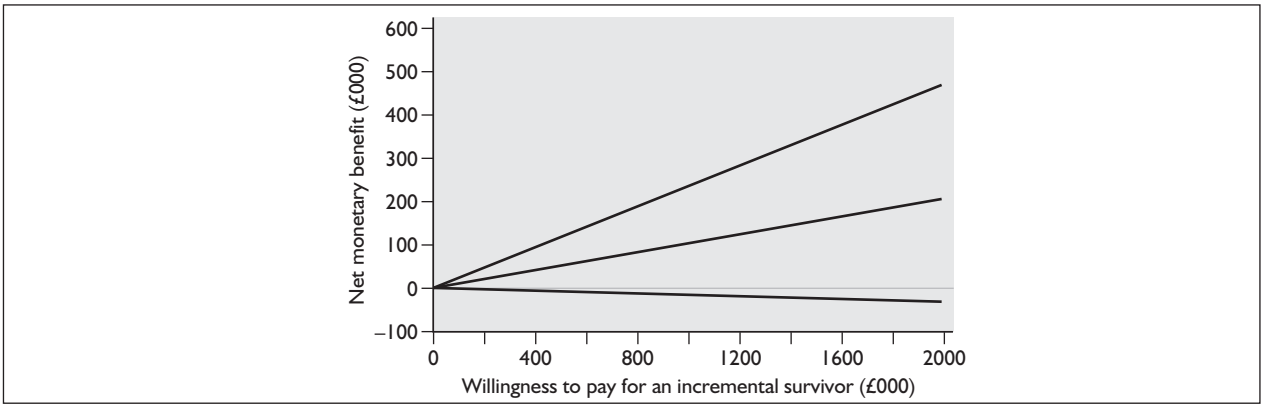


***FIGURE 20*** *Mean values and 95% confidence intervals of the net monetary benefit of active treatment over placebo at 3 months.*

## Longer-term resource use – analysis of patient diaries and interviews

A total of eight patient diaries and follow-up interviews were carried out; thus, there were insufficient data to make meaningful between-group comparisons. A total of 66 patients were entered into the CHHIPS study following implementation of protocol amendment 7, which permitted collection of health economics data. Of these, 39 (59%) were ineligible as per protocol (not discharged home, trial withdrawal, unable to complete diary). Of the remaining potentially eligible patients (41%), the co-ordinating centre was not informed of discharge in one-third of cases (nine patients). Among the remaining 18 patients, eight provided a completed diary, 11 completed the 3-month telephone interview and seven could not be contacted or refused interview. The results of the analysis of diaries and interviews are therefore presented as a cost description (*Table 27*; for details of costing see Appendix 3).

## Secondary analyses

*Table 28* summarises the secondary analyses of cost-effectiveness data, with short-term (14-day) survival, and short- and long-term death and dependency as outcomes. When considering short-term survival, on average, active treatment is slightly more expensive and also slightly more effective than placebo, resulting in a cost of only £238 per incremental survivor. Active treatment has at least a 50% probability of being cost-effective as long as a decision-maker is willing to pay at least £100 for an incremental survivor.

***TABLE 26*** *Cost–utility analyses*

| | | 14 days | 3 months |
|---|---|---|---|
| *n* | Active | 113 | 18 |
| | Placebo | 59 | 14 |
| Cost | Active | £2536 | £5067 |
| | Placebo | £2525 | £10,835 |
| Increment (95% CI) | | £12 (–231 to 265) | –£5768 (–15,118 to 975) |
| QALY | Active | 0.028 | 0.094 |
| | Placebo | 0.027 | 0.054 |
| Increment (95% CI) | | 0 (–0.001 to 0.002) | 0.039 (0.001–0.081) |
| ICER | | £41,471 | –£146,608 |
| Probability (£30,000) | | 48.00% | 97.50% |
| INB (£30,000) (95% CI) | | –8 (–270 to 258) | 7119 (17–16489) |

ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; QALY, quality-adjusted life-year.

***TABLE 27*** *Resource use post discharge*

| Payer | *n* | Mean cost (£) per patient per 3-month period (SD) |
|---|---|---|
| NHS | 8 | 801 (745) |
| Social services | 7 | 851 (1400) |
| Patient | 8 | 111 (167) |

All figures are adjusted to cost per patient per 3-month period post discharge. Mean values suggest that social services costs are comparable to NHS costs at approximately £850, with the patient paying around £110. The largest single cost component is indirect cost. In this context this is the value of carers' time spent caring. The total societal cost per patient per quarter post discharge is estimated at £4360 (see Appendix 3, *Table 34*).

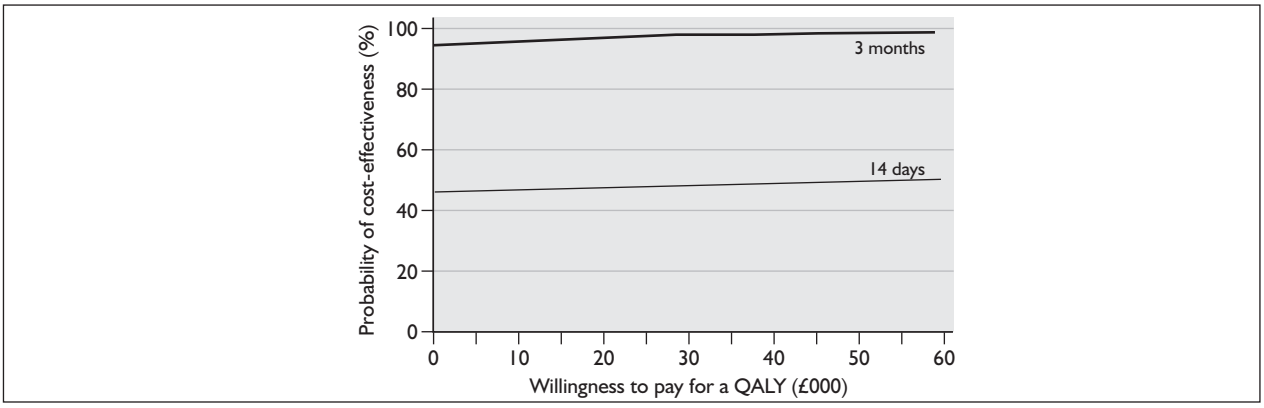


***FIGURE 21*** *Cost-effectiveness acceptability curves at 14 days and 3 months.*

***TABLE 28*** *Secondary analyses of cost-effectiveness data, two-way analyses*

| | *n* | | Cost | | Outcome | | Incremental cost (95% CI) | Incremental outcome (95% CI) | Mean ICER | Threshold |
|---|---|---|---|---|---|---|---|---|---|---|
| | Active | Placebo | Active | Placebo | Active | Placebo | | | | |
| Survival, 14 days | 113 | 59 | £2536 | £2525 | 0.947 | 0.898 | £12 (–£232 to £246) | 0.049 (–0.038 to 0.142) | £238 | £100 |
| Death and dependency, 14 days | 113 | 59 | £2536 | £2525 | 0.389 | 0.407 | £12 (–£222 to £261) | –0.017 (–0.169 to 0.135) | (Placebo dominant) | Placebo always > 50% probability of cost-effectiveness |

ICER, incremental cost-effectiveness ratio.

# Chapter 4
# Discussion

The CHHIPS trial is the first acute stroke trial to report a comparison of the effects of different antihypertensive agents administered by different routes on acute BP changes after cerebral infarction and haemorrhage. It is also able to report on the tolerability of such measures, in particular after 72 hours and at 2 weeks, and the incidence of adverse events and mortality at 3 months. The screening data allowed us to assess the applicability of the use of such depressor therapy in the general acute stroke population admitted to hospital along with the potential use of measures that could raise blood pressure in cerebral infarct patients with relative hypotension on admission. However, because of the problems with recruitment the trial was underpowered to answer the primary outcome measure of whether pharmacological manipulation of blood pressure in acute stroke alters death or dependency at 2 weeks.

## Recruitment

The recruitment to the CHHIPS trial was less than had been initially planned; only 11% of the numbers projected for the depressor limb were enrolled during the 30 months of the trial in the five active centres and the pressor limb was terminated early as it became evident that even meaningful numbers allowing a proof of concept analysis would not be obtained. Originally the trial was powered on a recruitment rate of 1650 patients over a 30-month period for 10 centres (approximately five to six patients per month per centre); however, for the depressor arm only 1.2 patients per month per centre were recruited by the five participating units. The reasons for this disparity can be explained by analysis of the screening data, an area that has not been reported on by any other BP trial in acute stroke. Although the screening data from each site do not cover the entire study period, it is clear that there were a number of major reasons why patients were excluded from the study. A large proportion of patients were ineligible for the depressor arm because, although they were hypertensive, they were on antihypertensive treatment at the time of their stroke. There is an increasing body of evidence indicating a rise in the use of antihypertensives in the UK for both primary and secondary stroke prevention. The OXVASC study[88] has shown an increase in the use of antihypertensives, with 25% of patients in the 1980s being on antihypertensive medication at the time of their first incident stroke compared with 42% in 2002–4; in terms of secondary prevention, 35% were on depressor therapy at the time of stroke recurrence in the 1980s compared with 58% in 2002–4, with a reduction in primary stroke incidence from 1.65 to 1.45 per 1000 population. This increased prescribing of antihypertensive agents has recently been enhanced by the introduction of the Quality and Outcomes Framework targets for general practitioners, which has stimulated better control of blood pressure in the community. Data from hospital sources also suggest that more stroke patients are now being admitted on antihypertensive therapy than even 5 years ago.

It is clear that one-third of potentially eligible patients were excluded because they were not assessed by the trial staff sufficiently early. They were thus excluded because they were outside the time window, an area that could be potentially improved upon if more personnel were available to aid recruitment. Another large group of patients that may have been initially eligible, having a SBP > 160 mmHg, could not be included as, by the time of screening, BP values had fallen to within the normal range as defined by the study protocol; earlier assessment again may have potentially enhanced recruitment.

Of those eligible, over one-third were recruited to the trial, which is in keeping with, or better than, other intensive acute stroke trials.[89,90] The question of whether antihypertensive therapy should be continued or stopped in stroke patients already on such therapy at the time of their stroke is currently being addressed by other ongoing trials (COSSACS,[91] ENOS[92]) and therefore these patients were excluded from the CHHIPS study (see below).

As previously stated, five sites failed to take up the offer of funding for a research nurse to run the trial, despite expressing a strong interest during the initial stages of the application. Most

of these centres considered on reflection that the study was too intensive, in terms of drug preparation, administration and monitoring, to participate and to be nurse led. This may now be overcome to some extent by the data presented here showing the safety of the drugs used and that intensive monitoring after administration as performed in CHHIPS is not necessary. Three of the four main recruiting centres were offering thrombolysis for acute ischaemic stroke, but this had a minimal effect on recruitment into the CHHIPS study. Other reasons for non-participation are given in the results section on screening data. A series of protocol amendments were made to try and improve recruitment, such as extending the depressor recruitment window by 12 hours and including dysphagic patients previously receiving antihypertensives; however, the effects of these changes on recruitment were somewhat disappointing. Possible ways of increasing future recruitment could include a much shorter admission to assessment time, which would be helped by nurse screening (the screening in CHHIPS was performed in the vast majority of cases by the one clinical research fellow per centre); a simpler protocol (a single antihypertensive agent versus placebo, although dysphagic and non-dysphagic limbs would still be required); lower BP entry criteria and less requirement for intensive BP monitoring; a significantly increased number of participating centres; the non-dysphagic arms being nurse led; and more staff able to screen and randomise patients (which would help for those patients admitted outside normal working hours and at weekends). The last factor in particular would be helped by using the support provided by the recently established Stroke Research Network. The trial was adopted by the Stroke Research Network, but the setting up of this probably came too late to aid participation and recruitment.

As regards recruitment to the pressor arm of the trial, this was undertaken only by the four centres that were allocated clinical research fellows as it was considered inappropriate for this limb of the trial to be conducted by a research nurse in view of the potential clinical risks. As can be seen from the screening data, less than 0.5% of all stroke admissions were potentially eligible for the pressor arm using the CHHIPS criteria. Only one patient was recruited, who received placebo, and this limb of the trial was stopped after 14 months after consultation with the HTA when it became evident that insufficient numbers would be recruited during the time frame of the trial. The reasons for failure to recruit to this limb of the trial have already been outlined. Access to rapid neuroradiology before randomisation did not appear to be a major factor in the failure to enter such patients as it has in some other acute stroke trials. Failure was more closely related to the other entry criteria, in particular the previous use of antihypertensive medication. If a pressor study is to be contemplated in the future, major changes to the inclusion and exclusion criteria that CHHIPS employed will have to be made, in particular the upper limit of entry BP could perhaps be raised.

## Compliance and adverse events associated with randomised treatment

As might be expected, the greatest number of treatment discontinuations came within the first 72 hours following randomisation, although treatment was generally well tolerated, with nearly three-quarters of all patients completing the 14-day schedule, and treatment allocation was never broken during trial progress. This percentage of patients continuing treatment until the end of the trial period (73%) was greater than the 64% reported in the similarly sized BEST trial,[53] in which beta-blockers were used but with a comparable treatment period. The few other BP-lowering trials in acute stroke were either of considerably shorter duration,[93] did not report data on discontinuation rates[58] or were not placebo controlled. Overall there was no significant difference in the number of withdrawals between either the labetalol or lisinopril groups and the placebo group, but small numbers limit the power of the study to detect small differences. There were more discontinuations in the dysphagic group than in the non-dysphagic group for all three treatments arms, but again active treatment was not associated with an increase in SAEs. In fact, the largest number of SAEs was seen in the placebo dysphagic arm of the trial and the fewest was in the oral labetalol group. Discontinuation of treatment because of an SAE was reported in 10% of the total trial population, with slightly more SAEs in the active treatment than in the placebo group, although this difference was not statistically significant. Of the fatal events that occurred during the first 14 days, more were seen in the placebo group than in either active treatment arms combined, although the number of events was too small to draw any firm conclusions.

## Primary outcome measure and early neurological deterioration

The three arms of the study were well matched in terms of known baseline prognostic indicators, for example age, stroke severity and type, BP levels and degree of premorbid disability, although nearly half were dysphagic at randomisation in each group compared with the expected 25%. Death and dependency in the placebo group at 2 weeks was 59%, which was exactly as predicted, the power calculations being based on a 60% level. This degree of dependency and death may appear high but, given the severity of stroke in those enrolled (about two-thirds of those recruited having a partial or total anterior cerebral circulation event), it is to be expected and is in keeping with observational data.[94] Active treatment, however, had no effect on this primary short-term outcome measure (OR 1.03, 95% CI 0.80–1.33), but the confidence intervals were wide, with the possibility of a 20% benefit of treatment or a 33% deterioration with active blood pressure lowering; however, the numbers in the trial did not allow the detection of smaller but still clinically significant changes. Similarly, it was not possible to assess if there was any heterogeneity in the effects according to stroke subtype of additional BP lowering (e.g. cerebral infarct from haemorrhage). From a trial safety point of view the greater BP reduction seen with lisinopril or labetalol compared with placebo over the first 24 hours did not result in any evidence of neurological deterioration at 72 hours.

## Secondary outcome measures – blood pressure reduction and targets

It is well known that BP tends to fall spontaneously in the first few days after stroke, and the blood pressure changes seen in the placebo group within the first 24 hours and by day 14 in CHHIPS are similar to those reported in observational studies.[27,95] 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 and using novel methods of administration, i.e. the sublingual route. This is the first study to our knowledge to compare different routes of administration as well as different antihypertensive agents in the acute stroke situation. Until now, the administration of depressor agents to stroke patients who are dysphagic (this group comprising nearly 50% of the trial population) has been difficult and has usually meant using the intravenous route with its associated problems.

The results show that the active treatments chosen in the CHHIPS trial (i.e. lisinopril and labetalol) were more effective than placebo at reducing post-stroke BP within 24 hours of randomisation; this difference was statistically significant for the treatment groups combined and for lisinopril versus placebo, although the differences for labetalol did not reach statistical significance at the 5% level. Intravenous labetalol did, however, produce a significant SBP fall by 4 hours compared with placebo, an earlier SBP reduction than that seen with the oral preparation of labetalol or lisinopril or with sublingual lisinopril. Over 80% of subjects in the intravenous labetalol arm reached the target SBP at 4 hours, meaning that no further drug would have been potentially given until 8 hours post randomisation. This probably explains the subsequent SBP rise at 8 hours in those receiving intravenous labetalol, BP values being only slightly lower than the BP values in those receiving placebo at this time point. The trial therefore emphasises the relatively short duration of action of intravenous labetalol, and future studies would need to administer this agent on a more regular basis than the current CHHIPS protocol allowed for, especially with regard to the 16-hour gap between the potential 8-hour post-randomisation dose and the next dose at 24 hours. The intravenous dose of labetalol used in CHHIPS was larger than the dose that some authorities have suggested for controlling BP before thrombolysis, although the target BP levels before thrombolysis were higher than in this trial. Sublingual lisinopril would appear to be an effective and well-tolerated alternative to the intravenous route of administrating antihypertensive agents in acute stroke, meaning that it could potentially be given by paramedics on initial patient contact or by nurses in the A&E department on patient arrival before a formal swallow assessment has taken place. The BP changes at 24 hours for the active group combined are similar to those obtained using the intravenous calcium channel blocker nimodipine[54] or transdermal glyceryl trinitrate.[59] Beta-blocker therapy in the BEST trial[53] resulted in half of the depressor effect seen here, whereas other placebo-controlled studies using oral nimodipine[93] and oral candesartan[70] found no BP-lowering effect of these agents acutely.

Treatment targets were set to an optimum SBP level for decreased death and disability based on observational data,[10] with a target SBP of between 145 and 155 mmHg by 4 and 8 hours from randomisation; if the target was not achieved, additional therapy was given. Previous stroke BP trials have not set BP targets or used an incremental dosage approach to achieve goal BP levels. By 4 hours 77% of patients receiving labetalol (oral and intravenous routes combined) had achieved the target SBP reduction, but by 24 hours this had fallen to just over 50% and was not statistically different from the number at the target SBP in the placebo group. This suggests, as previously stated, that the action of labetalol, probably because of the more rapid effects of the intravenous route, is more effective than that of lisinopril initially but that the effect is relatively short-lived and repeated dosing or continuous infusion may be the preferred method to achieve sustained SBP reduction. This would, however, necessitate a longer duration of intensive monitoring, and further work is required to clarify this issue. Lisinopril was able to achieve the target BP in nearly two-thirds of patients by 4 hours and in over half at 8 and 24 hours with little difference in achieved targets between the sublingual and oral routes. From a practical viewpoint, lisinopril, although not achieving rapid BP control in the first 4 hours, did appear to achieve more sustained control over the first 24 hours and is certainly easier to administer than intravenous labetalol for the dysphagic patient. Whether rapid early BP reduction as achieved with labetalol is better in terms of a greater reduction in death and disability than the slower antihypertensive effect achieved with lisinopril cannot be commented on because of the study size.

Compared with the placebo group, SBP, but not DBP, was significantly lower at 2 weeks in the active treatment groups combined by a mean of 7 mmHg. Few other studies have continued antihypertensive treatment for this duration; one study that did[59] found no antihypertensive effect comparing glyceryl trinitrate with placebo by day 7. All major secondary prevention trials of blood pressure lowering post stroke (which have shown the effectiveness of ACEIs or angiotensin receptor blockers and/or thiazide-like diuretics) have had a minimum entry criterion from stroke onset of 2 weeks and it was not thought to be ethical to continue trial treatment longer than the 14-day period.

## Secondary outcome measures – 3-month mortality

In keeping with many other acute intervention stroke trials, mortality at 3 months was also assessed. Despite the relatively small number of events, a borderline significant reduction in death was found in the actively treated group, with the risk of death being increased over twofold in the placebo group. The death rate at 3 months in the CHHIPS placebo group of 20% was very similar to that seen in other acute stroke trials which have included the same percentage of severe stroke patients as in CHHIPS. For example, the IMAGES trial,[96] a randomised placebo-controlled study of intravenous magnesium in acute stroke, found a 90-day mortality rate of 19% in the placebo group, and GIST, a placebo-controlled trial of insulin and potassium in acute stroke patients with mildly raised blood glucose levels, reported a 27% mortality rate at 3 months.[97] We did not assess deaths alone at 2 weeks as this was not the primary outcome measure, but the Kaplan–Meier plot suggests that the divergence in mortality between the active and placebo groups in CHHIPS was evident from very early on following randomisation and increased with time. This could not be explained by baseline differences between the active and placebo groups as they were well balanced. However, care must be taken in interpreting these results in view of the small number of events and the results being possibly due to chance. Interestingly, despite the lack of BP change compared with placebo during the first week of treatment with candesartan, the ACCESS study found a similar level of reduction in cardiovascular events at 12 months to that of CHHIPS. We did not set out to collect dependency data at 3 months in all patients, but a random sample was collected to be used in the cost–benefit analysis. The data we did obtain also suggest a positive benefit for active BP lowering in reducing death and disability at 3 months, but again small numbers preclude any statistically meaningful analysis of the data.

## Cost-effectiveness

We were unable to detect any statistically significant differences in costs between the active and placebo treatments, again mainly because of the small numbers and lack of long-term dependency

data in all subjects. However, there were trends for active treatment to be both more effective (more survivors) and less expensive than placebo, although further trials with larger sample sizes are required to verify or refute this hypothesis.

The 3-month cost–utility analysis results should be treated with appropriate caution because of the very small sample sizes and the very high risk of selection bias; indeed, at this power we were unable even to detect a mean cost differential of 50% as statistically significant, and 23 of the 33 observations were present by virtue of the patient having passed away and therefore the utility score was by definition zero. The finding of a significant improvement in QALYs in the active treatment group, although consistent with other outcome measures and expectations, may well be spurious.

To our knowledge this is the first study examining the cost-effectiveness of antihypertensive medication immediately post stroke. Previous studies have focused on either primary or secondary prevention of stroke and heart attack in patients with hypertension or other forms of cerebrovascular disease. These studies generally support the use of angiotensin type 2 receptor antagonists[98,99] and statins[100] for primary or secondary prevention of cardiovascular events in these patients. Our economic evaluation relied almost exclusively on length of stay as the major predictor of cost as the study drugs themselves were a very small component of the total cost and too few data on post-discharge resource use were collected to make a meaningful contribution to the economic evaluation. The perspective of the analysis was therefore limited to the acute hospital admitting the stroke patient. Nevertheless, length of stay is the major determinant of acute care cost in stroke rehabilitation,[101,102] and therefore our estimates of cost based on length of stay are likely to be reasonably reliable indicators of the cost of treating patients in the acute setting.

Our original intention was to analyse cost–utility from a societal perspective. Unfortunately, because of the small sample sizes we were unable to make meaningful comparisons of such and therefore the perspective was limited to the acute care setting until first discharge. This excluded readmissions, wider NHS and social services costs, patient out-of-pocket costs and indirect costs. However, based on our small sample of societal costs we estimated the acute care costs to first discharge to represent 66% of the total societal cost [mean acute cost across all patients = £8537 (average across totals from *Table 24*); mean other NHS, social services, out-of pocket and indirect costs = £4359 (Appendix 3, *Table 40*)]. This is a substantial proportion of the total societal cost, but inferences as to the impact of active treatment on societal cost-effectiveness must be made with due caution. Additional data are required to determine the cost-effectiveness of lisinopril/labetalol compared with placebo from a societal perspective.

The time horizon for the cost–utility analysis was 3 months. However, at this point approximately one-quarter of patients were yet to be discharged. Caution must therefore be exercised in generalising these results as differences in length of stay between the treatment groups may remain after the 3-month follow-up period.

## Ongoing studies

It is important to appreciate that there other ongoing trials assessing the effects of BP lowering after stroke, and these are briefly reviewed below.

### Depressor

The COSSACS study is a prospective, randomised, blinded end point study randomising patients to continue or stop existing antihypertensive therapy for a 2-week period following acute stroke, using death and dependency at 2 weeks as the primary outcome. The study design excludes dysphagic patients as all therapy has to be given orally.[91]
The ENOS study is a prospective, multicentre, randomised, parallel-group, single-blind, placebo-controlled trial testing the safety and efficacy of a nitric oxide donor (transdermal glyceryl trinitrate) and of continuing or discontinuing existing antihypertensive medication within 48 hours of acute ischaemic and haemorrhagic stroke onset for a 7-day treatment period. The primary outcome is death and dependency at 3 months.[92] Similarly to CHHIPS, recruitment in this trial has been problematic, the trial starting 6 years ago and despite having over 60 centres having recruited only 18% of the target numbers. The Scandinavian Candesartan Acute Stroke Trial (SCAST) is a multicentre, randomised, placebo-controlled, double-blind trial of the angiotensin type 1 receptor blocker candesartan versus placebo in acute stroke. The trial aims to assess whether candesartan given to non-dysphagic stroke patients with a SBP ≥ 140 mmHg within 30 hours after acute stroke reduces the risk of death or major disability at 6 months – the primary outcome measure; the risk of the combined event of vascular death, myocardial infarction or stroke during the first 6

months is powered to detect a 6% absolute relative risk compared with the proposed 9% adjusted relative risk in CHHIPS in the primary outcome measure (www.strokecentre.org/trials). This study is of a similar design to the ACCESS trial and excludes dysphagic stroke patients but not those already on antihypertensive therapy. After 3 years over 50% of the 2500 subjects have been recruited among the 150-plus centres.

### Pressor

There is very little evidence to support the routine use of pressor therapy in patients with relative hypotension following acute stroke. A recent review identified many case series but only one other small randomised controlled trial investigating the use of pressor therapy in the setting of acute stroke.[79] Our trial highlights the difficulties in recruiting patients into such a study. It may be that, in the future, as stroke services develop with the wider provision of hyperacute treatment and rapid assessment and admissions protocols, a large-scale multicentre trial of pressor therapy in acute stroke will become more feasible.

## Conclusions

In conclusion, both labetalol and lisinopril lowered BP to a greater degree than placebo in acute stroke patients within 36 hours of symptom onset, without causing adverse side effects or an early increase in stroke severity. Sublingual lisinopril and intravenous labetalol were also effective hypotensive agents in the immediate post-stroke period in dysphagic patients. However, active therapy did not reduce death and dependency at 2 weeks, the primary outcome measure, although the trial was underpowered to detect small, but clinically significant, changes in this and the other main outcome measures. Of interest was the reduction in stroke mortality at 3 months with active therapy, a finding in keeping with one other acute BP-lowering stroke trial, although care must be taken in interpretation of the CHHIPS results in view of the small sample size. Further work is now much needed to confirm these results and to assess if there are differences in the effectiveness, in terms of reducing death or dependency, of labetalol compared with lisinopril after acute stroke and whether the introduction of earlier BP lowering post stroke than was achieved in CHHIPS would be of greater benefit, especially with regard to use before thrombolysis. The role for increasing BP in acute stroke remains unresolved, although the number in whom this therapy could be applied is very small using the CHHIPS trial entry criteria. The fact that we are still uncertain as to the best management of BP in the acute stroke situation is of serious concern, as highlighted in two recent guidelines on acute stroke management.[103,104] The positive findings from the CHHIPS trial need to be taken further in formulating the definitive trial of BP lowering in acute stroke.

## Research recommendations

To improve recruitment to acute stroke trials in general:

1. Increase the number of recruiting centres (double the number you first thought of), assessing their 'real' ability for recruitment, in terms of number of patients seen, and their suitability, as determined from their local stroke register and their levels of staffing and facilities (not those promised by the time that the trial starts). This may include approaching centres outside the UK, although this has potential problems with regard to provision of the trial drugs and provision of the indemnity.
2. At each proposed recruiting centre assess the number of other potentially conflicting acute stroke trials being undertaken or contemplated and their impact on recruitment potential.
3. Identify a local researcher in each centre who is interested in the specific trial and not just the lead stroke researcher for that centre.
4. Ensure that the trial is suitable to be adopted by the Stroke Research Network or the Local Comprehensive Research Network.
5. Funding bodies should not expect 'quick' results; most large trials, even pragmatic ones, take many years to complete and very few large studies have been completed in 36–48 months, even with commercial funding. This should be stated by the funding body so that undue pressure is not put on the researchers to try and reach goal numbers in an unrealistic time frame because long-term funding will not be readily available.
6. Ensure that funding to each centre is adequate and that nursing as well as medical staffing levels and the level of experience are sufficient to be able to run the trial. Also, ensure that suitable monitoring equipment and facilities are available and that no dramatic changes to the stroke services are expected during the course of the proposed trial, for example closure of the unit or transfer of the unit to a different hospital.

7. Make sure that the study is as simple as possible so that non-experienced research staff are able to undertake the protocol; this is especially important when dedicated trial staff are away on holiday or sick leave or because of other routine causes. Dedicated trial staff cannot be present at all times and each centre should have a fallback position for when staff members are away to enable recruiting to be continued.
8. Provide adequate funding for academic trials to match that given by similar commercial studies so that triallists are not penalised for undertaking academic studies.
9. Try and predict how the results of other ongoing trials, changes in medical practice, effects of guidelines, etc. will potentially affect recruitment during the period of the trial.

To improve recruitment to a future acute blood pressure stroke trial:

1. The CHHIPS triallists (and also the referees) believe that, despite the data to date, a clear answer to the problem of how to manage blood pressure immediately post stroke is unclear, although the CHHIPS data do give some leads. Therefore, we subscribe to the need for a revised CHHIPS trial, which should be carried out taking into account the important findings obtained to date but with a simpler methodology. First, the pressor arm should not be contemplated as this limb of the trial appears to be neither logical nor practical. The centres undertaking CHHIPS, and those that contemplated doing so, were concerned with the intensity and duration of monitoring that was put in place by the investigators, who were concerned about patient safety. The data obtained from CHHIPS to date for the depressor arm suggest that, at the dosages used, the two hypotensive agents are safe and therefore the level of monitoring does not have to be as intense as initially set out.
2. We suggest that a single hypotensive agent should be used against matching placebo; from the initial data and considering the practicalities, lisinopril, which can be given orally or sublingually, therefore negating the need for intravenous infusions and intensive monitoring, would seem to be the ideal agent. Investigators were very wary of giving intravenous hypotensive agents without very close monitoring in a high-dependency unit, which would not be necessary with lisinopril. This agent could also be given by trained trial nurses, reducing the need for expensive medical staff.
3. Given the results of the CHHIPS trial we would recommend that the same criteria as originally set out are adopted but that only one hypotensive agent is used, markedly reducing the numbers needed to be recruited from 1650 to 1100. To improve recruitment and increase the applicability of the data to day-to-day practice, we would also recommend that entry SBP be reduced from 160 mmHg to 140 mmHg. We would also consider randomising those patients who were already on antihypertensive medication before their stroke. The primary end point should again be death or dependency, but at 3 months and not 2 weeks as in the original protocol. Adequate funding to match that of similar commercial trials, for example the SCAST trial, should be made available and the study should be allowed to recruit outside the UK with provision for supplying medical indemnity for the trial as required.

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## Participating centres

Leicester: JF Potter, T Robinson, P Eames, N Shah, A Mistri; Newcastle-upon-Tyne: G Ford, A Dixit, J Davis; Exeter: M James, P Johnson; Bournemouth: D Jenkinson, T Black, A Orpen; Liverpool: A Sharma, E Bacabac, John Jones; Wansbeck: S Huntley, C Price.

## CHHIPS committees

### *Writing Committee*

JF Potter (principal investigator), TG Robinson, GA Ford, A Mistri, M James, J Chenova, C Jagger.

### *Trial Steering Committee*

H Markus (Chairman), C Bulpitt, A Drummond, GA Ford, C Jagger, J Knight (Stroke Association representative), JF Potter (principal investigator), T Robinson.

### *Data and Safety Monitoring Committee*

G Beevers (Chairman), S Walters (independent statistician); D Thomas (independent clinician).

## Publications

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# Appendix 1

## Trial medication discontinuations

| Reason for discontinuation | Number of patients |
|---|---|
| Serious adverse event | 18 (labetalol 6, lisinopril 8, placebo 4) |
| No route to administer | 10 (9 – no NG or PEG tube; 1 – no i.v.) |
| High blood pressure | 5 |
| Protocol violation/trial withdrawal | 4 |
| Bronchospasm | 2 |
| Low blood pressure | 1 |
| Neurological deterioration | 2 |
| Patient request | 1 |
| Bradycardia | 1 |
| Paroxysmal atrial fibrillation requiring open-label beta-blocker | 1 |
| Incorrect discontinuation (rise in creatinine but not to level specified in protocol) | 1 |
| Relative request | 1 |
| Total | 47 |

i.v., intravenous; NG, nasogastric; PEG, percutaneous endoscopic gastrostomy.

# Appendix 2

# Serious adverse event reporting form

CHHIPS Controlling Hypertension and Hypotension Immediately Post Stroke trial

Depressor arm

Patient initials | | Patient number | | | | | | | | | Treatment number | | | | | | |

## Serious adverse event form

SAE form initiated by: NIHSS increase ≥4 Other

(*Please circle*)

Date of event | | | | | | | D D M M Y Y

Time of event | | | | | H H M M

### *A. Event: (Please circle)*

| | | | |
|---|---|---|---|
| 1. Fatal | Yes | No | |
| If no, serious because: | Life-threatening | Significantly disabling | Medical intervention |
| | Prolonged hospitalisation | Teratogenic | Carcinogenic |
| 2. System | | | |
| Cerebrovascular | Unspecified stroke | TIA | HTI |
| | Stroke in evolution | Recurrent stroke (ischaemic) | Recurrent stroke (haemorrhagic) |
| | Hydrocephalus | Seizure | Other (state) |
| Cardiorespiratory | Myocardial infarction | Heart failure | Arrhythmia (state) |
| | Aortic aneurysm | Hypertension | Systemic embolism (state) |
| | Pulmonary embolus | Deep vein thrombosis | Other (state) |
| Infection | Bronchopneumonia | Urinary tract | Endocarditis |
| | Septicaemia | Other (state) | |
| Metabolic | Renal failure | Hyperglycaemia | Hypoglycaemia |
| | Hyponatraemia | Hypokalaemia | Other (state) |
| Haematological | Anaemia | Thrombocytopenia | Other (state) |
| Pharmacological | Anaphylaxis | Rash | Other (state) |
| Other | Gastrointestinal (state) | Musculoskeletal (state) | Other (state) |

***B. Severity: (Please circle)***

Mild Moderate Severe

***C. Causality (relationship to study): (Please circle)***

Yes No Unsure

***D. Study continuation: (Please circle)***

Yes (treatment continued) Yes (treatment interrupted) No (treatment discontinued)

***E. Diagnostic evidence:***

| | | | Details: |
|---|---|---|---|
| Pathological | Yes | No | |
| Radiological | Yes | No | |
| ECG | Yes | No | |
| Bacteriology | Yes | No | |
| Biochemistry | Yes | No | |
| Haematology | Yes | No | |
| Clinical | Yes | No | |
| Other | Yes | No | |

***F. Additional information:***

| |
|---|
| |
| |
| |

Signature (of study staff completing form):

Contact: telephone: 0116 000 0000; facsimile: 0116 000 0000; e-mail: chhips@le.ac.uk

# Appendix 3

# Resource use and costs

## Resource use quantities

***TABLE 29*** *Mean quantities of resource per patient at 14 days*

| | ***n* (a, b, c)** | **Labetalol (a)** | **Placebo (b)** | **Lisinopril (c)** |
|---|---|---|---|---|
| Mean length of stay (days) (SD) | 56, 59, 57 | 11.57 (4.263) | 11.36 (4.429) | 11.23 (4.464) |
| Tablets used (SD) | 56, 60, 57 | 34.68 (24.812) | 44.92 (30.386) | 29.84 (24.886) |
| Vials used (SD) | 56, 60, 57 | 4.23 (6.881) | 5.62 (8.403) | 5.05 (8.348) |

***TABLE 30*** *Mean quantities of resource per patient at 3 months*

| | ***n* (a, b, c)** | **Labetalol (a)** | **Placebo (b)** | **Lisinopril (c)** |
|---|---|---|---|---|
| Mean length of stay (days) (SD) | 53, 57, 53) | 45.75 (34.66) | 49.47 (54.98) | 40.98 (34.87) |
| Tablets used (SD) | 56, 60, 57 | 34.68 (24.812) | 44.92 (30.386) | 29.84 (24.886) |
| Vials used (SD) | 56, 60, 57 | 4.23 (6.881) | 5.62 (8.403) | 5.05 (8.348) |

## Cost description to 3 months

The following tables summarise resource use, unit costs and resulting total costs from patient diaries and questionnaires.

***TABLE 32*** *Social services use post discharge*

| Item | Source | *n* | Mean use per patient per week (SD) |
|---|---|---|---|
| Home help social services visits | Diary | 8 | 0.99 (2.450) |
| Meals on Wheels | Diary | 8 | 0.59 (1.679) |
| Respite at home (hours) | Questionnaire Q3.1 | 10 | 0.25 (0.791) |
| Respite away from home (days) | Questionnaire Q3.2 | 10 | 0.00 (0.000) |
| | | | Mean use per patient over study period (SD) |
| Commode | Questionnaire Q4.2 | 10 | 0.2 (0.422) |
| Raised toilet seat | Questionnaire Q4.2 | 10 | 0.1 (0.316) |
| Wheelchair | Questionnaire Q5 | 10 | 0.30 (0.483) |
| Special mattress | Questionnaire Q5 | 10 | 0.10 (0.316) |
| Walking stick | Questionnaire Q5 | 10 | 0.20 (0.422) |
| Other | Questionnaire Q5 | 10 | 0.20 (0.422) |
| Shower | Questionnaire Q6 | 10 | 0.20 (0.422) |
| Rails inside | Questionnaire Q6 | 10 | 0.40 (0.516) |
| Bathroom/toilet modification | Questionnaire Q6 | 10 | 0.10 (0.316) |
| Other | Questionnaire Q6 | 9 | 0.11 (0.333) |

***TABLE 33*** *Private resource use post discharge*

| Item | Source | *n* | Mean use per patient per week (SD) |
|---|---|---|---|
| Home help private visits | Diary | 8 | 0.23 (0.648) |
| Incontinence pads | Questionnaire Q4 | 10 | 6.30 (10.667) |
| Disposable sheets | Questionnaire Q4 | 10 | 0.2 (0.632) |
| Reusable sheets | Questionnaire Q4 | 10 | 0.2 (0.632) |

***TABLE 34*** *Indirect resource quantities post discharge*

| Item | Source | *n* | Hours per patient per week (SD) |
|---|---|---|---|
| Main carer personal care, etc. (hours) | Questionnaire Q1.1 | 10 | 9.95 (15.63) |
| Other carer personal care, etc. (hours) | Questionnaire Q1.2 | 8 | 0.33 (0.707) |

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***TABLE 35*** *Unit costs*

| Item (unit) | Unit cost | Source/notes |
|---|---|---|
| IP admission for stroke | £2462 | NHS reference costs 2005/6, Appendix NSRC4, sheet TNELIP, A22, non-transient stroke or CVA > 69 or w cc. 11-day mean LoS |
| IP admission excess day cost | £176 | NHS reference costs 2005/6, Appendix NSRC4, sheet TNELIPXS, A22, non-transient stroke or CVA > 69 or w cc |
| Hospital outpatient visit | £118 | General medicine follow-up visit, adult. NHS reference costs 2005/6, Appendix NSRC4, sheet TOPS FUA, specialty 300F |
| A&E attendance | £66 | A&E no investigation referred/discharged. NHS reference costs 2005/6, Appendix NSRC4, sheet TA&E, HRG V08 |
| Day hospital | £571 | NHS reference costs 2005/6, Appendix NSRC4, sheet TDC, HRG A22, non-transient stroke or CVA > 69 or w ccs |
| Social services day centre | £29.50 | Daily cost of social care day care. PSSRU 2006, p. 55[a] |
| Lunch club | £8.30 | RISE scheme as detailed in *The baker's dozen: unit costs and funding*, Table 1. PSSRU 2006, p. 38[a] |
| GP home visit | £69 | Based on 13.2 minutes home visit plus 12 minutes travel time, including direct care staff and training costs. PSSRU 2006, p. 143[a] |
| GP surgery visit | £25 | Based on 10.0 minutes surgery consultation including direct care staff and training costs. PSSRU 2006, p. 143[a] |
| Other doctor home visit | £69 | Assumed same as GP home visit |
| Physiotherapist home visit | £44 | Community physiotherapist home visit including qualification costs. PSSRU 2006, p. 127[a] |
| Physiotherapist other visit | £16 | Community physiotherapist clinic visit including qualification costs. PSSRU 2006, p. 127[a] |
| Occupational therapist home visit | £44 | Community occupational therapist home visit including qualification costs. PSSRU 2006, p. 128[a] |
| Occupational therapist other visit | £16 | Community occupational therapist clinic visit including qualification costs. PSSRU 2006, p. 128[a] |
| Speech/language therapist home visit | £44 | Community speech/language therapist home visit including qualification costs. PSSRU 2006, p. 129[a] |
| Speech/language therapist other visit | £16 | Community speech/language therapist clinic visit including qualification costs. PSSRU 2006, p. 129[a] |
| Specialist nurse home visit | £73.30 | Community nurse specialist, hour of client contact including qualification costs. Travel at £1.30 per visit. Note: assumes visit lasts an hour. PSSRU 2006, p. 138[a] |
| Specialist nurse other visit | £72.00 | Community nurse specialist, hour of client contact including qualification costs. Note: assumes visit lasts an hour. PSSRU 2006, p. 138[a] |
| Auxiliary nurse home visit | £17 | GP practice nurse home visit including qualification costs. PSSRU 2006, p. 140[a] |
| Auxiliary nurse other visit | £10 | GP practice nurse consultation including qualification costs. PSSRU 2006, p. 140[a] |
| Home help, social services (hour) | £16 | Local authority home care worker per hour face to face weekday contact. PSSRU 2006, p. 152[a] |
| Home help, private (hour) | £13 | Prices of independently provided personal home care where > 75% of clients have special needs. PSSRU 2006, p. 153[a] |
| Meals on Wheels (meal) | £3.50 | Weekly cost/7. PSSRU 2006, p. 52[a] |
| Respite care, own home (hour) | £9.75 | Assumed same as 'Respite care, other location' per hour based on an 8-hour day |
| Respite care, other location (day) | £78 | Voluntary sector activity-based respite care for people with learning disabilities. PSSRU 2006, p. 88[a] |
| Incontinence pad (pad) | £0.58 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Disposable bed sheet (sheet) | £0.85 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Reusable bed sheet (sheet) | £5.94 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Commode/chamber pot (item) | £52.00 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |

*continued*

***TABLE 35*** *Unit costs*

| Item (unit) | Unit cost | Source/notes |
|---|---|---|
| Urinal/bedpan/bottle | £18.56 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Sheath | £5 | Nominal price |
| Plastic on bed | £5.94 | Assumed same as reusable bed sheet |
| Indwelling catheter | £15 | Assumed GP nurse clinic visit plus nominal £5 for catheter |
| Self-administered catheter | £5 | Nominal price |
| Raised toilet seat | £18.56 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Wheelchair | £19.50 | 3 months' use of self- or attendant-powered chair including capital and revenue costs. PSSRU 2006, p. 117[a,b] |
| Hoist | £2306 | Median cost of hoist. PSSRU 2006, p. 118[a,b] |
| Orthopaedic mattress | £222.13 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Chair pad | £7.42 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Stair lift | £2912 | Median cost of stairlift. PSSRU 2006, p. 118[a,b] |
| Door answering system | £431 | Median cost of entry phones. PSSRU 2006, p. 118[a,b] |
| Walking frame | £33.42 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Walking stick | £5.19 | www.handyhealthcare.co.uk, excluding VAT (2007 price converted to 2006) |
| Shower installation | £1789 | Median cost of relocation of bath or shower. PSSRU 2006, p. 118[a,b] |
| Kitchen alterations | £3492 | Median cost of kitchen redesign. PSSRU 2006, p. 118[a,b] |
| Door alterations | £533 | Median cost of joinery work (external door). PSSRU 2006, p. 118[a,b] |
| Ramp outside house | £340 | Median cost of simple concrete ramp. PSSRU 2006, p. 118[a,b] |
| Ramp inside house | £340 | Assumed same as external ramp |
| Handrails | £46 | Median cost of grab rail. PSSRU 2006, p. 118[a,b] |
| Other access alterations | £306 | Assumed mean cost of door, ramp and handrail alterations |
| Bathroom and toilet alterations | £2947 | Median cost of bathroom redesign. PSSRU 2006, p. 118[a,b] |
| Carer time (hour) | £13.00 | Mean gross hourly pay 2006. ONS annual survey of hours and earnings, 2006 |
| 5 mg tablet, lisinopril | £0.0479 | BNF 51[c] (generic lisinopril £1.34/28-tablet pack) |
| 50 mg tablet, labetolol | £0.0677 | BNF 51[c] (Trandate® £3.79/56-tablet pack – 50 mg not available as non-proprietary) |
| 5 mg sublingual, lisinopril | £0.0479 | BNF 51[c] (generic lisinopril £1.34/28-tablet pack). Assumed same as tablets |
| 50 mg intravenous labetalol | £1.06 | BNF 51[c] (based on 20-ml ampoule of 5 mg/ml labetalol hydrochloride at £2.12) |

A&E, accident & emergency; CVA, cerebrovascular accident; HRG, Health Resource Group; IP, inpatient; LoS, length of stay; ONS, Office for National Statistics; w cc, with complications. Price year 2006. Change in consumer price index in the period March 2006–March 2007 = 3.1%.

a Personal Social Services Research Unit. *Unit costs of health and social care*, compiled by L Curtis and A Netten. PPSRU, University of Kent, Canterbury; 2006.

b Approach to costing adaptations to home: used median cost reported in PSSRU rather than annuitised as this is money required to be spent; have used annuitised cost for consumables such as a wheelchair as these could be used by someone else after the patient has finished with them.

c British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary* (BNF). No. 51, March 2006. London: BMA and RPS; 2006.

***TABLE 36*** *Cost of NHS service use post discharge*

| Item | Source | *n* | Mean cost per patient per week (SD) |
|---|---|---|---|
| Outpatient appointments | Diary | 8 | £33.39 (£46.139) |
| A&E attendances | Diary | 8 | £0.00 (£0.000) |
| Day hospital attendances | Diary | 8 | £0.00 (£0.000) |
| GP home visits | Diary | 8 | £3.63 (£4.084) |
| GP other visits | Diary | 8 | £5.08 (£5.825) |
| Other doctor home visits | Diary | 8 | £0.96 (£2.711) |
| Physiotherapist home visits | Diary | 8 | £5.73 (£10.345) |
| Physiotherapist other visits | Diary | 8 | £0.94 (£1.753) |
| Occupational therapist home visits | Diary | 8 | £7.94 (£17.322) |
| Occupational therapist other visits | Diary | 8 | £0.72 (£1.463) |
| Speech/language therapist home visits | Diary | 8 | £0.61 (£1.728) |
| Speech/language therapist other visits | Diary | 8 | £0.00 (£0.000) |
| Specialist nurse home visits | Diary | 8 | £5.60 (£11.709) |
| Specialist nurse other visits | Diary | 8 | £1.29 (£3.637) |
| Auxilliary nurse home visits | Diary | 8 | £0.00 (£0.000) |
| Auxilliary nurse other visits | Diary | 8 | £0.00 (£0.000) |
| Other home visits | Diary | 8 | £0.24 (£0.668) |
| Other other visits | Diary | 8 | £0.63 (£1.768) |
| Total NHS cost per week | | 8 | £66.75 (£62.11) |
| Total NHS cost over 3 months | | 8 | £801.05 (£745.31) |

***TABLE 37*** *Cost of social services use post discharge*

| Item | Source | *n*[a] | Cost |
|---|---|---|---|
| ***Weekly recurrent items*** | | | ***Mean cost per patient per week (SD)*** |
| Home help social services visits | Diary | 8 | £15.78 (£39.197) |
| Meals on Wheels | Diary | 8 | £2.08 (£5.878) |
| Respite at home, hours | Questionnaire Q3.1 | 10 | £0.24 (£0.77) |
| Respite away from home, days | Questionnaire Q3.2 | 10 | £0.00 (£0.00) |
| Total cost per week[b] | | 8 | £18.16 (£38.53) |
| ***Capital purchases*** | | | ***Cost per patient (SD)*** |
| Commode | Questionnaire Q4.2 | 10 | £10.40 (£21.93) |
| Raised toilet seat | Questionnaire Q4.2 | 10 | £1.86 (£5.87) |
| Wheelchair | Questionnaire Q5 | 10 | £5.85 (£9.42) |
| Special mattress | Questionnaire Q5 | 10 | £22.21 (£70.24) |
| Walking stick | Questionnaire Q5 | 10 | £1.04 (£2.19) |
| Other | Questionnaire Q5 | 10 | £10.00 (£21.08) |
| Shower | Questionnaire Q6 | 10 | £357.80 (£754.31) |
| Rails inside | Questionnaire Q6 | 10 | £18.40 (£23.75) |
| Bathroom/toilet modification | Questionnaire Q6 | 10 | £294.70 (£931.92) |
| Other | Questionnaire Q6 | 9 | £34.00 (£102.00) |
| Total cost[b] | | 9 | £468.24 (£887.97) |
| Equivalent total cost per week | | 9 | £39.02 (£74.00) |
| Total social services cost per week | | 7 | £70.92 (£116.67) |
| Total cost over 3 months | | 7 | £851.09 (£1400.02) |

a Sample size for each component and summary measure.
b Totals do not amount to sum of components as a result of missing data.

***TABLE 38*** *Cost of private expenditure post discharge*

| Item | Source | *n*[a] | Mean cost per patient per week (SD) |
|---|---|---|---|
| Home help private visits | Diary | 8 | £2.98 (£8.426) |
| Incontinence pads | Questionnaire Q4 | 10 | £3.65 (£6.19) |
| Disposable sheets | Questionnaire Q4 | 10 | £0.17 (£0.54) |
| Reusable sheets | Questionnaire Q4 | 10 | £1.19 (£3.76) |
| Total cost[b] | | 8 | £9.24 (£13.88) |
| Total private cost over 3 months | | 8 | £110.93 (£166.52) |

a Sample size for each component and summary measure.
b Totals do not amount to sum of components as a result of missing data.

***TABLE 39*** *Indirect cost post discharge*

| Item | Source | *n*[a] | Cost per patient per week (SD) |
|---|---|---|---|
| Main carer personal care, etc., hours | Questionnaire Q1.1 | 10 | £129.35 (£203.17) |
| Other carer personal care, etc., hours | Questionnaire Q1.2 | 8 | £4.33 (£9.19) |
| Total cost[b] | | 9 | £148.06 (£208.40) |
| Total indirect cost over 3 months | | 9 | £1776.67 (£2500.80) |

a Sample size for each component and summary measure.
b Totals do not amount to sum of components as a result of missing data.

***TABLE 40*** *Grand total cost post discharge*

| Item | *n* | Cost per patient (SD) |
|---|---|---|
| Total direct cost per week | 7 | £130.59 (£123.68) |
| Total indirect cost per week | 9 | £148.06 (£208.40) |
| Total cost per week | 6 | £363.26 (£323.24) |
| Total direct cost over 3 months | 7 | £1567.04 (£1484.19) |
| Total indirect cost over 3 months | 9 | £1776.67 (£2500.80) |
| Total cost per 3 months | 6 | £4359.14 (£3878.88) |

# Appendix 4

# Assessment scales

## (a) Modified Rankin Scale

| Grade | Description |
|---|---|
| ***Independent*** | |
| 0 | No symptoms |
| 1 | Minor symptoms: symptoms that do not interfere with lifestyle |
| 2 | Minor handicap: symptoms that do lead to some restriction in lifestyle, but do not interfere with patients' capacity to look after themselves |
| ***Dependent*** | |
| 3 | Moderate handicap: symptoms that appreciably restrict the patient's lifestyle or that prevent totally independent existence, or both |
| 4 | Moderately severe handicap: symptoms that clearly prevent independent existence, although patient does not need constant attention |
| 5 | Severe handicap: totally dependent, patient requiring constant attention day and night |

## (b) Barthel Index

| Function | Description |
|---|---|
| Bathing | 0 dependent |
| | 1 independent (including bath/shower transfers) |
| Bladder | 0 incontinent/catheterised |
| | 1 occasional accident |
| | 2 continent |
| Bowels | 0 incontinent |
| | 1 occasional accident |
| | 2 continent |
| Dressing | 0 dependent |
| | 1 needs help |
| | 2 independent |
| Feeding | 0 unable |
| | 1 needs help |
| | 2 independent |
| Grooming | 0 needs help with personal care |
| | 1 independent |
| Mobility | 0 immobile |
| | 1 wheelchair independent |
| | 2 walks with help of one person |
| | 3 independent |
| Stairs | 0 unable |
| | 1 needs help (verbal, physical, carrying aid) |
| | 2 independent up and down |
| Toilet use | 0 dependent |
| | 1 needs some help |
| | 2 independent |
| Transfers | 0 unable, no sitting balance |
| | 1 major help (physical, one or two people) |
| | 2 minor help (verbal or physical) |
| | 3 independent |

## (c) EQ-5D (EuroQoL)

We are trying to find out what you think about your health. I will ask you a few brief and simple questions about your own health state today. I will explain the task fully as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

*First I am going to read out some questions. Each question has a choice of three answers. Please tell me which answer best describes your own health state today. Do not choose more than one answer in each group of questions.*

***IF RESPONDENT HAS DIFFICULTY IN ANSWERING THEN REPEAT QUESTION VERBATIM. FOR EACH QUESTION RING APPROPRIATE NUMBER ON ANSWER SHEET.***

Question 1: Mobility

*First I'd like to ask you about mobility.*

Would you say you have:

1. No problems in walking about?
2. Some problems in walking about?
3. Are you confined to bed?

Question 2: Self-care

*Next I'd like to ask you about self-care.*

Would you say you have:

1. No problems with self-care?
2. Some problems washing or dressing yourself?
3. Are you unable to wash or dress yourself?

Question 3. Usual activities

*Next I'd like to ask you about usual activities, for example work, study, housework, family or leisure activities.*

Would you say you have:

1. No problems with performing your usual activities?
2. Some problems with performing your usual activities?
3. Are you unable to perform your usual activities?

Question 4: Pain/discomfort

*Next I'd like to ask you about pain or discomfort.*

Would you say you have:

1. No pain or discomfort?
2. Moderate pain or discomfort?
3. Extreme pain or discomfort?

Question 5: Anxiety/depression

*Finally I'd like to ask you about anxiety or depression.*

Would you say you are:

1. Not anxious or depressed?
2. Moderately anxious or depressed?
3. Extremely anxious or depressed?

***PLEASE REMEMBER IT IS IMPORTANT TO HAVE ONE AND ONLY ONE RESPONSE TO EACH GROUP OF THREE RESPONSES***

## (d) National Institute of Health Stroke Scale

| NIH Stroke Scale item | Function | Score |
|---|---|---|
| 1a. Level of consciousness | Alert | 0 |
| | Drowsy | 1 |
| | Stuporous (requires repeated stimulation) | 2 |
| | Coma (reflex responses only) | 3 |
| 1b. Level of consciousness questions (month, age) | Both correct | 0 |
| | One correct | 1 |
| | Incorrect | 2 |
| 1c. Level of consciousness commands (open, close eyes; make fist, let go | Obeys both correctly | 0 |
| | Obeys one correctly | 1 |
| | Incorrect | 2 |
| 2. Best gaze (eyes open – patient follows examiners finger or face) | Normal | 0 |
| | Partial gaze palsy | 1 |
| | Forced deviation | 2 |
| 3. Visual (introduce visual stimulus/threat to patient's visual field quadrants) | No loss | 0 |
| | Partial hemianopia | 1 |
| | Complete hemianopia | 2 |
| | Bilateral hemianopia | 3 |
| 4. Facial palsy (show teeth, raise eyebrows and squeeze eyes shut) | Normal | 0 |
| | Minor asymmetry | 1 |
| | Partial (lower face paralysis) | 2 |
| | Complete | 3 |
| 5a. Motor arm – left (elevate extremity 90° and score drift/movement) | No drift | 0 |
| | Drift | 1 |
| | Some effort against gravity | 2 |
| | No effort against gravity | 3 |
| | No movement | 4 |
| | Amputation, joint fusion | 9 |
| 5b. Motor arm – right (elevate extremity 90° and score drift/movement) | No drift | 0 |
| | Drift | 1 |
| | Some effort against gravity | 2 |
| | No effort against gravity | 3 |
| | No movement | 4 |
| | Amputation, joint fusion | 9 |
| 6a. Motor leg – left (elevate extremity 30° and score drift/movement) | No drift | 0 |
| | Drift | 1 |
| | Some effort against gravity | 2 |
| | No effort against gravity | 3 |
| | No movement | 4 |
| | Amputation, joint fusion | 9 |

*continued*

| NIH Stroke Scale item | Function | Score |
|---|---|---|
| 6b. Motor leg – right (elevate extremity 30° and score drift/movement) | No drift | 0 |
| | Drift | 1 |
| | Some effort against gravity | 2 |
| | No effort against gravity | 3 |
| | No movement | 4 |
| | Amputation, joint fusion | 9 |
| 7. Limb ataxia (finger to nose, heel down shin) | Absent | 0 |
| | Present in upper or lower | 1 |
| | Present in both | 2 |
| 8. Sensory (pin prick to face, arm, trunk and leg – compare side to side) | Normal | 0 |
| | Partial loss | 1 |
| | Dense loss | 2 |
| 9. Best language (name items, describe a picture and read sentences) | No aphasia | 0 |
| | Mild–moderate aphasia | 1 |
| | Severe aphasia | 2 |
| | Mute | 3 |
| 10. Dysarthria (evaluate speech clarity by patient repeating listed words) | Normal articulation | 0 |
| | Mild–moderate slurring | 1 |
| | Severe, near unintelligible or worse | 2 |
| 11. Extinction and inattention (use information from prior testing to identify neglect or double simultaneous stimuli testing) | No neglect | 0 |
| | Partial neglect | 1 |
| | Profound neglect | 2 |

## (e) Oxfordshire Community Stroke Project classification

Patients presenting with a stroke can be classified according to their collection of symptoms and signs. These are:

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

Classification depends on three main features:

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

This is a clinical classification prior to neuroimaging.

| Features | Classification |
|---|---|
| All three present | TACS |
| Two out of three present | PACS |
| Drowsy + unilateral weakness (visual + higher cerebral involvement assumed) | TACS |
| Motor/sensory/sensorimotor involvement affecting two or more out of arm/face/leg or ataxic hemiparesis | LACS |
| Cerebellar syndrome or brainstem involvement | POCS |
| Isolated speech or visual involvement | PACS |
| Motor or sensory involvement affecting only one area (face or arm or leg) | PACS |

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## Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***

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