



Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial

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Summary

Background Raised blood pressure is common after acute stroke and is associated with an adverse prognosis. We sought to assess the feasibility, safety, and effects of two regimens for lowering blood pressure in patients who have had a stroke.

Methods Patients who had cerebral infarction or cerebral haemorrhage and were hypertensive (systolic blood pressure [SBP] >160 mm Hg) were randomly assigned by secure internet central randomisation to receive oral labetalol, lisinopril, or placebo if they were non-dysphagic, or intravenous labetalol, sublingual lisinopril, or placebo if they had dysphagia, within 36 h of symptom onset in this double-blind pilot trial. The doses were titrated up if target blood pressure was not reached. Analysis was by intention to treat. This trial is registered with the National Research Register, number N0484128008.

Findings 179 patients (mean age 74 [SD 11] years; SBP 181 [SD 16] mm Hg; diastolic blood pressure [DBP] 95 [SD 13] mm Hg; median National Institutes of Health stroke scale [NIHSS] score 9 [IQR 5–16] points) were randomly assigned to receive labetalol (n=58), lisinopril (n=58), or placebo (n=63) between January, 2005, and December, 2007. The primary outcome—death or dependency at 2 weeks—occurred in 61% (69) of the active and 59% (35) of the placebo group (relative risk [RR] 1.03, 95% CI 0.80–1.33; p=0.82). There was no evidence of early neurological deterioration with active treatment (RR 1.22, 0.33–4.54; p=0.76) despite the significantly greater fall in SBP within the first 24 h in this group compared with placebo (21 [17–25] mm Hg vs 11 [5–17] mm Hg; p=0.004). No increase in serious adverse events was reported with active treatment (RR 0.91, 0.69–1.12; p=0.50) but 3-month mortality was halved (9.7% vs 20.3%, hazard ratio [HR] 0.40, 95% CI 0.2–1.0; p=0.05).

Interpretation Labetalol and lisinopril are effective antihypertensive drugs in acute stroke that do not increase serious adverse events. Early lowering of blood pressure with lisinopril and labetalol after acute stroke seems to be a promising approach to reduce mortality and potential disability. However, in view of the small sample size, care must be taken when these results are interpreted and further evaluation in larger trials is needed.

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Introduction

Raised blood pressure is common after acute stroke; more than half of patients have a systolic blood pressure (SBP) reading higher than 160 mm Hg on admission.^{1,2} Raised blood pressure can be harmful because it increases the risk of cerebral oedema, haemorrhagic transformation of the infarct,³ or expansion of the haematoma,⁴ and is associated with poor short-term^{5,6} and long-term⁷ outcomes.

However, the natural history is for a spontaneous fall in blood pressure in the 4–10 days postictus.⁸ Furthermore, abnormalities in cerebrovascular haemodynamics after acute stroke,⁹ particularly the impairment of dynamic cerebral autoregulation,¹⁰ mean that cerebral blood flow is dependent on systemic blood pressure, and further reductions might risk penumbral viability. Low blood pressure (SBP <140 mm Hg) in the acute stroke period is also associated with a poor prognosis.^{11,12} Data from the International Stroke Trial (IST) indicate a U-shaped relation between baseline

SBP and 2-week mortality and late (6-month) death or dependency: the risk of early death increases by 3.8% for every 10 mm Hg rise in SBP above 150 mm Hg.¹³

The best possible management of blood pressure after acute stroke is uncertain, as highlighted in the various acute stroke management guidelines¹⁴ and in a recent Cochrane meta-analysis.¹⁵ Preliminary evidence supports the use of the antihypertensive drug labetalol, a combined alpha blocker and beta blocker, to control blood pressure in patients with either acute haemorrhagic¹⁶ or acute ischaemic¹⁷ stroke. Inhibitors of angiotensin-converting enzyme (ACE) but not thiazide diuretics can reduce blood pressure after acute stroke without reducing cerebral blood flow^{18,19} and are effective for the prevention of secondary stroke.²⁰

We assessed the efficacy and safety of early blood pressure reduction—within 36 h of cerebral infarction or haemorrhage—in this pilot, randomised, double-blind, placebo-controlled trial of two blood pressure-lowering regimens.

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See [Reflection and Reaction](#)

page 23

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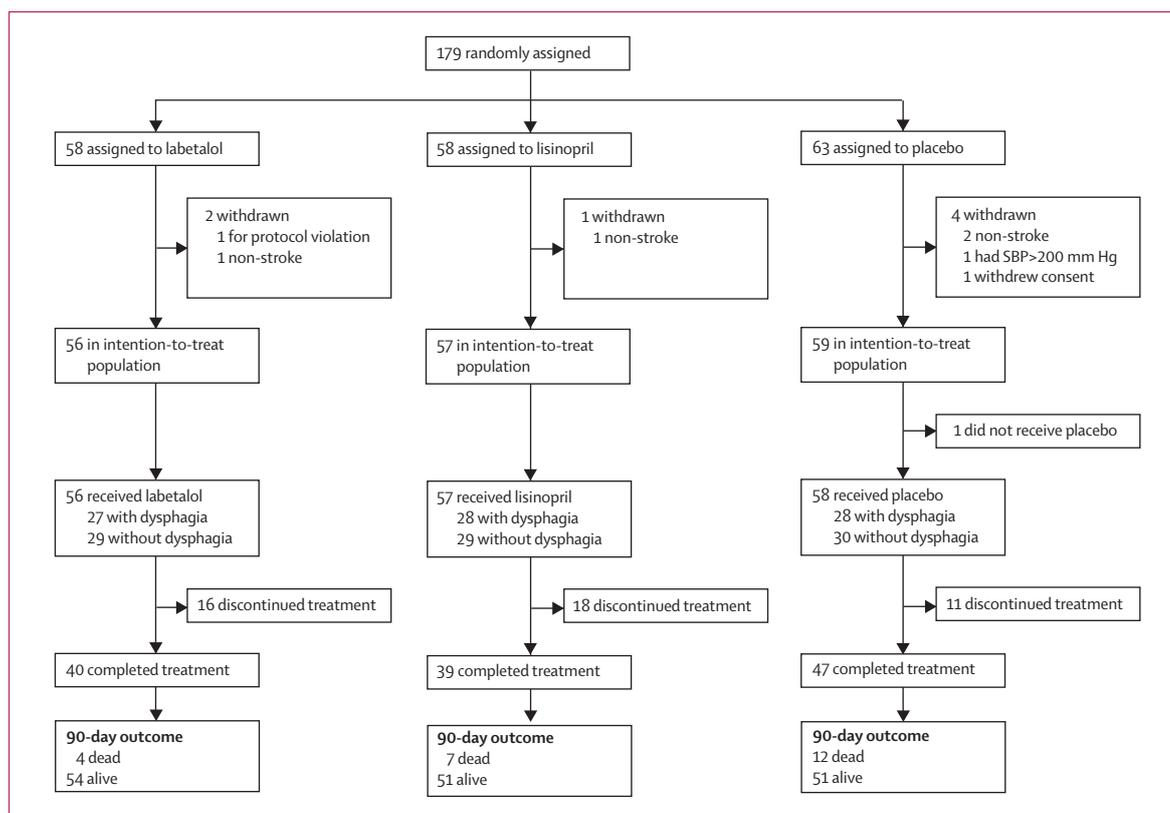


Figure 1: Trial protocol

Methods

Patients

Full details of this trial are described in detail elsewhere.²¹ Patients were recruited at six centres in the UK (Leicester, Newcastle-upon-Tyne, Exeter, Bournemouth, Liverpool, and Wansbeck) from January, 2005, to December, 2007. Patients were older than 18 years, had a fixed neurological deficit that lasted for 60 min or longer, and a clinical diagnosis of acute stroke. Time of stroke onset required clear definition; in patients who woke with a suspected stroke, the time of onset was taken as the last time the patient was documented to be free of symptoms. Inclusion criteria were cerebral infarction (but not undergoing thrombolytic treatment) or primary intracerebral haemorrhage (PICH), symptom onset within 36 h, and hypertension defined as SBP greater than 160 mm Hg from the mean of six supine blood pressure recordings taken over 10 min with a validated A&D UA-767 blood pressure monitor with a cuff of a suitable size. Exclusion criteria included hypertensive encephalopathy, co-existing cardiac or vascular emergency, SBP greater than 200 mm Hg and/or diastolic blood pressure (DBP) greater than 120 mm Hg in association with PICH, pre-existing antihypertensive therapy in patients without dysphagia, impaired level of consciousness (National Institutes of Health stroke scale [NIHSS] section 1a score ≥ 2 points), contraindications to

trial therapy, pre-morbid dependence (modified Rankin scale [mRS] score >3 points), any co-existing life-threatening condition with a life expectancy of less than 6 months, and diagnosis of non-stroke on subsequent neuroimaging. To increase recruitment to the depressor arm of the trial, amendments were made to the original protocol that included an increase in the time from stroke onset to randomisation from 24 h to 36 h, the inclusion of patients with a prestroke mRS score of 3 points instead of 2 points, and the inclusion of patients with dysphagia who were on antihypertensive treatment before the onset of stroke. These amendments were made by the trial steering committee. The pressor arm of the CHHIPS trial, which used phenylephrine to raise blood pressure in patients with ischaemic stroke who presented with hypotension, was terminated early owing to recruitment problems and is not described here. Informed patient consent (written where possible), consent from a relative, or assent from an independent clinician were obtained for all patients. The study and the amendments were approved by the Trent Multicentre Research Ethics Committee.

Procedures

Patients were randomly assigned by secure internet central randomisation (with a block size of six) to receive either active treatment or matched placebo in a 2:1 ratio.

Specific baseline neurological assessments were done at randomisation, 72 h, and 14 days and included NIHSS, mRS, and Oxfordshire Community Stroke Project (OCSP) classifications. Dysphagia status was assessed before randomisation with standardised bedside swallow

assessment done by staff with appropriate training. The routine care of patients with suspected stroke with respect to investigations, acute management other than blood pressure, and rehabilitation were done in accordance with standard local practice, including antithrombotic therapy and neuroimaging within 72 h of randomisation. Standard secondary preventive treatment was initiated by the local investigators. After 2 weeks, patients at all centres were routinely started on an ACE inhibitor with or without a diuretic irrespective of whether they were normotensive or hypertensive, unless they were deemed to be unsuitable for such therapy. Decisions with regard to future antihypertensive therapy were delayed until the end of the trial intervention (2 weeks).

Study drugs were manufactured centrally by DHP Pharma (Powys, Wales, UK). Patients with hypertension but without dysphagia were randomly assigned to oral labetalol (50 mg), oral lisinopril (5 mg), or matching oral placebo. Patients with hypertension and dysphagia received either an intravenous bolus injection of 50 mg labetalol given over 1–4 min and sublingual placebo, 5 mg sublingual lisinopril and intravenous placebo, or sublingual and intravenous placebo. Patients were kept supine for 30 min after each intravenous bolus injection. Placebo and active tablets were matched for size, shape, and colour; similarly, the vials of labetalol and placebo for intravenous administration were matched for size, shape, and colour.

Blood pressure in the brachial artery was monitored at 30-min intervals for 8 h post-dose; patients who developed symptomatic or asymptomatic hypotension (SBP <140 mm Hg) during this period had their study medication discontinued. At 4 h, patients who did not reach the target SBP (145–155 mm Hg or a reduction in SBP of 15 mm Hg compared with SBP at randomisation) were given further doses: patients who were non-dysphagic received 5 mg oral lisinopril, 50 mg oral labetalol, or oral matching placebo; patients with dysphagia received 5 mg sublingual lisinopril and intravenous placebo, or a 50 mg bolus injection of intravenous labetalol and sublingual placebo, or sublingual and intravenous matching placebo. A similar additional treatment dose was given to patients who did not reach the target SBP after 8 h post-randomisation. No further trial medication was given after 8 h post-randomisation until 24 h after the initial dose.

The treatment regimens for patients who were non-dysphagic were continued up to day 14 as follows: 5, 10, or 15 mg oral lisinopril once per day in the morning with matching placebo in the evening; 50, 100, or 150 mg oral labetalol twice per day; or oral matching placebo twice per day. Patients who were dysphagic received established treatment regimens for 72 h as follows: 5, 10, or 15 mg sublingual lisinopril in the morning with sublingual and intravenous placebo in

	Labetalol (n=56)	Lisinopril (n=57)	Active (lisinopril and labetalol) (n=113)	Placebo (n=59)
Men	34 (61%)	30 (53%)	64 (57%)	31 (53%)
Age (years)	74 (11)	75 (11)	74 (11)	74 (11)
SBP (mm Hg)	181 (16)	182 (17)	182 (17)	181 (16)
DBP (mm Hg)	93 (14)	96 (12)	95 (13)	96 (12)
OCSP				
Total anterior	19 (34%)	20 (35%)	39 (35%)	22 (37%)
Partial anterior	15 (27%)	21 (37%)	36 (32%)	18 (31%)
Lacunar	17 (30%)	11 (19%)	28 (25%)	16 (27%)
Posterior	4 (7%)	5 (9%)	9 (8%)	3 (5%)
Unknown	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Premorbid mRS				
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 (4%)	1 (2%)
NIHSS	9 (6–16)	10 (5–16)	9 (5–16)	9 (5–17)
Dysphagic	27 (48%)	28 (49%)	55 (49%)	28 (47%)
Stroke				
No history	53 (95%)	50 (88%)	103 (91%)	56 (95%)
Unknown	1 (2%)	0 (0%)	1 (1%)	0 (0%)
No history of TIA	51 (91%)	52 (91%)	103 (91%)	55 (93%)
Diabetes				
No history	52 (93%)	53 (93%)	105 (93%)	55 (93%)
Unknown	3 (5%)	1 (2%)	4 (4%)	1 (2%)
Smoking				
No	24 (43%)	33 (58%)	57 (50%)	24 (41%)
Ex-smoker	21 (38%)	15 (26%)	36 (32%)	19 (32%)
Current smoker	11 (20%)	9 (16%)	20 (18%)	16 (27%)
Hypercholesterolaemia				
No history	39 (70%)	43 (75%)	82 (73%)	37 (63%)
Unknown	2 (4%)	0 (0%)	2 (2%)	0 (0%)
IHD				
No history	47 (84%)	53 (93%)	100 (88%)	54 (92%)
Unknown	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Time to treatment (h)	19.2 (6.6)	20.5 (8.5)	19.8 (7.6)	17.4 (6.6)
Type of stroke				
Ischaemic	33 (59%)	31 (54%)	64 (57%)	35 (59%)
PICH	9 (16%)	9 (16%)	18 (16%)	7 (12%)
CT scan				
No relevant abnormality	14 (25%)	17 (30%)	31 (27%)	15 (25%)
Died before CT done	0 (0%)	0 (0%)	0 (0%)	2 (3%)

Data are mean (SD) or number (%) except NIHSS, for which data are median (IQR). OCSP=Oxford Community Stroke Project scale. SBP=systolic blood pressure. DBP=diastolic blood pressure. mRS=modified Rankin scale. NIHSS=National Institutes of Health stroke scale. TIA=transient ischaemic attack. IHD=ischaemic heart disease. PICH=primary intracerebral haemorrhage.

Table 1: Baseline characteristics of the CHHIPS patients at randomisation

the evening; 50, 100, or 150 mg bolus intravenous injection of labetalol twice per day and sublingual placebo; or sublingual and intravenous matching placebo twice per day. At 72 h, the patients with dysphagia had their swallow reflex reassessed, and those with continuing dysphagia received treatment with lisinopril, labetalol, or matching placebo suspension by way of a nasogastric or percutaneous endoscopic gastrostomy feeding tube. Those patients who regained their swallow reflex were given lisinopril, labetalol, or matching placebo orally.

Dependency was measured at baseline and after 2 weeks with the mRS. Neurological deficit was assessed with the NIHSS at baseline, 72 h, and 2 weeks by trained research staff in the participating centres, whereas 3-month follow up was done centrally by the Leicester coordinating centre. Further blood pressure measurements were recorded at 24 h and at 2 weeks.

All serious adverse events reported during the 2-week treatment period were categorised as either mild, moderate, severe, or fatal. Causality was recorded in terms of whether it was related to the treatment (definite, uncertain, or no causality) and the system affected. All serious adverse events were reviewed by the trial steering committee and the independent data safety monitoring committee every 6 months.

The primary endpoint of the trial was death or dependency at 2 weeks, with dependency defined as a mRS score of greater than 3 points. The secondary objectives were to establish the safety of this regimen, as assessed by the absence of early (<72 h) neurological deterioration (an increase in NIHSS score of 4 points or more), to compare the safety and efficacy of two different treatment regimens and routes of administration in terms of blood pressure control and serious adverse events throughout the 14-day treatment period, and to assess potential differences in 3-month mortality among the treatment and placebo groups.

This study is registered with the National Research Register, number N0484128008.

Statistical analysis

Continuous measures were roughly normally distributed, and binary outcomes—death and dependency at 2 weeks or a change in NIHSS score of 4 points or more at 72 h—were analysed by logistic regression. Regression analysis was used to compare continuous outcomes by and across treatment groups. Repeated measures analysis was done on the changes in blood pressure by use of generalised estimating equation modelling with unstructured correlation; the model included the terms time, treatment, and time by treatment interaction. Analyses of active treatment compared with placebo were done first and then, where appropriate, comparisons across the three treatment groups. To protect the results from multiple tests, Fisher's protected least-square difference method was used. Power calculations were based on the

	Labetalol (n=56)	Lisinopril (n=57)	Active (labetalol and lisinopril) (n=113)	Placebo (n=59)	Relative risk (active versus placebo)	p value
Dead or dependent	34 (61%)	35 (61%)	69 (61%)	35 (59%)	1.03 (0.80–1.33)	0.82
Not dead or dependent	22 (39%)	22 (39%)	44 (39%)	24 (41%)

Data are number (%) or relative risk (95% CI).

Table 2: CHHIPS primary outcomes

	ICH	mRS=4 at 2 weeks	mRS=5 at 2 weeks	mRS >3 at 2 weeks	Dead at 2 weeks	Dead or dependent at 2 weeks	Dead at 3 months
Labetalol	9	4	4	8	0	8	1
Lisinopril	9	2	3	5	1	6	1
Placebo	7	2	1	3	0	3	0
Total	25	8	8	16	1	17	2
Active	18	6	7	13	1	14	2

Table 3: Outcome in patients with intracerebral haemorrhage at randomisation

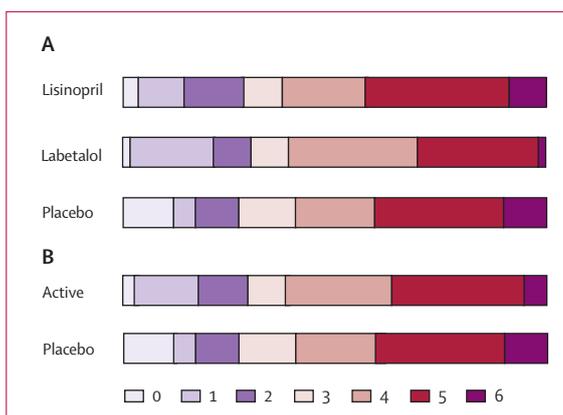


Figure 2: Death or dependency at 2 weeks

Primary outcome shown as differences in modified Rankin Scale (mRS) between the lisinopril, labetalol, and placebo groups (A) and for active treatment (lisinopril and labetalol groups combined) and placebo (B). mRS score of 0=no residual disability; score of 5=bedbound and requiring constant care; 6=death.

For National Research Register see <http://www.nrr.nhs.uk>

assumption that 60% of the placebo group would be dead or dependent at 2 weeks; therefore, for active treatment to produce a proposed relative reduction in death or dependency of 15% with a power of 80% at the 5% significance level, 550 patients would be needed in each group. Statistical significance was set at the 5% level; if no significant difference was found across three groups for an outcome measure, no further subgroup analysis was done. Death at up to 3 months post-randomisation was recorded from the UK National Health Service register; cause of death was taken from the death certificates. Survival data were analysed by Cox's proportional hazards model with non-parametric Kaplan–Meier plots. All analyses were done on an intention-to-treat basis with Stata version 9.2 statistical software.

	Labetalol (n=56)	Lisinopril (n=57)	Active (labetalol and lisinopril) (n=113)	Placebo (n=59)	Relative risk (active versus placebo)	p value
Increase in NIHSS score of 4 points or more or dead at 72 h	1 (2%)	7 (12%)	8 (7%)	6 (10%)	0.69 (0.25–1.91)	0.48
Increase in NIHSS score of 4 points or more at 72 h	1 (2%)	6 (10%)	7 (6%)	3 (5%)	1.22 (0.32–4.54)	0.76
Decrease in NIHSS score of 4 points or more at 72 h	51 (91%)	48 (84%)	99 (88%)	52 (88%)
No significant change in NIHSS Score (change \leq 3 points from baseline) at 72 h	4 (7%)	2 (4%)	6 (5%)	1 (2%)
Dead at 72 h	0 (0%)	1 (2%)	1 (1%)	3 (5%)

Data are number (%) or relative risk (95% CI). Data are presented for the labetalol and lisinopril groups separately and combined. NIHSS=National Institutes of Health Stroke Scale.

Table 4: Changes in neurological status as assessed by a NIHSS change \geq 4 or death at 72 h by active treatment groups versus placebo

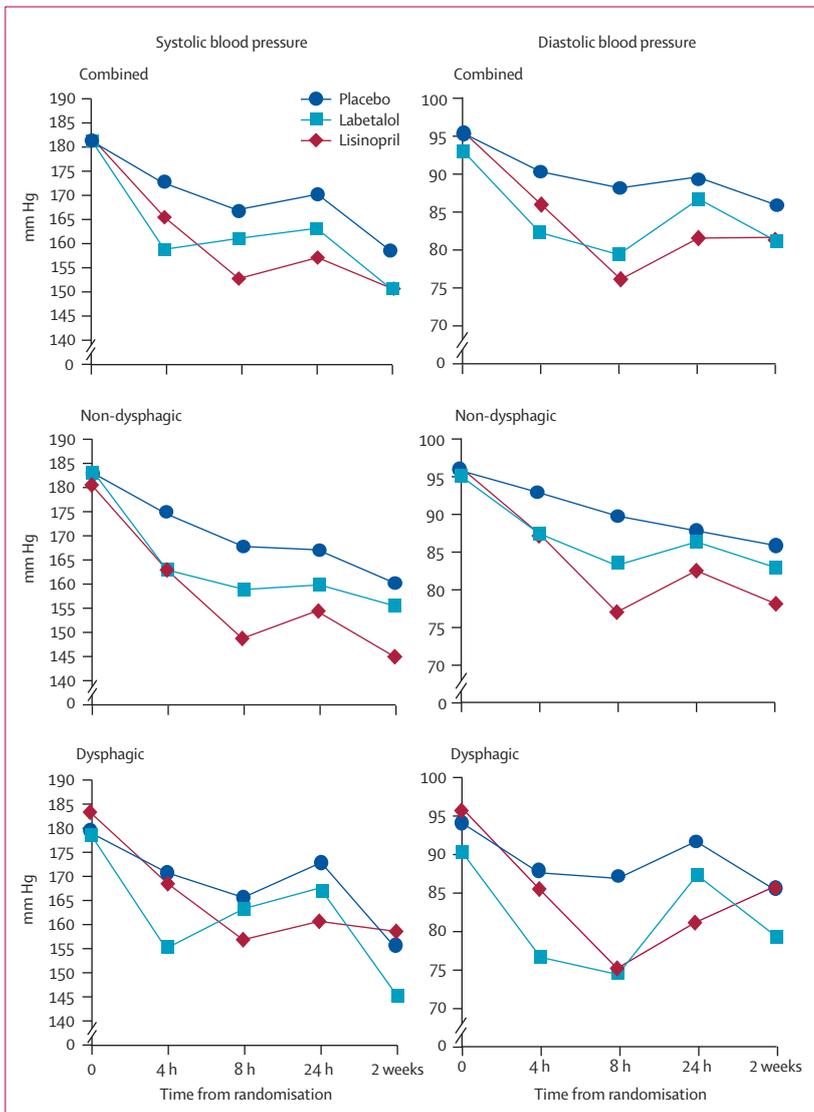


Figure 3: Changes in systolic and diastolic blood pressure
 Changes recorded over the first 24 h and at 2 weeks for the three treatment groups for the dysphagic, non-dysphagic, and combined dysphagic and non-dysphagic groups. SD values (SBP/DBP) omitted for clarity but values at 24 h are as follows (SD values are similar at all time points): combined=placebo 21/17 mm Hg, lisinopril 24/18 mm Hg, labetalol 22/17 mm Hg; non-dysphagic=placebo 23/18 mm Hg, lisinopril 23/19 mm Hg, labetalol 19/16 mm Hg; dysphagic=placebo 21/17 mm Hg, lisinopril 25/19 mm Hg, labetalol 25/19 mm Hg. SBP=systolic blood pressure. DBP=diastolic blood pressure.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

179 patients (11%) who were screened and eligible for inclusion in CHHIPS were randomly assigned; six patients were subsequently withdrawn owing to a protocol violation or non-stroke diagnosis, and one patient for withdrawal of consent. Figure 1 shows the trial profile. 126 of 172 patients (73%) completed the full 14-day protocol treatment; one patient was withdrawn before any allocated treatment, and 45 patients discontinued study medication at some point during the first 2 weeks (16 patients [28%] in the labetalol group, 18 patients [32%] in the lisinopril group, and 11 patients [21%] in the placebo group; $p=0.45$). More patients with dysphagia than patients without dysphagia stopped the randomised therapy ($p=0.001$).

At randomisation, the labetalol, lisinopril, and placebo groups were well matched for sex, age, SBP, DBP, pre-morbid mRS score, NIHSS score, and dysphagia status. Table 1 shows the characteristics of the patients at baseline.

Death or dependency at 2 weeks occurred in 61% (69 of 113 patients) in the combined active treatment group and in 59% (35 of 59 patients) in the placebo group (relative risk [RR] 1.03, 95% CI 0.80–1.33; $p=0.82$), with similar results across the three groups ($p=0.97$) even after adjusting for time to treatment (table 2; figure 2). At 2 weeks, there was one stroke-related death in the labetalol group, five deaths in the lisinopril group (four related to stroke and one of respiratory cause) and six deaths in the placebo group (two related to stroke and 4 of respiratory causes). Table 3 shows data only for patients with cerebral haemorrhage.

Active therapy was not associated with increased early neurological deterioration at 72 h, which was seen in seven patients (6%) in the combined active treatment group and three patients (5%) in the placebo group (RR 1.22, 0.32–4.54; $p=0.76$; table 4). Similarly, anti-hypertensive treatment was not associated with the

combined outcome of death or neurological deterioration at 72 h (RR 0.69, 0.25–1.91; $p=0.48$); there was one death in the active treatment group and three deaths in the placebo group at 72 h.

By 24 h after randomisation, blood pressure had fallen in each of the three groups and this reduction was maintained at 2 weeks (figure 3). There was a statistically greater decrease in SBP from baseline over the 24 h period in the combined active treatment group compared with the reduction in the placebo group (mean difference 10 mm Hg, 95% CI 3–17; $p=0.004$). Analysis across the three treatment groups showed an overall difference between the groups ($p=0.005$) due to a significant reduction in SBP with lisinopril compared with placebo (mean reduction 14 mm Hg, 5–22; $p=0.001$), but a smaller reduction was seen with labetalol compared with placebo (mean reduction 7 mm Hg, –1 to 15; $p=0.096$). There was a similar reduction in DBP, with a significant difference between the 3 groups over 24 h ($p=0.021$). A greater reduction was seen with lisinopril (mean reduction 7 mm Hg, 1–13; $p=0.019$) than with labetalol (mean increase 0.3 mm Hg, –6 to 6; $p=0.9$) compared with placebo. When the patients with dysphagia were analysed separately, there was an overall significant difference between treatments during the first 24 h for SBP and DBP ($p=0.0001$ for both). A borderline significant reduction in SBP was seen in the lisinopril group compared with placebo at 8 h (mean decrease 10 mm Hg, –1 to 21; $p=0.07$) and a significant reduction at 24 h (mean decrease 12 mm Hg, 2–23; $p=0.024$), but not at 4 h. By contrast, the patients in the labetalol group with dysphagia had a significant reduction in SBP compared with placebo at 4 h (mean decrease 16 mm Hg, 5–26; $p=0.005$), but not at 8 h or 24 h.

At 2 weeks, the reduction in SBP was greater with active treatment than with placebo (mean reduction 8 mm Hg, 0.2–16.0; $p=0.045$) but DBP was similar among the active and placebo groups (mean reduction 4 mm Hg, –0.8 to 9.0; $p=0.10$).

Figure 4 shows the data on the patients who reached the target reduction in SBP at 4 h and 8 h and the data on the patients who reached the target reduction in SBP at 4 h and maintained it at 8 h. The proportion of patients who received additional doses at 4 h was 23% (13) in the labetalol group, 39% (22) in the lisinopril group, and 63% (71) in the placebo group; at 8 h, the numbers were 7% (4), 12% (7), and 39% (44), respectively. Of the patients who received intravenous labetalol, 81% (45) reached the target SBP at 4 h, but by 8 h half of this group were above the target SBP, whereas 57% (32) of those who received sublingual lisinopril achieved target SBP at 4 h, with 88% (50) maintaining target SBP at 8 h. By 24 h, 57% (32) of patients in the labetalol group, 65% (37) of patients in the lisinopril group, and 46% (52) of patients in the placebo group had achieved target blood pressure levels.

96 serious adverse events were reported in 58 patients; 23 patients had more than one event. There was no

significant difference in the number of serious adverse events reported between the three intervention groups: 28 in the labetalol group; 33 in the lisinopril group; and 35 in the placebo group (active treatment *vs* placebo

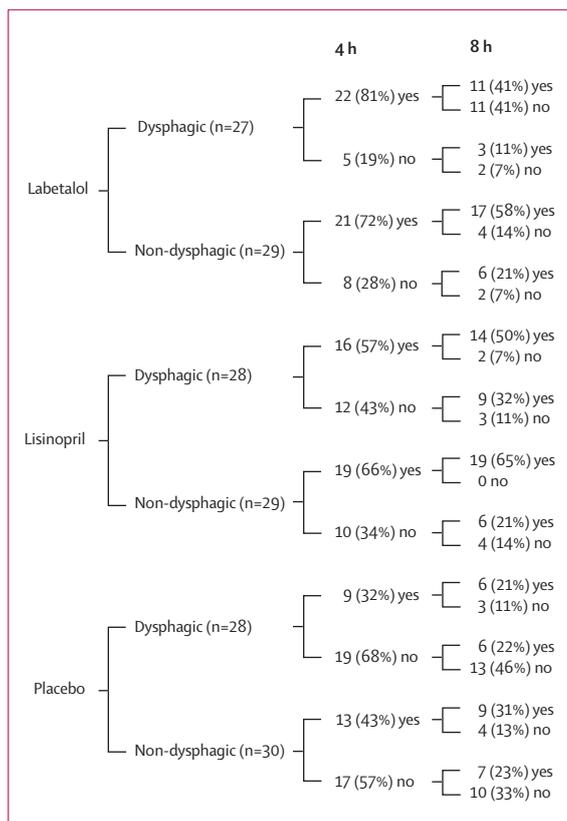


Figure 4: Patients in whom SBP targets were reached and maintained at 4 h and 8 h by treatment arms for dysphagic and non-dysphagic groups. Data are number (%).

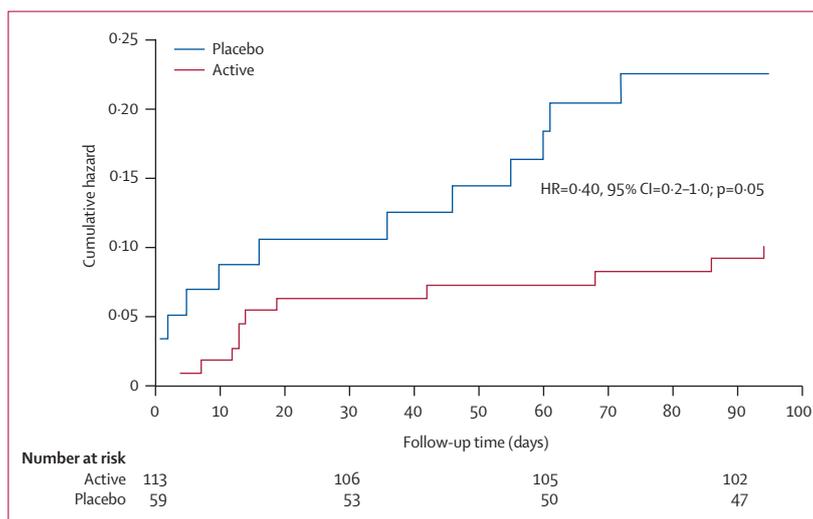


Figure 5: Kaplan-Meier survival estimates for the active treatment and placebo groups for the 90-day post-randomisation period.

RR 0·91, 0·69–1·12; $p=0\cdot50$). Treatment was discontinued in 18 patients owing to serious adverse events: six patients in the labetalol group, eight patients in the lisinopril group, and four patients in the placebo group. One fatal adverse event was reported in the labetalol group due to the initial stroke, six in the placebo group (four due to respiratory causes and two due to stroke) and five (four due to stroke and one due to respiratory causes) in the lisinopril group. 37 patients discontinued treatment for other reasons: absence of nasogastric or percutaneous endoscopic gastrostomic route for drug administration in ten patients, withdrawal owing to high blood pressure in five patients (two in the labetalol group, one in the lisinopril group, and two in the placebo group), four for protocol violations, and three withdrawals at the request of the patient or a relative. In each group, more serious adverse events were reported by the patients with dysphagia than by those without (labetalol: 18 patients with dysphagia vs ten patients without dysphagia; lisinopril: 17 patients with dysphagia vs 16 patients without dysphagia; placebo: 25 patients with dysphagia vs ten patients without dysphagia). A causal relationship was inferred between study medication and serious adverse events by the local investigators for four patients (two in the labetalol group and two in the lisinopril group) but there was no unblinding of treatment allocation in these patients until the trial had finished. Of those in whom a causal relationship was reported, one patient in the labetalol group and one patient in the lisinopril group developed bronchospasm, which required nebulised bronchodilators; both events were reported to be of moderate severity. At the discretion of the local investigators, the patient in the labetalol group continued study medication, whereas the patient in the lisinopril group did not. One patient in the labetalol group had an extension of the presenting intracerebral haemorrhage seen on repeat CT scan but without further neurological deterioration; this was graded as a severe adverse event and led to interruption of study medication. One patient in the oral lisinopril group was withdrawn because of hypotension.

90-day mortality was reduced in the active treatment group compared with placebo (11 of 113 [10%] vs 12 of 59 [20%], HR 0·4, 95% CI 0·2–1·0; $p=0\cdot05$; figure 5). Causes of death in the labetalol group were cardiac ($n=1$) and stroke ($n=3$); causes of death in the lisinopril group were cardiac ($n=1$), respiratory ($n=1$), and stroke ($n=5$); in the placebo group, causes of death were stroke ($n=6$) and respiratory ($n=6$).

Discussion

The CHHIPS study is a placebo-controlled trial of the effects of different antihypertensive drugs given by oral and non-oral routes on early death and dependency, safety, tolerability, hypotensive effects, and 3-month mortality in patients with acute cerebral infarction or haemorrhage and raised blood pressure.

Death or dependency in the placebo group at 2 weeks was in keeping with observational studies and intervention trials that recruited patients with moderate to severe strokes. Active treatment had no effect on the primary outcome; however, the confidence intervals were wide in view of the study size, and the trial was not powered to detect smaller but still clinically significant changes: the trial had 80% power to detect at the 5% significance level an absolute difference in death or dependency at 2 weeks of 22%, and was underpowered to detect the proposed reduction in risk owing to reduced recruitment within the time period of funding. The main reasons for under-recruitment were ineligibility at hospital admission because blood pressure did not reach the entry criteria (42%) and a larger than expected number of patients on antihypertensive treatment at presentation (39%), although 36% of those who were eligible were randomised. These factors would need to be considered when planning future blood pressure-lowering trials. Owing to the small number of events, we could not assess whether there was any heterogeneity in the effects of additional blood pressure lowering according to stroke subtype (eg, cerebral infarct vs haemorrhage). From the viewpoint of trial safety, the greater reduction in blood pressure seen with lisinopril and labetalol compared with placebo did not result in any evidence of an increased risk of early neurological deterioration.

The greatest number of discontinuations in treatment occurred within the first 72 h after randomisation, and more patients with dysphagia than patients without dysphagia in all three treatment arms discontinued treatment. More severe adverse events were seen in the patients with dysphagia in the placebo arm of the trial, and the least in the oral labetalol group. Treatment was generally well tolerated, with no significant difference in the proportion of patients that continued active treatment until the end of the trial period (68% lisinopril and 72% labetalol) compared with the placebo group; furthermore, more patients continued treatment than were reported in the similarly sized BEST trial²² of beta blockers in acute stroke, which had a comparable treatment period. The few other blood pressure-lowering trials in acute stroke were either considerably shorter, did not report data on discontinuation rates, or were not placebo controlled. More early deaths were seen in the placebo group than in the combined active treatment group, although the number of events was too small to draw any firm conclusions.

The decreases in blood pressure in the placebo group at 24 h and 2 weeks that are reported in CHHIPS are similar to those reported in observational studies.²³ Treatment blood pressure targets were set to a SBP that is associated from observational data with the lowest risk of death and disability¹³ and with a view to restrict the absolute fall in blood pressure. Previous trials of blood pressure in stroke have not set blood pressure targets or

used an incremental dose approach to achieve goal blood pressure targets, and the results of this trial suggest that such an approach is feasible and effective. Giving depressor drugs to patients with stroke who were dysphagic on admission (nearly 50% of the trial population and 30–40% of the general population with acute stroke) has been difficult and usually meant the use of the intravenous route, with its associated problems. Our results show that lisinopril and labetalol are effective in reducing blood pressure in the acute stroke period. At 4 h, intravenous labetalol significantly lowered SBP more than did oral labetalol, oral lisinopril, or sublingual lisinopril; more than 80% of patients in this group reached target SBP at 4 h, meaning that no further drug would be given until 8 h post-randomisation. The relatively short half-life of intravenous labetalol probably explains the subsequent rise in SBP at 8 h in this group and suggests that future studies should give doses more frequently to maintain blood pressure control. Sublingual lisinopril seems to be a well-tolerated and efficacious alternative to intravenous labetalol in acute stroke, but the less rapid onset of antihypertensive effect means that it could potentially be given in the prehospital setting by paramedics or on arrival at the emergency department before the swallow reflex has been assessed. Whether the rapid early reduction in blood pressure that is achieved with intravenous labetalol led to the greater reduction in mortality than the slower onset antihypertensive effect achieved with lisinopril is unclear.

The changes in blood pressure for the combined active group at 24 h were similar to those obtained with the intravenous calcium-channel blocker nimodipine²⁴ or transdermal glyceryl trinitrate²⁵ but were greater for the lisinopril group than for the combined ACE-inhibitor results of previous and much smaller trials, as shown in a recent Cochrane review.¹⁵ Beta-blocker therapy in the BEST trial¹³ resulted in half the blood pressure-lowering effect than seen here (no comparative data are available on the effects of labetalol in acute stroke), whereas other placebo-controlled studies with oral nimodipine²⁶ and oral candesartan²⁷ found no blood pressure-lowering effect of these drugs in the acute setting. Active treatment was associated with sustained blood pressure lowering compared with placebo at 2 weeks. Few other investigators have continued antihypertensive treatment for this duration; one group that did found no antihypertensive effect when comparing glyceryl trinitrate with placebo by day 7,²⁵ which possibly shows the tolerance that develops to therapy with nitrates. The potential benefits of raising blood pressure in acute stroke have been discussed elsewhere,²⁸ but recruitment to the pressor (phenylephrine) arm of CHHIPS was severely restricted because of the inclusion and exclusion criteria. If such a trial was contemplated, different entry criteria would have to be used to ensure adequate recruitment.

A borderline significant reduction in mortality at 90 days was reported in the actively treated group, with the risk of death being more than halved in this group. The 3-month mortality of 20% in the placebo group was similar to that reported in other trials of acute stroke that have included similar proportions of patients with moderate to severe stroke.^{29,30} The divergence in mortality between active and placebo groups was evident from early on after randomisation and increased with time; the difference could not be explained by baseline differences between active and placebo groups. These findings might be due to differences in subsequent antihypertensive or other secondary preventive treatment that was started after the trial period ended at 2 weeks, although we have no evidence of this and all patients received optimum secondary preventive measures as set out in the stroke guidelines at each centre. However, care must be taken in interpreting these results; owing to the small number of events, these findings could be due to chance. Our findings agree with those of the ACCESS trial, which showed that candesartan, an antagonist of angiotensin II, given within 72 h of stroke onset halved future vascular events despite not acutely reducing blood pressure compared with placebo.²⁶ More recently, the INTERACT trial showed aggressive lowering of blood pressure within 6 h of primary intracerebral haemorrhage reduced haematoma growth but did not alter 90-day mortality.³¹

In conclusion, labetalol and lisinopril effectively lowered blood pressure in patients with acute stroke without causing adverse side-effects or early neurological deterioration when given within 36 h of symptom onset. Sublingual lisinopril and intravenous labetalol were effective hypotensives in patients with dysphagia. However, this trial was underpowered to detect a small to moderate effect on death and dependency at 2 weeks, which was the primary outcome measure. Of interest was the reduction in stroke mortality at 3 months with active therapy, which is in keeping with the results of the ACCESS trial,²⁶ although care must be taken in the interpretation of these trials in view of the small number of events. The scarcity of sufficient data to enable us to advise on the best management of blood pressure in acute stroke is a serious concern, and the positive findings from the CHHIPS pilot trial strongly support the need for further trials of blood pressure lowering in acute stroke with treatments that have been shown to be effective and safe.

Contributors

JFP was principal investigator, developed the trial, sought and obtained funding, and was responsible for the overall running, analysis, and writing of the manuscript. TGR was a co-investigator who was responsible for developing the trial, and applied for trial funding; he is also a member of the trial steering committee and co-wrote the manuscript and subsequent revisions. GAF helped to develop the trial, applied for trial funding, was a member of the trial steering committee, and advised on and reviewed the writing of the manuscript. AM was the principal trial coordinator; he was involved in enrolling patients in

Leicester and in data entry and analysis, and reviewed the manuscript. MJ was a coapplicant for funding, helped in patient recruitment, writing, and reviewing the manuscript. JC was responsible for data entry and analysis was a coapplicant for funding. CJ was responsible for the overall statistical analysis and reviewed the manuscript. All members of the writing committee take responsibility for the final manuscript.

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Conflicts of interest

We have no conflicts of interest.

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