



Effects of antihypertensive treatment after acute stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial

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Summary

Background Up to 50% of patients with acute stroke are taking antihypertensive drugs on hospital admission. However, whether such treatment should be continued during the immediate post-stroke period is unclear. We therefore aimed to assess the efficacy and safety of continuing or stopping pre-existing antihypertensive drugs in patients who had recently had a stroke.

Methods The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) was a UK multicentre, prospective, randomised, open, blinded-endpoint trial. Patients were recruited at 49 UK National Institute for Health Research Stroke Research Network centres from January 1, 2003, to March 31, 2009. Patients aged over 18 years who were taking antihypertensive drugs were enrolled within 48 h of stroke and the last dose of antihypertensive drug. Patients were randomly assigned (1:1) by secure internet central randomisation to either continue or stop pre-existing antihypertensive drugs for 2 weeks. Patients and clinicians who randomly assigned patients were unmasked to group allocation. Clinicians who assessed 2-week outcomes and 6-month outcomes were masked to group allocation. The primary endpoint was death or dependency at 2 weeks, with dependency defined as a modified Rankin scale score greater than 3 points. Analysis was by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Register, number ISRCTN89712435.

Findings 763 patients were assigned to continue (n=379) or stop (n=384) pre-existing antihypertensive drugs. 72 of 379 patients in the continue group and 82 of 384 patients in the stop group reached the primary endpoint (relative risk 0·86, 95% CI 0·65–1·14; p=0·3). The difference in systolic blood pressure at 2 weeks between the continue group and the stop group was 13 mm Hg (95% CI 10–17) and the difference in diastolic blood pressure was 8 mm Hg (6–10; difference between groups p<0·0001). No substantial differences were observed between groups in rates of serious adverse events, 6-month mortality, or major cardiovascular events.

Interpretation Continuation of antihypertensive drugs did not reduce 2-week death or dependency, cardiovascular event rate, or mortality at 6 months. Lower blood pressure levels in those who continued antihypertensive treatment after acute mild stroke were not associated with an increase in adverse events. These neutral results might be because COSSACS was underpowered owing to early termination of the trial, and support the continuation of ongoing research trials.

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Introduction

Raised blood pressure is common after acute stroke; more than three-quarters of patients have a systolic blood pressure greater than 140 mm Hg on admission to hospital.^{1,2} This increased blood pressure is associated with poor prognosis^{3,4} and might be caused by raised intracranial pressure,⁵ increased sympathetic nervous system activity,⁶ abnormal baroreceptor sensitivity,⁷ and haematoma expansion.⁸ A spontaneous decrease in blood pressure usually occurs 4–10 days after stroke,⁹ but substantial reductions in blood pressure can be associated with cerebral hypoperfusion as a consequence of post-stroke cerebral dysautoregulation.¹⁰ Data from the International Stroke Trial¹¹ suggest a U-shaped relation

between baseline systolic blood pressure (within 48 h of stroke) and short-term (14-day mortality) and long-term (6-month death and dependency) outcomes: for every 10 mm Hg below 150 mm Hg, the risk of early death increased by 3·6% and late death and dependency increased by 17·9%; and for every 10 mm Hg above 150 mm Hg, the risk of early death increased by 3·8% but there was no substantial increase in death and dependency; the lowest risk of death or dependency was at a systolic blood pressure of 150 mm Hg.

Data from randomised controlled trials suggest that blood pressure can be safely reduced after acute stroke^{12–15} and can improve long-term mortality¹⁴ and reduce recurrent vascular events.¹² However, Cochrane

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meta-analyses^{16,17} and several international acute stroke management guidelines^{18–22} have shown that the optimal management of blood pressure after acute stroke is not known. Hypertension is a major modifiable risk factor for stroke prevention, and more than 50% of patients with acute stroke are already taking antihypertensive drugs at the time of their admission to hospital. Whether to continue or stop antihypertensive drugs in the acute period after stroke is therefore a common clinical dilemma.

We aimed to assess the efficacy and safety of continuing or stopping pre-existing antihypertensive drugs.

Methods

Patients

The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) was a UK multicentre, prospective, randomised, open, blinded-endpoint trial of patients within 48 h of non-dysphagic, ischaemic, or haemorrhagic stroke and within 48 h of the last dose of antihypertensive drugs. Full details of the trial are described elsewhere.²³

Patients were recruited at 49 UK National Institute for Health Research Stroke Research Network centres from January 1, 2003, to March 31, 2009. Patients aged over 18 years who had a clinical diagnosis of acute stroke were eligible. Inclusion criteria were cerebral infarction (but not undergoing thrombolytic treatment) or primary intracerebral haemorrhage; symptom onset within 48 h; a prestroke modified Rankin scale (mRS) score of 0–3 points; and on antihypertensive drugs with the last dose having been taken within 48 h before random

allocation. Time of stroke onset required a clear definition; thus, in patients who woke with a suspected stroke, the time of onset was taken as the last time the patient was known to be asymptomatic. To increase recruitment, the trial steering committee amended the protocol (approved May 26, 2005) to increase the time from stroke onset to random allocation from 24 h to 48 h, to increase the time from last dose of antihypertensive treatment to random allocation from 36 h to 48 h, and to include patients with a prestroke mRS score of 0–3 points instead of the original 0–2 points. Exclusion criteria were hypertensive encephalopathy; coexisting cardiac or vascular urgency; systolic blood pressure greater than 200 mm Hg or diastolic blood pressure greater than 120 mm Hg associated with known primary intracerebral haemorrhage; contraindications to stopping or indications for continuing antihypertensive treatment; dysphagia; impaired consciousness (National Institutes of Health stroke scale [NIHSS] section 1a score ≥ 2 points); women of childbearing potential; premonitory dependency (mRS > 3 points); any coexisting life-threatening condition with an estimated life expectancy of less than 6 months; and no evidence of stroke on neuroimaging.

Informed consent from the patient (written where possible), assent from a relative (with confirmation of assent from the patient when able), or assent from an independent clinician was obtained for all patients. The study and amendments were approved by the Trent Research Ethics Committee (MREC/02/4/051).

Randomisation and masking

Patients were randomly assigned (1:1) with a block size of four by secure internet central randomisation. Allocation to continue or stop pre-existing antihypertensive treatment for a 2-week period was done by use of a computer with stratification by age at entry (< 75 years and ≥ 75 years). Patients and clinicians who randomly assigned patients were unmasked to group allocation. 2-week outcomes were assessed by clinicians masked to treatment allocation; the secure internet data collection facility did not allow 2-week data to be entered by a clinician who had done either randomisation or baseline data entry. 6-month outcomes were assessed by an investigator at the trial coordinating centre (A Moore) who was masked to treatment allocation.

Procedures

Baseline assessments included NIHSS, Oxfordshire community stroke project (OCSP) classification, mRS, and Barthel index. Casual blood pressure was calculated in all centres as the mean of two sets of three supine brachial blood pressure readings 10 min apart by use of a UA-767 blood pressure monitor (A&D Medical, San Jose, CA, USA). Casual blood pressure was monitored throughout the treatment period, and patients were withdrawn from the study if they had symptomatic sustained hypotension (systolic blood pressure < 100 mm Hg) or at the discretion of the treating clinician.

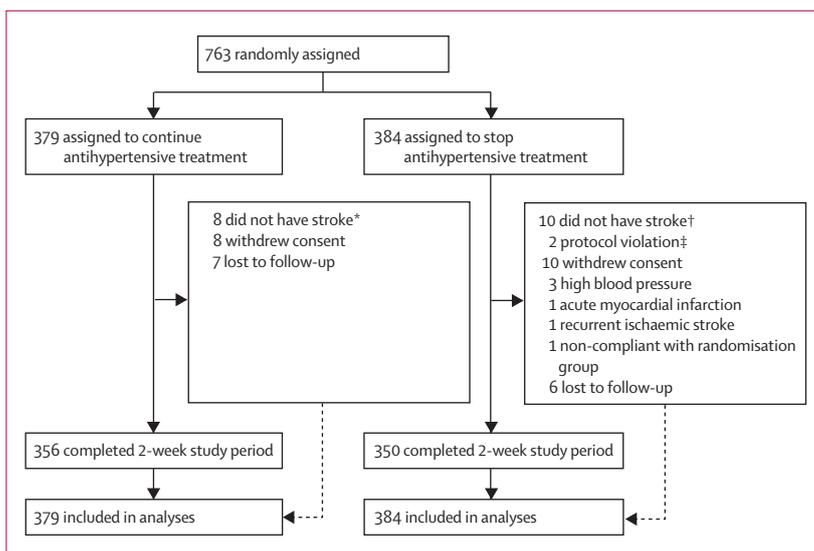


Figure 1: Trial profile

*One patient had complex regional pain syndrome, one epilepsy, one meningitis, one non-organic syndrome, three secondary tumour, and one was not specified. †One patient had Bell's palsy, one mononeuritis multiplex, two primary tumour, two secondary tumour, one subdural haematoma, one transient ischaemic attack, one viral labyrinthitis, and one was not specified. ‡One patient was randomly assigned more than 48 h after last antihypertensive dose and one had contraindication to cessation of antihypertensive treatment.

Study assessments, NIHSS, mRS, Barthel index, and casual blood pressure were repeated at 2 weeks. At 6 months, patients who had died were identified from the National Health Service (NHS) register. Those who were still alive were contacted by telephone for follow-up; patients or guardians did the International Stroke Trial²⁴ and EuroQoL²⁵ questionnaires and reported the patient's present residence and treatments (including antihypertensive drugs).

All other routine aspects of the management of patients, including neuroimaging, acute treatment, and standard secondary prevention therapy, were managed at the discretion of the local investigator. Use of antihypertensive drugs after the 2-week study period was at the discretion of the local investigator.

The primary endpoint was death or dependency at 2 weeks, with dependency defined as an mRS score of greater than 3 points. The early secondary outcome measures at 2 weeks included neurological status (as measured by NIHSS score, with neurological deterioration defined as an increase of at least 4 points) and functional status (as measured by the Barthel index), casual blood pressure changes between admission and 2 weeks, destination after discharge, and serious adverse events. The late secondary outcome measures at 6 months included mortality, fatal and non-fatal stroke recurrence, health-related quality of life, and place of residence. Deaths up to 6 months after randomisation were recorded from the NHS register and the cause of death was taken from the death certificates.

All serious adverse events reported during the 2-week treatment period were categorised as mild, moderate, severe, or fatal. Whether adverse events were related to the treatment (definite, uncertain, or no causality) and the systems affected by the adverse event were recorded by the local investigator. Serious adverse events were reviewed by the trial steering committee and an independent data safety monitoring committee at 6-monthly intervals.

This trial is registered with the International Standard Randomised Controlled Trial Register, number ISRCTN89712435.

Statistical analysis

We estimated that 2900 patients would be needed to detect a 10% reduction (absolute risk reduction of 6%) in death and dependency between the continue and stop groups at 2 weeks, with 90% power at the 5% significance level, assuming an overall rate of death and dependency of 60% at 2 weeks.²³ We used multinomial logistic regression to assess whether treatment effect differed across baseline mRS categories.

For the primary outcome (death and dependency at 2 weeks), we did χ^2 tests to establish the difference between the groups; we did logistic regression when adjustment was needed. Major cardiovascular events at 6 months and mortality data were analysed by χ^2 tests, and survival data were analysed by a non-parametric

log-rank test with a Kaplan-Meier plot. All patients who were randomly assigned were included in the analyses.

Continuous measures—age; systolic and diastolic blood pressure; concentrations of haemoglobin, platelets,

	Continue (n=379)	Stop (n=384)
Men	210 (55%)	216 (56%)
Age (years)	74 (11)	74 (11)
White*	288 (90%)	300 (93%)
Systolic blood pressure (mm Hg)	149 (23)	150 (22)
Diastolic blood pressure (mm Hg)	80 (13)	81 (14)
Oxford Community Stroke Project classification†		
Total anterior	38 (10%)	34 (9%)
Partial anterior	149 (40%)	163 (43%)
Lacunar	143 (38%)	144 (38%)
Posterior	42 (11%)	40 (10%)
Stroke type on neuroimaging‡		
Acute ischaemic	243 (67%)	211 (58%)
Haemorrhagic transformation of infarct	5 (1%)	4 (1%)
Primary intracerebral haemorrhage	19 (5%)	19 (5%)
Non-relevant§	86 (24%)	121 (33%)
Not stroke	8 (2%)	10 (3%)
National Institutes of Health stroke scale score	4 (3–8)	4 (2–7)
Premorbid modified Rankin scale score		
0	250 (66%)	247 (64%)
1	71 (18%)	66 (17%)
2	43 (11%)	54 (14%)
3	15 (4%)	17 (4%)
Baseline Barthel index	13 (8–19)	13 (8–19)
Time since last antihypertensive taken (h)	19.5 (7.0–29.6)	13.1 (6.7–28.3)
Time since stroke onset (h)	23.6 (18.6–35.8)	23.4 (17.5–34.2)
Past medical history		
Stroke	63 (17%)	87 (23%)
Transient ischaemic attack	74 (20%)	66 (17%)
Hypertension	369 (97%)	375 (98%)
Diabetes	69 (18%)	60 (16%)
Hypercholesterolaemia	173 (46%)	177 (46%)
Ischaemic heart disease	77 (20%)	75 (20%)
Atrial fibrillation	72 (19%)	78 (20%)
Peripheral vascular disease	20 (5%)	22 (6%)
Smoking		
Present	63 (17%)	57 (15%)
Past	145 (38%)	142 (37%)
Alcohol (units per week)	0.5 (0–8)	0 (0–6)
Family history of stroke	78 (21%)	73 (19%)
Number of antihypertensive drugs being taken at baseline¶		
1	153 (41%)	147 (38%)
2	135 (36%)	159 (42%)
≥3	88 (23%)	77 (20%)

Data are number (%), mean (SD), or median (IQR). Percentages might not add up to 100% because of rounding. *320 patients in the continue group and 321 in the stop group. †372 patients in the continue group and 381 in the stop group. ‡361 patients in the continue group and 365 in the stop group. §No evidence of acute ischaemic or haemorrhagic stroke or non-stroke diagnoses (eg, non-acute stroke or no evidence of stroke and alternative diagnoses excluded on imaging). ¶376 patients in the continue group and 383 in the stop group.

Table 1: Demographics and baseline characteristics

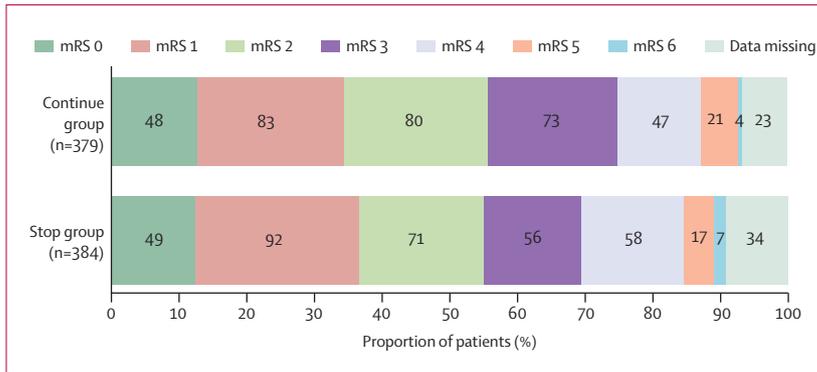


Figure 2: Primary outcome
 Distribution of mRS scores in the continue and stop groups. mRS score of 0=no residual disability; 5=bedbound and requiring 24 h care; 6=dead. Relative risk 0.86 (95% CI 0.65–1.14; p=0.3). mRS=modified Rankin scale.

potassium, and total cholesterol; and electrocardiogram heart rate—were roughly normally distributed. Linear regression was used to compare blood pressure at 2 weeks by treatment group. Barthel index, NIHSS score, mean weekly alcohol consumption, white cell count, time since stroke onset, time since the last antihypertensive drug, and sodium, urea, creatinine, and glucose concentrations had skewed distributions. We compared 2-week NIHSS and Barthel index scores by treatment group by use of non-parametric Kruskal-Wallis tests. We used Stata version 9.2 statistical software for all analyses.

Role of the funding source

The sponsor (University Hospitals of Leicester NHS Trust) and funders (The Health Foundation and The Stroke Association) had no role in the study design, data collection, data analysis, data interpretation, or the writing of the 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

COSSACS started on Jan 1, 2003, and ended on March 31, 2009; however, because of slow recruitment and lack of continued funding, the trial was stopped before target recruitment was reached. 763 patients (426 men) were randomly assigned to continue or stop treatment (figure 1). Patients had a mean age of 74 years (SD 11), a mean baseline blood pressure of 150/81 mm Hg (22/13), and were assigned within a median of 23.6 h

(IQR 17.9–34.8) after stroke onset and 16.0 h (6.8–28.9) after the last dose of antihypertensive drug. Neuroimaging was done within a median of 1 (IQR 1–2) day from stroke onset (472 of 726 had neuroimaging before or on the day of randomisation): 454 had acute infarction, nine haemorrhagic transformation of acute infarction, 38 primary intracerebral haemorrhage, 207 non-relevant change, and 18 did not have evidence of stroke (table 1). The continue and stop groups were well matched for baseline variables (table 1), including classes of antihypertensive, antithrombotic, and cholesterol-lowering drugs taken (data not shown) and electrocardiography (data not shown).

706 of 763 patients completed the full 2-week study period: 20 patients were withdrawn after random allocation (18 had no evidence of stroke on imaging and two had a protocol violation); 18 patients withdrew consent or did not confirm the previously provided relative or independent clinician consent; six were withdrawn by the local investigator (stop group: three had high blood pressure that needed treatment, one had acute myocardial infarction, one had recurrent ischaemic stroke, and one was non-compliant with trial treatment group); and 13 patients were lost to 2-week follow-up (figure 1).

The primary outcome of death or dependency at 2 weeks occurred in 72 of 379 patients in the continue group and 82 of 384 patients in the stop group (relative risk 0.86, 95% CI 0.65–1.14; p=0.3; figure 2). There was no evidence that the two groups differed across mRS categories at 2 weeks (p=0.47). When the data were adjusted for age, 96 of 391 patients older than 75 years and 58 of 372 patients aged 75 years or less reached the primary outcome (odds ratio [OR] 1.78, 95% CI 1.24–2.57; p=0.002); this difference remained after adjusting for smoking, alcohol, sex, evidence of acute stroke on neuroimaging, and history of diabetes, stroke, or atrial fibrillation (OR 1.76, 95% CI 1.11–2.81; p=0.017). No interaction effect was found between age and treatment group (p=0.96). Baseline systolic blood pressure and baseline diastolic blood pressure were not markedly associated with the primary outcome (systolic p=0.30; diastolic p=0.63).

At 2 weeks, mean blood pressure was 140/76 mm Hg (SD 22/14) in the continue group (change from baseline –9/–4 mm Hg [23/14]) and 153/84 mm Hg (24/14) in the stop group (change from baseline 3/2 mm Hg [25/14];

	Continue (n=379)	Stop (n=384)	Difference (95% CI)	p
Systolic blood pressure (mm Hg)	140 (138 to 142)	153 (151 to 156)	13 (10 to 17)	<0.0001
Diastolic blood pressure (mm Hg)	76 (75 to 76)	84 (83 to 86)	8 (6 to 10)	<0.0001
National Institutes of Health stroke scale score	3.8 (3.2 to 4.3)	3.5 (2.9 to 4.0)	0.3 (–0.5 to 1.1)	0.46
Barthel index score	15.6 (15.0 to 16.2)	16.0 (15.4 to 16.6)	–0.5 (–1.3 to 0.4)	0.30
Data are mean (95% CI).				

Table 2: Early secondary clinical outcomes

table 2). The difference at 2 weeks in systolic blood pressure between the continue group and the stop group was 13 mm Hg (95% CI 10–17; $p<0.0001$) and the difference in diastolic blood pressure was 8 mm Hg (6–10; $p<0.0001$). Daily blood pressure readings based on routine ward recordings are not reported.

At 2 weeks, four patients in the continue group had died and the status of three patients was unknown; in the stop group, seven patients had died and the status of 16 patients was unknown (table 3). At 2 weeks, there were no marked differences between groups in the NIHSS ($p=0.46$) and the Barthel index ($p=0.30$; table 2). 158 of 356 patients who completed the 2-week study period in the continue group and 147 of 350 patients in the stop group remained in hospital at 2 weeks.

At 6 months, 32 of 379 patients in the continue group and 29 of 384 patients in the stop group had died (table 3; figure 3; log-rank $p=0.98$). In the continue group, the cause of death was stroke in five patients, respiratory in four, cardiovascular in two, pulmonary embolism in one, neoplastic in one, sepsis in one, and unknown in 18. In the stop group, the cause of death was stroke in four patients, pulmonary embolism in two, neoplastic in two, infection in one, and unknown in 20. 166 of 332 patients in the continue group and 171 of 331 patients in the stop group who were alive at 6 months were able to live independently (table 3). There were 50 self-reported major cardiovascular events at 6 months: 12 recurrent strokes in the continue group and 12 in the stop group, 11 cardiovascular events in the continue group and eight in the stop group, and three other vascular events in the continue group and four in the stop group.

We did a post-hoc analysis in a subgroup of patients in whom ischaemic stroke was confirmed on CT scan. Of 444 patients who had a neuroimaging diagnosis of acute ischaemic stroke (including haemorrhagic transformation) and 2-week outcome data, 46 of 241 patients in the continue group were dead or dependent (mRS>3) at 2 weeks compared with 55 of 203 in the stop group (relative risk reduction 0.70, 95% CI 0.51–0.99; $p=0.045$). The OCSF classification for these patients was: total anterior circulation syndrome in 47 of 444 patients, partial anterior circulation syndrome in 186, lacunar syndrome in 153, and posterior circulation syndrome in 55 (data missing for 3 patients). There were no marked differences in baseline data between the continue and stop groups. For those patients without diagnosis of acute ischaemic or haemorrhagic stroke confirmed on neuroimaging (ie, non-relevant), the OCSF classification was: total anterior circulation syndrome in 14 of 198 patients, partial anterior circulation syndrome in 79, lacunar syndrome in 89, and posterior circulation syndrome in 16, with a relative risk reduction for continuation compared with cessation of treatment of 1.1 (95% CI 0.6–2.1; $p=0.76$).

96 serious adverse events were reported in 78 patients: 45 events in 34 patients in the continue group and 51 events in 44 patients in the stop group. 13 patients had

	Continue (n=379)	Stop (n=384)
Alive	332 (88%)*	331 (86%)†
Independent (mRS 0)	124	118
Independent (mRS 1–2)	42	53
Dependent (mRS 3–5)	110	112
Dead	32 (8%)	29 (8%)
Within 2 weeks	4	7
Between 2 weeks and 6 months	28	22
Lost to follow-up	15 (4%)	24 (6%)

Data are number (%). mRS=modified Rankin scale. Dependency categories were derived from the responses to the International Stroke Trial telephone-administered questionnaire. An answer yes to the question "Do you need help from another person for everyday activities?" indicated dependency (mRS 3–5). If the patient answered no, they were asked the question "Do you feel that you have made a complete recovery from your stroke?" and an answer of yes (mRS 0) or no (mRS 1–2) indicated independence. *Dependency status was not known in 56 patients. †Dependency status was not known in 48 patients.

Table 3: Mortality and functional outcomes at 6 months

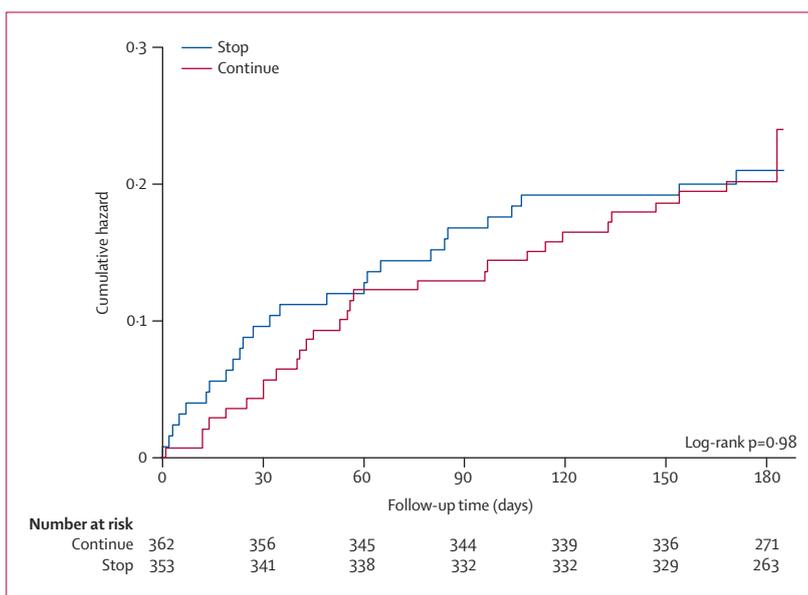


Figure 3: Kaplan-Meier survival estimates

more than one event (seven patients had 18 events in the continue group and six patients had 13 events in the stop group) and treatment was discontinued in 32 patients (16 patients in each group). Four fatal adverse events were reported in the continue group (stroke in three patients and pulmonary embolism in one) and seven in the stop group (stroke in four patients, pulmonary embolism in one, infection in one, and neoplasm in one).

Discussion

In this prospective, randomised, open, blinded-endpoint study, continuation compared with cessation of pre-existing antihypertensive drugs was not associated with a substantial reduction in 2-week death and dependency. However, because the study was stopped before target recruitment had been achieved, the trial only had 9% power to detect a difference of 10% in death and

dependency. Treatment continuation was associated with lower blood pressure at 2 weeks and showed no evidence of increased serious adverse events or neurological deterioration compared with cessation of treatment. The finding that continuation of existing antihypertensive treatment after acute stroke shows no evidence of harm is consistent with the results of intervention trials that suggest that early blood-pressure reduction does not result in an increase in adverse effects.^{12,14,15} The Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) trial¹⁴ included patients within 36 h after acute haemorrhagic or ischaemic stroke onset, and the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS)¹² and a post-hoc analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial¹⁵ included patients within 72 h after acute ischaemic stroke onset. However, starting treatment with antihypertensive drugs during the acute period of stroke was not associated with marked improvement in outcome at 1 week (ACCESS),¹² 2 weeks (CHHIPS),¹⁴ or 30 days (PRoFESS).¹⁵ A meta-analysis of these trials was not deemed appropriate because COSSACS addressed the issue of continuing or stopping pre-existing antihypertensive treatment, whereas the other trials were concerned with initiating antihypertensive treatment after acute stroke.

Although antihypertensive treatment resulted in reduced 3-month mortality compared with placebo in CHHIPS,¹⁴ and ACCESS¹² reported reduced recurrent vascular events at 12 months compared with placebo, neither COSSACS (6 months) nor PRoFESS (3 months) reported reductions in mortality or in recurrent vascular events. COSSACS was underpowered; if there had been a sufficient number of trial participants, a difference in systolic blood pressure of 9 mm Hg between the continue and stop groups might have been associated with substantial benefit, as reported in a recent meta-regression:²⁶ a reduction in systolic blood pressure of 8 mm Hg was associated with an odds ratio for early death of 0.87 (95% CI 0.54–1.23), and a reduction of 14 mm Hg was associated with an odds ratio for end-of-trial death and dependency of 0.95 (0.11–1.72). However, mean baseline systolic blood pressure in patients in the COSSACS trial was the same as the lowest risk level reported in the U-shaped relation between systolic blood pressure and outcome in the International Stroke Trial;¹¹ this might explain why further blood pressure reduction was not beneficial.

To date, most trials have enrolled patients late in the post-acute stroke time window; COSSACS recruited a median of 24 h after stroke onset. The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT)¹³ enrolled patients within a hyperacute timeframe, up to 6 h after stroke, and reported a substantial reduction in haematoma expansion with intensive compared with routine antihypertensive treatment. The

benefits or risks of hyperacute antihypertensive treatment are probably only short term, but the evidence base at present is not sufficient. However, antihypertensive treatment in the acute setting might have early secondary prevention benefits.^{12,14}

All patients in COSSACS had a clinical diagnosis of stroke confirmed from clinical history or neuroimaging (predominantly CT). Consistent with other studies,²⁷ almost two-thirds of patients with ischaemic stroke had signs of acute ischaemia on CT imaging. Fewer patients with acute ischaemic stroke confirmed on neuroimaging were dependent (mRS >3) or had died at 2 weeks in the continue compared with the stop group. This might be a chance finding, but one explanation for the positive treatment effect in this subgroup of patients is that patients with acute stroke caused by large-vessel disease, who would usually have positive CT brain imaging, might respond differently to antihypertensive drugs compared with patients with small-vessel disease. Future trials of blood-pressure lowering in acute stroke should include detailed assessment of the different stroke subtypes.

The effects of blood-pressure lowering might be different in patients with primary haemorrhage and large infarcts, particularly in those with coexisting large-vessel stenosis or occlusion. The detrimental effects of hypertension-associated haematoma expansion⁸ and cerebral oedema⁵ can be reduced by blood-pressure lowering. However, cerebral hypoperfusion after blood-pressure reduction in patients with impaired cerebrovascular autoregulation might be more harmful when a patient also has a larger infarct, increased penumbral zone, or poor collateral circulation.¹⁰ Blood-pressure reductions associated with magnesium seemed to be associated with poorer outcome in patients with cortical syndromes in the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial.²⁸ However, this was also a neutral trial with a positive post-hoc analysis and therefore the different results are perhaps not surprising. Furthermore, different antihypertensive drug classes might have differential effects on cerebral blood flow:²⁹ for example, blood-pressure lowering in acute stroke associated with β blockers and calcium-channel blockers might be detrimental,¹⁷ although the small number of patients prevented a clear comparison between antihypertensive classes. However, in the CHHIPS trial,¹⁴ in which angiotensin-converting enzyme inhibitors and β blockers were administered by different routes in patients with or without dysphagia, there were similar antihypertensive effects between those with dysphagia and those without, although formal assessment of cerebral blood flow was not done.

The COSSACS trial has several limitations. First, COSSACS excluded patients with dysphagia because regulatory approval for COSSACS required drugs to be administered by their licensed route and format (ie, orally). However, patients with dysphagia are commonly given antihypertensive drugs by crushed tablets or as a

suspension (orally or by nasogastric tube), and antihypertensive drug treatment by non-oral routes has been assessed.¹⁷ Second, COSSACS included mainly patients with mild stroke (median NIHSS score 4), and only 5% of patients had had haemorrhagic stroke. In keeping with this, the 2-week death and dependency rate was only 19% in the continue group and 21% in the stop group, although this low rate might also be a result of increased application of evidence-based stroke care, including stroke units, in the UK.³⁰ Therefore, COSSACS does not provide information on benefit or harm of continuing or stopping pre-existing antihypertensive treatment in patients with moderate or severe stroke, and ongoing trials should include this population. Third, the risk of recurrent disabling stroke is highest early after minor stroke,³¹ but previous studies have reported that early blood-pressure lowering results in potential benefits at 3 months (CHHIPS)¹⁴ and 12 months (ACCESS).¹² We therefore chose to include endpoints at 2 weeks and 6 months, rather than the commonly used 3-month endpoint, with the aim of identifying any early benefits with regard to safety and later secondary prevention. Fourth, the median time to recruitment after stroke onset was 24 h. Although this timescale is comparable with ACCESS,¹² it does not enable the risks and benefits of hyperacute blood-pressure lowering to be assessed. Fifth, diagnostic confirmation by neuroimaging was only available in 65% of patients before the day of randomisation, although prerandomisation neuroimaging is ideally a prerequisite for acute stroke trials. Neuroimaging before randomisation is becoming more feasible in the UK because of the increased availability of neuroimaging facilities for diagnosis of stroke. Finally, dependency was defined by an mRS of 4 or 5, and not a score of 3 or more, because of a protocol amendment to increase recruitment; about 4% of trial participants had an mRS of 3 at baseline, which shows that acute stroke patients often have pre-morbid disability.

Given the death and dependency rate of 21% in the COSSACS stop group, 15 406 patients would have been needed to show a relative reduction of 10% in the primary outcome at a 90% power and 5% significance level. Therefore, COSSACS is substantially underpowered to address the efficacy of continuing or stopping antihypertensive drugs after acute stroke. The low recruitment rate also shows the difficulty in recruiting patients to trials in which they must consent to potentially stop their pre-existing antihypertensive treatment.³² Nonetheless, these results support the continuation of ongoing trials to assess the introduction of antihypertensive treatment in patients with acute stroke and hypertension (eg, the Efficacy in Nitric Oxide [ENOS] trial,³³ the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial [INTERACT2],³⁴ and the Scandinavian Candesartan Acute Stroke Trial [SCAST]), and whether to continue or stop pre-existing treatment (ENOS). Larger numbers

of patients are needed to investigate several factors that affect the efficacy of blood-pressure reduction in acute stroke, including: stroke type (ischaemic vs haemorrhagic), origin (large vs small vessel), site (cortical vs subcortical), antihypertensive class, duration of treatment, and amount of blood-pressure reduction. In addition, these trials must assess hyperacute blood-pressure lowering, because COSSACS and other trials have suggested that this strategy might be safe in the subacute period.

In conclusion, in COSSACS there was no obvious harm associated with continuing compared with stopping pre-existing antihypertensive drugs for a 2-week period. Continuation of antihypertensive drugs might be associated with reduced 2-week death and dependency in patients with ischaemic stroke confirmed on neuroimaging. However, this post-hoc subgroup analysis requires further evaluation in patient populations with well defined stroke subtypes, and ongoing trials should address this and other important questions (eg, treatment in the hyperacute period after stroke).

Contributors

TGR was chief investigator and was responsible for the overall running, analysis, and writing of the report. TGR and JFP developed the trial and sought and obtained funding. GAF, CJB, CJ, MAJ, JK, HSM, and NRP contributed to the trial design. CJ oversaw the statistical analysis and commented on the report. GAF, CJB, CJ, JK (patient and carer representative), HSM (vice-chair), and NRP (chair) were members of the steering committee. JFP, GAF, CJB, HSM, AKM, and NRP reviewed the analysis and the report. JC did the statistical analysis. MAJ and HSM recruited patients, MAJ reviewed the report, and AKM was one of the trial coordinators.

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- Conflicts of interest**
- GAF has received honoraria, and travel and accommodation expenses from Boehringer Ingelheim. CJB has received travel and accommodation expenses for speaking engagements on hypertension research from Institute de Recherches Internationales Servier. CJB's institution has received support from Institute de Recherches Internationales Servier for pharmaceutical hypertension trials. All other authors have no conflicts of interest.
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- References**
- 1 International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. *Lancet* 1997; **349**: 1569–81.
 - 2 CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischaemic stroke. *Lancet* 1997; **349**: 1641–49.
 - 3 Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* 2004; **43**: 18–24.
 - 4 Tikhonoff V, Zhang H, Richart T, Staessen JA. Blood pressure as a prognostic factor after acute stroke. *Lancet Neurol* 2009; **8**: 938–48.
 - 5 Fodstad H, Kelley PJ, Buchfelder M. History of the Cushing reflex. *Neurosurgery* 2006; **59**: 1132–37.
 - 6 Chamorro A, Amaro S, Vargas M, et al. Catecholamines, infection, and death in acute ischemic stroke. *J Neurol Sci* 2007; **252**: 29–35.
 - 7 Robinson TG, James M, Youde J, Panerai R, Potter J. Cardiac baroreceptor sensitivity is impaired after acute stroke. *Stroke* 1997; **28**: 1671–76.
 - 8 Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke* 2004; **35**: 1364–67.
 - 9 Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. *Stroke* 1986; **17**: 861–64.
 - 10 Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation* 2008; **118**: 176–87.
 - 11 Leonardi-Bee J, Bath PMW, Phillips SJ, Sandercock PAG, for the IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke* 2002; **33**: 1315–20.
 - 12 Schrader J, Luders S, Kulschewski A, et al. The ACCESS Study. Evaluation of acute candesartan cilexetil therapy in stroke survivors. *Stroke* 2003; **34**: 1699–703.
 - 13 Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008; **7**: 391–99.
 - 14 Potter JF, Robinson TG, Ford GA, et al. Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol* 2009; **8**: 48–56.
 - 15 Bath PMW, Martin RH, Palesch Y, et al. Effect of telmisartan on functional outcome, recurrence, and blood pressure in patients with acute mild ischemic stroke: a PROFESS subgroup analysis. *Stroke* 2009; **40**: 3541–46.
 - 16 Geeganage C, Bath PMW. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev* 2008; **4**: CD000039.
 - 17 Blood pressure in Acute Stroke Collaboration. Vasoactive drugs for acute stroke. *Cochrane Database Syst Rev* 2000; **4**: CD002839.
 - 18 Bath P, Chalmers J, Powers W, et al. International Society of Hypertension (ISH): statement on the management of blood pressure in acute stroke. *J Hypertens* 2003; **21**: 665–72.
 - 19 Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults—2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke* 2007; **38**: 2001–23.
 - 20 Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary working groups. *Circulation* 2007; **115**: e478–534.
 - 21 National Collaborating Centre for Chronic Conditions. Stroke: national clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). London, UK: Royal College of Physicians, 2008. <http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=254> (accessed April 1, 2010).
 - 22 The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25**: 457–507.
 - 23 The COSSACS Trial Group. COSSACS (Continue or Stop post-Stroke Antihypertensives Collaborative Study): rationale and design. *J Hypertens* 2005; **23**: 455–58.
 - 24 Dennis M, Wellwood I, Warlow C. Are simple questions a valid measure of outcome? *Cerebrovasc Dis* 1997; **7**: 22–27.
 - 25 Dorman P, Waddell F, Slattery J, Dennis M, Sandercock P. Are proxy assessments of health status after stroke with the EuroQoL questionnaire feasible, accurate, and unbiased? *Stroke* 1997; **28**: 1883–87.
 - 26 Geeganage CM, Bath PMW. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension* 2009; **54**: 775–81.

- 27 Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000; **355**: 1670–74.
- 28 Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet* 2004; **363**: 439–45.
- 29 Sare GM, Gray LJ, Bath PMW. Effect of antihypertensive agents on cerebral blood flow and flow velocity in acute ischaemic stroke: systematic review of controlled studies. *J Hypertens* 2008; **26**: 1058–64.
- 30 Royal College of Physicians. National Sentinel Stroke Audit Organisational Audit 2009. <http://www.rcplondon.ac.uk/media/Press-releases/Documents/Stroke-Organisational-Audit-2009.pdf> (accessed April 1, 2010).
- 31 Rothwell P, Warlow C. Timing of transient ischaemic attacks preceding ischaemic stroke. *Neurology* 2005; **64**: 817–20.
- 32 Potter J, Mistri A, Brodie F, et al. Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS)—a randomised controlled trial. *Health Technol Assess* 2009; **13**: 1–95.
- 33 The ENOS Investigators. Glyceryl trinitrate vs. control, and continuing vs. stopping temporarily antihypertensive therapy in acute stroke: rationale and design of the Efficacy of Nitric Oxide in Stroke (ENOS) trial. *Int J Stroke* 2006; **1**: 245–49.
- 34 Delcourt C, Huang Y, Wang J, et al. The second (main) phase of an open, randomised, multicentre study to investigate the effectiveness of an intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT2). *Int J Stroke* 2010; **5**: 110–16.