Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint study

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Summary

Background

Up to 50% of acute stroke patients are taking blood pressure (BP) lowering therapy on hospital admission. It is unclear whether such therapy should be continued during the immediate post-stroke period.

Methods

Patients already taking BP-lowering therapy, within 48 hours of both acute stroke and last dose of BP-lowering medication, were randomised to continue or stop pre-existing medication for two weeks. Primary endpoint was 2-week death or dependency analysed by intention-to-treat. This trial is registered with the International Standard Randomised Controlled Trial Register, number ISRCTN89712435.

Findings

763 patients (mean age 74 [SD 11] years; systolic BP [SBP] 150 [SD 22] mmHg; diastolic BP [DBP] 81 [SD 13] mmHg; median National Institutes of Health Stroke Scale score 4 [IQR 2-7] points) were assigned to continue (n=379) or stop (n=384) pre-existing BP-lowering therapy. Death or dependency (Modified Rankin Score >3) at 2 weeks – occurred in 19% (72) of the continue and 21% (82) of the stop group (relative risk 0.86, 95% CI 0.65-1.14; p=0.3). BP was lower (p<0.0001) at 2 weeks in the continue compared to stop group: SBP 13 mmHg (95% CI

(10, 17)), DBP 8 mmHg (95% CI (6, 10)). No significant differences were observed between groups in serious adverse event rates, 6-month mortality or major cardiovascular events.

Interpretation

Significantly lower BP levels, in those who continued BP-lowering therapy following acute mild stroke, were not associated with an increase in adverse events, but did not reduce 2-week death or dependency, cardiovascular event rate or mortality at 6 months. These neutral results may reflect lack of power since COSSACS was terminated prematurely.

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Introduction

Raised blood pressure (BP) levels are common following acute stroke with more than three-quarters of patients having a systolic BP (SBP) greater than 140 mmHg on admission [1,2]. These elevated levels are associated with a poor prognosis [3,4]; possible underlying pathophysiological mechanisms include raised intracranial pressure [5], increased sympathetic nervous system activity [6], abnormal baroreceptor sensitivity [7] and haematoma expansion [8]. The natural history is for a spontaneous BP fall over 4 to 10 days post-ictus [9], but significant BP reductions may be associated with cerebral hypoperfusion as a consequence of post-stroke cerebral dysautoregulation [10]. Indeed, data from the International Stroke Trial indicate a U-shaped relationship between baseline SBP (within 48 hours of ictus) and short- (14-day mortality) and long-term (6-month death and dependency) outcomes, with an increased risk of early death by 3.6% and late death and dependency by 17.9% for every 10 mmHg below 150 mmHg, and an increased risk of early death by 3.8% and a non-significant rise in late death and dependency for every 10 mmHg above 150 mmHg; the lowest risk corresponding to a SBP of 150 mmHg [11].

Preliminary data from recent randomised controlled trials suggest that BP can be safely reduced following acute stroke [12-15], and may be associated with improved long-term mortality [14] and reduced recurrent vascular events [12]. However, the optimal management of BP after acute stroke remains uncertain, as evident in recent Cochrane meta-analyses [16,17], and highlighted in a number of international acute stroke management guidelines [18-22]. Importantly, hypertension is a major modifiable risk factor for stroke prevention, and more than 50% of patients are already taking BP-lowering

therapy at the time of their admission for acute stroke. It is therefore a common clinical dilemma as to whether to continue or stop such treatment in the acute stages following stroke.

The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) assessed the efficacy and safety of continuing or stopping pre-existing BP-lowering therapy in a United Kingdom multi-centre, prospective, randomised, open, blinded-endpoint trial of non-dysphagic, ischaemic and haemorrhagic stroke patients within 48 hours of ictus and within 48 hours of the last dose of BP-lowering therapy.

Methods

Patients

Full details of this trial are described elsewhere [23]. Patients were recruited at 49 United Kingdom National Institute of Health Research Stroke Research Network centres (Appendix) from 1 January 2003 to 31 March 2009. Patients were eligible if they were older than 18 years and had 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 known to be asymptomatic. Inclusion criteria were cerebral infarction (but not undergoing thrombolytic treatment) or primary intracerebral haemorrhage (PICH), symptom onset within 48 hours, and currently taking BP-lowering therapy with the last dose having been taken within 48 hours of randomisation. Exclusion criteria included hypertensive encephalopathy, co-existing cardiac or vascular urgency, SBP

greater than 200mmHg and/ or diastolic (DBP) greater than 120mmHg in association with known PICH, contraindications to stopping or indications for continuing BP lowering therapy, dysphagia, impaired level of consciousness (National Institutes of Health stroke scale (NIHSS) section 1a score ≥2 points), females of childbearing potential, premorbid dependency (modified Rankin score (mRS) >3 points), any co-existing life threatening condition with an estimated life expectancy of less than 6 months, and diagnosis of non-stroke on subsequent neuroimaging. To increase recruitment, amendments were made to the original protocol that included an increase in the time from stroke onset to randomisation from 24 to 48 hours, an increase in the time from last dose of BP lowering therapy to randomisation from 36 to 48 hours, and the inclusion of patients with a pre-stroke mRS score of 3 points instead of the original 0 to 2 points. These amendments were made by the trial steering committee. Informed patient consent (written where possible), assent from a relative (with subsequent confirmation of assent by 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 by secure internet central randomisation (with a block size of 4). Allocation (1:1) to continue or stop pre-existing BP-lowering therapy for a 2-week period was done by use of a computer with stratification by the following category: age at entry (<75, and ≥75 years). Patients and randomising clinicians were unmasked to treatment allocation. Two-week outcomes were undertaken by a clinician masked to treatment allocation; the secure internet data collection facility not allowing 2-week data entry by a

clinician that had undertaken either randomisation or baseline data entry. Six-month outcomes were undertaken by the trial co-ordinating centre, masked to treatment allocation.

Procedures

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. BP-lowering therapy following the 2-week study period was at the discretion of the local investigator. Baseline assessments included NIHSS, Oxfordshire Community Stroke Project (OCSP) classification, mRS and Barthel Index (BI). Casual BP was taken as the mean of two sets of three supine brachial BP readings 10 minutes apart, using an A&D UA-767 BP monitor in all centres. In addition, casual BP was monitored throughout the treatment period, and patients with symptomatic sustained hypotension (SBP <100mmHg), or at the discretion of the treating clinician, were withdrawn from the study.

Study assessments, NIHSS, mRS, BI and casual BP using a validated BP monitor (A&D UA-767) were repeated at 2 weeks by a researcher blinded to the patient's randomisation status. Long-term follow-up at 6 months was undertaken by the trial co-ordinating centre and a researcher blinded to the patient's randomisation status. Death was noted from the NHS Register. Those patients still alive were contacted by telephone, and the International Stroke Trial [24] and EuroQoL [25] questionnaires administered to the patient or proxy. In addition, current residence and treatment (including BP-lowering therapy) were recorded.

All serious adverse events reported during the 2-week treatment period were categorised as 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 by the local investigator. Serious adverse events were reviewed by the trial steering and independent data safety monitoring committees at 6-monthly intervals.

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 early secondary outcome measures at 2 weeks included neurological and functional status, casual BP changes between admission and 2 weeks, discharge destination 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.

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

Statistical analysis

Continuous measures, including age, SBP, DBP, haemoglobin, platelets, potassium, total cholesterol and ECG heart rate, were approximately normally distributed. Linear regression

was used to compare 2-week BPs by treatment group. BI, NIHSS, alcohol consumption, white cell count, sodium, urea, creatinine, glucose, time since stroke onset and time since the last BP-lowering therapy was taken had skewed distributions. Non-parametric Kruskal-Wallis tests were used to compare 2-week NIHSS and BI by treatment group. For the primary outcome (death and dependency at 2 weeks), chi-squared test was performed to test the difference between the groups and the difference reported as a risk ratio; logistic regression was used when adjustment was needed with results presented as odds ratios. It was estimated that 2900 trial participants would be required for a 10% reduction (absolute risk reduction of 6%) in death and dependency between the continue and stop groups at 2 weeks to be detected, with 90% power at the 5% significance level, assuming an overall rate of death and dependency of 60% at 2 weeks [23]. Multinomial logistic regression was used to assess whether treatment effect differed across baseline mRS categories. Post-hoc analysis was undertaken in the CT-confirmed ischaemic stroke subgroup. Deaths up to 6 months post-randomisation were recorded from the NHS register, cause of death being taken from the death certificates. Major cardiovascular events at 6 months were analysed along with the mortality data by chi-squared tests. Survival data were analysed by a non-parametric log-rank test with a Kaplan-Meier plot. All analyses were made on an intention-to-treat basis using Stata version 9.2 statistical software.

Role of the funding source

The sponsor (University Hospitals of Leicester NHS Trust) and funders (The Health Foundation, The Stroke Association) 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

COSSACS started on 1 January 2003 and ended on 31 March 2009, but was terminated before target recruitment was reached (due to slow recruitment and lack of continued funding) when 763 patients (56% male), of mean age 74 years (11), with baseline BP 150 (22)/ 81 (13) mmHg) had been randomised within a median (IQR) of 23.6 (17.9, 34.8) hours following stroke onset and 16.0 (6.8, 28.9) hours following last dose of BP-lowering therapy, and included in the intention-to-treat analysis (Figure 1). Patients underwent neuroimaging to exclude non-stroke diagnoses within a median of 1 (IQR: 1 to 2) days from stroke onset (65% undergoing neuroimaging before or on the day of randomisation); 454 (63%) showed acute infarction, 9 (1%) haemorrhagic transformation of acute infarction, 38 (5%) primary intracerebral haemorrhage, 207 (29%) non-relevant change, and 18 (3%) non-stroke diagnosis. At randomisation, the continue and stop groups were well matched for measured baseline variables (Table 1), with respect to number of baseline antihypertensive therapy (Table 1), classes of antihypertensive, antithrombotic, and cholesterol lowering therapy (data not shown), and routine baseline investigations, including haematology, biochemistry and electrocardiography (data not shown).

The per protocol population numbered 743 patients; twenty patients being withdrawn post-randomisation, in 18 cases due to non-stroke diagnosis (Continue – complex regional pain

syndrome 1, epilepsy 1, meningitis 1, non-organic syndrome 1, secondary tumour 3, not specified 1; Stop – Bell's palsy 1, mononeuritis multiplex 1, primary tumour 2, secondary tumour 2, subdural haematoma 1, transient ischaemic attack 1, viral labyrinthitis 1, not specified 1), and in 2 cases due to protocol violation (Stop - >48 hours following last BP lowering dose 1, contraindication to stop BP lowering treatment 1) (Figure 1). 706 patients (92.5%) completed the full 2-week study protocol: 18 cases due to withdrawal of consent/ lack of confirmation of relative or independent clinician assent (Continue 8, Stop 10), , 6 cases by the local investigator (Stop - BP high and requiring treatment 3, acute myocardial infarction 1, recurrent ischaemic stroke 1, non-compliant with trial treatment arm 1), and13 patients lost to 2-week follow-up (Continue 7, Stop 6) (Figure 1).

Primary Endpoint

The primary outcome of death or dependency (mRS>3) at 2 weeks occurred in 19% (72 patients) in the continue group and 21% (82 patients) in the stop group (Figure 2, relative risk [RR] 0.86, 95% CI 0.65-1.14; p=0.3). There was no evidence that the treatment effect (continue or stop pre-existing BP lowering therapy) differed across 2-week mRS categories (p=0.47). In the treatment adjusted model, age (75 years old+, N=391 (51%)) was significantly associated with poorer outcome (Odds Ratio [OR] 1.78, 95% CI (1.24, 2.57), p=0.002). When adjusted further for smoking, alcohol, gender, neuroimaging evidence of acute stroke, history of diabetes, stroke and atrial fibrillation the effect of age remained significant (OR 1.76, 95%CI (1.11, 2.81), p=0.017). No interaction effect was found between age and treatment group. Neither baseline SBP nor baseline DBP was found to be significantly correlated with the primary outcome.

BP Difference Between Groups

At 2 weeks, mean BP in the continue group was 140 (22)/ 76 (14)mmHg and in the stop group was 153 (24)/ 84 (14)mmHg (Table 2), representing a change of -9 (23)/ -4 (14) and 3 (25)/ 2 (14)mmHg, respectively, compared to baseline. SBP and DBP were significantly ($p<0.0001$) lower at 2 weeks in the continue compared to the stop arm with a difference of 13 mmHg (95% CI 10, 17) and 8 (95% CI 6, 10), respectively. Daily BP readings based on routine ward recordings are not reported.

Other Secondary Endpoints

At 2 weeks, there were 4 deaths in the continue group (unknown alive/ dead status in 3) and 7 deaths in the stop group (unknown alive/ dead status in 16). There were no significant differences in early (2-week) secondary neurological (NIHSS) and functional (BI) outcomes between continue and stop arms (Table 2). At 2 weeks, 158 patients (42%) remained hospital in-patients in the continue group compared to 147 patients (38%) in the stop group.

By 6 months, 32 patients in the continue group and 29 patients in the stop group had died, providing an overall 6-month mortality of 8.0% (n=61) in both groups (Continue: stroke 5, respiratory 4, cardiovascular 2, pulmonary embolism 1, neoplastic 1, sepsis 1, unknown 18; Stop: stroke 4, pulmonary embolism 2, neoplastic 2, infection 1, unknown 20) (Table 3, Figure 3). In addition, functional outcome was derived from the International Stroke Trial telephone-administered questionnaire (Table 3). No differences were found in self-reported

major cardiovascular event rates at 6 months: recurrent stroke (Continue: 12 vs. Stop: 12), cardiovascular (11 vs. 8), and other vascular (3 vs. 4).

In a post-hoc analysis of 444 patients with a definite neuroimaging diagnosis of acute ischaemic (including haemorrhagic transformation) stroke and complete 2-week outcome data, fewer patients were dead or dependent (mRS>3) at 2 weeks in the continue compared to stop group, 46 (19.1%) vs. 55 (27.1%), respectively, with a relative risk reduction of 0.70 (95% CI: 0.51 to 0.99, p=0.045). The OCSP classification for these patients was: TACS (11%), PACS (42%), LACS (35%), POCS (12%). No significant differences were observed in baseline data between these groups. For those patients without neuroimaging-confirmed acute ischaemic or haemorrhagic stroke diagnosis (i.e. non-relevant change), the OCSP classification was: TACS (7%), PACS (40%), LACS (45%), POCS (8%), with a relative risk reduction of 1.1 (95% CI: 0.6 to 2.1, p=0.76).

Adverse Events

96 serious adverse events were reported in 76 patients with 20 patients having more than one event, and treatment being discontinued in 32 patients (16 patients in each group). Four fatal adverse events were reported in the continue group (stroke 3, pulmonary embolism 1), and seven in the stop group (stroke 4, pulmonary embolism 1, infection 1, neoplastic 1).

Discussion

In this prospective, randomised, open, blinded-endpoint study, continuing compared to stopping pre-existing BP-lowering therapy was associated with a significantly lower BP over the first 2 weeks. This strategy demonstrated no evidence of increased serious adverse events or neurological deterioration, but was not associated with a significant reduction in 2-week death and dependency. However, due to study closure before target recruitment had been achieved owing to lack of further funding, the trial only had 9% power at the 5% level to detect a difference of 10% in death and dependency. Nonetheless, the finding in this largest acute stroke BP trial to report to date that continuing existing BP-lowering therapy following acute stroke shows no evidence of harm is consistent with recently reported intervention trials, which suggest that early BP reduction does not result in adverse effects. The Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) addressed a 36-hour time window [14], and the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) [12] and a posthoc analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) [15] addressed a 72-hour window from acute ischaemic (ACCESS, CHHIPS, PRoFESS) and haemorrhagic (CHHIPS) stroke onset. However, to date, this treatment approach has not been associated with significant benefit in early outcome at 1 (ACCESS) or 2 weeks (CHHIPS), or 30 days (PRoFESS). It was not considered appropriate to undertake a meta-analysis of these trials, as COSSACS addressed the issue of continuing or stopping pre-existing BP-lowering therapy, whereas the other trials were concerned with the introduction of denovo BP-lowering therapy.

Though CHHIPS and ACCESS suggested later benefits with reduced 3-month mortality and 12-month recurrent vascular events, respectively, this was not seen in either COSSACS (6 months) or PRoFESS (3 months). In the case of COSSACS, there was insufficient power to detect important benefits. Had there been sufficient trial participants, a 9 mmHg SBP difference between the continue and stop arms might be expected to be associated with significant benefit as reported in a recent meta-regression; SBP reduction of 8 mmHg was associated with an odds ratio of 0.87 (95% CI: 0.54-1.23) for early death, and of 14 mmHg for an odds ratio of end-of-trial death and dependency of 0.95 (95% CI: 0.11-1.72) [26]. However, baseline SBP in the COSSACS population was identical to the lowest risk level reported in the U-shaped relationship between SBP and outcome in the International Stroke Trial, and may explain why further BP reduction was not beneficial [11].

To date, the majority of trials have recruited patients relatively late within the post-acute stroke time window; COSSACS recruiting a median of 24 hours after stroke onset. Only the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) recruited within a hyperacute time frame, up to 6 hours; demonstrating a significant reduction in haematoma expansion with intensive compared to routine BP-lowering therapy [13]. It is likely that short-term benefit (or harm) is more likely to be realised with hyperacute BP-lowering treatment, and the current evidence base is not sufficient to comment on this reliably. However, current results do suggest that BP-lowering treatment introduced acutely may have early secondary prevention benefits.

All patients in COSSACS had a clinical diagnosis of stroke confirmed from clinical history and/or neuroimaging, predominantly CT. Consistent with other studies, two-thirds of patients with ischaemic stroke had signs of acute ischaemia on CT imaging, and a post-hoc analysis was undertaken for this group only. As previously presented, fewer patients with neuroimaging-confirmed acute ischaemic stroke were dead or dependent (mRS>3) at 2 weeks in the continue compared to stop group, 46 (19.1%) vs. 55 (27.1%), respectively, with a relative risk reduction of 0.70 (95% CI: 0.51 to 0.99, p=0.045). This may be a chance finding, but one explanation for the positive treatment effect in this group of patients is that patients with acute stroke due to large vessel disease, who would mostly have positive CT brain imaging, may respond differently to BP-lowering therapy compared to patients with small vessel disease. However, this finding does suggest that future trials of BP-lowering in acute stroke should phenotype stroke subtype with more detailed assessment.

It is possible that the implications of BP-lowering may be different in primary haemorrhage and larger infarcts, particularly with co-existent large vessel stenosis or occlusion. Certainly, the detrimental effects of hypertension-associated haematoma expansion [8] and cerebral oedema [5] may be reduced by BP lowering. However, cerebral hypoperfusion secondary to BP reduction in the presence of impaired cerebrovascular autoregulation may be more detrimental in association with a larger infarct, increased penumbral zone and poor collateral circulation [10]. Indeed, there was a trend for BP reductions associated with magnesium in the Intravenous Magnesium Efficacy in Stroke trial (IMAGES) to be associated with poorer outcome in patients with cortical syndromes [27]. However, this was also a neutral trial, with a positive post-hoc analysis, and it is perhaps not surprising that the

interpretation is different. Furthermore, it is possible that different antihypertensive classes may have differential effects on cerebral blood flow (CBF) [28], for example BP lowering in acute stroke associated with beta- and calcium channel blockade may be detrimental [17], though small numbers in the present study prevent meaningful comparison between antihypertensive classes. However, similar BP-lowering effects and no differences in safety were observed using different routes of administration in dysphagic and non-dysphagic patients with angiotensin converting enzyme inhibitors and beta-blockers in the CHHIPS Trial, though formal assessment of CBF was not made [14].

There a number of limitations with the COSSACS trial. Firstly, ~~I~~it was necessary to exclude dysphagic patients from COSSACS. It is common practice to administer BP-lowering therapy by crushing tablets or administering as a suspension, either orally or by nasogastric tube, to dysphagic patients. However, ~~, because~~ regulatory approval for COSSACS required medication to be administered by its licensed route and format. Furthermore, BP-lowering therapy can be administered by non-oral routes, and this has been examined in previous studies [17]. Secondly, ~~Therefore,~~ COSSACS is a trial of continuing or stopping pre-existing BP-lowering therapy in a mild stroke population (median NIHSS score 4), with few haemorrhagic stroke patients (5%). In keeping with this, a 2-week death and dependency rate of only 19% and 21% was reported in the continue and stop groups, respectively, though this may also reflect an increased application of evidence-based stroke care, including stroke units, in the United Kingdom [29]. Therefore, COSSACS does not provide information in respect of benefit or harm for a strategy of continuing or stopping pre-existing BP-lowering therapy in moderate or severe stroke patients, and it is important that

ongoing trials consider this population. Thirdly, it is known that the risk of recurrent disabling stroke is front-loaded after minor stroke [30], but that previous studies have indicated potential benefit associated with early BP-lowering interventions at 3 months (CHHIPS) [14] and 12 months (ACCESS) [12]. Therefore, end-points at 2 weeks and 6 months, rather than the commonly used 3-month end-point, were used to capture early safety and later secondary prevention benefit outcomes.

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As previously discussed, a further limitation was that the median time to recruitment following stroke onset was 24 hours. Though comparable with a previously completed trial, ACCESS [12], this does not inform the risks and benefits of hyperacute BP lowering. Furthermore, diagnostic confirmation by neuroimaging was only available in 65% of patients before on the day of randomisation, though pre-randomisation neuroimaging is ideally a prerequisite for acute stroke trials and increasingly deliverable with more recent United Kingdom stroke service developments. Finally, dependency was defined by a Modified Rankin Score of 4 or 5, excluding a score of 3, as patients were included with this level of dependency following a protocol amendment to enhance recruitment, accounting for approximately 4% of trial participants, and reflecting that acute stroke patients often have premorbid disability. ~~A further limitation of the trial relates to the missing 2-week and 6-month outcome data.~~

Given the observed death and dependency rate of 21% in the COSSACS stop arm, a study of 15,406 patients would have been required to demonstrate a relative reduction in the

primary outcome of 10% at a 90% power at a 2-sided α-level of 5%. Therefore, COSSACS is significantly underpowered to address the efficacy of continuing or stopping BP-lowering therapy following acute stroke, and was terminated because of a lack of continued funding. It also reflects the difficulty in recruiting to trials where patients consent to potentially stop their pre-existing BP-lowering therapy [310]. Nonetheless, these results support the continuation of ongoing trials to assess the introduction of de novo treatment in acute stroke hypertension (Efficacy in Nitric Oxide (~~Efficacy of Nitric Oxide in Stroke (~~ENOS) trial) [312], Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2), Scandinavian Candesartan Acute Stroke Trial (SCAST)), and whether to continue or stop pre-existing therapy (ENOS). In particular, larger numbers of patients are required to address the importance of a number of factors for the efficacy of BP reduction in acute stroke, including: stroke type (ischaemic vs. haemorrhagic), aetiology (large vs. small vessel), site (cortical vs. subcortical), antihypertensive class, duration of treatment, and degree of BP reduction. In addition, these trials must address hyperacute BP lowering, as COSSACS and other trials have suggested that this strategy appears safe in the subacute period.

In conclusion, in COSSACS, there was no obvious signal of harm associated with a strategy of continuing compared to stopping pre-existing BP-lowering therapy within 48 hours of acute ischaemic or haemorrhagic stroke onset and within 48 hours of last dose of BP-lowering therapy for a 2-week period. It is possible that continuing BP-lowering therapy is associated with reduced 2-week death and dependency, particularly in confirmed ischaemic stroke patients. However, this post-hoc subgroup analysis requires further evaluation in patient

populations with well-defined stroke subtype, and ongoing trials need to address this and other important questions in the management of this common clinical dilemma.

Contributors

TGR was chief investigator, developed the trial, sought and obtained funding, and was responsible for the overall running, analysis, and writing of the manuscript.

CJB contributed to the trial design, was a member of the steering committee overseeing conduct of the trial, and reviewed the analysis and manuscript.

JC was responsible for undertaking the statistical analysis.

GAF contributed to the trial design, was a member of the steering committee overseeing conduct of the trial, and reviewed the analysis and manuscript.

CJ contributed to the trial design, was a member of the steering committee overseeing conduct of the trial, oversaw the analysis, and commented on the manuscript.

MAJ contributed to the trial design, recruited patients, and reviewed the manuscript.

JK contributed to the trial design, and was the patient and carer representative on the steering committee.

AKM was one of the trial co-ordinators, and reviewed the analysis and manuscript.

HSM contributed to the trial design, was vice-chair of the steering committee overseeing conduct of the trial, recruited patients, and reviewed the analysis and manuscript.

JFP developed the trial, sought and obtained funding, and reviewed the analysis and manuscript.

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Conflicts of interest

No conflicts of interest declared.

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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 19435 patients with acute ischaemic stroke. Lancet 1997; 349: 1569-1581.
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: 1641-1649.
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 Neurology 2009; 8: 938-948.

5. Fodstad H, Kelley PJ, Buchfelder M. History of the Cushing reflex. Neurosurgery 2006; 59: 1132-1137.

6. Chamorro A, Amaro S, Vargas M, et al. Catecholamines, infection, and death in acute ischemic stroke. J ournal of Neurological Science 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: 1671-1676.

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: 1364-1367.

9. Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. Stroke 1986; 17: 861-864.

10. Qureshi AI. Acute hypertensive response in patients with stroke. Pathophysiology and management. Circulation 2008; 118: 176-187.

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: 1315-1320.

12. Schrader J, Luders S, Kulschewski A, et al. The ACCESS Study. Evaluation of acute candesartan cilexetil therapy in stroke survivors. Stroke 2003; 34: 1699-1703.

13. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurology 2008; 7: 391-399.

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 Neurology 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: 3541-3546.

16. Geeganage C, Bath PMW. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database of Systematic Reviews. 2008; 4: CD000039.

17. Blood pressure in Acute Stroke Collaboration. Vasoactive drugs for acute stroke. Cochrane Database of Systematic Reviews 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. Journal of Hypertension 2003; 21: 665-672.

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: 2001-2023.

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

Perpipheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary working groups. Circulation 2007; 115: e478-e534.

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, United Kingdom: Royal College of Physicians, 2008. http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=254 (accessed 01 Apr 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. Cerebrovascular Diseases 2008; 25: 457-507.

23. The COSSACS Trial Group. COSSACS (Continue or Stop post-Stroke Antihypertensives Collaborative Study): rationale and design. Journal of Hypertension 2005; 23: 455-458.

24. Dennis M, Wellwood I, Warlow C. Are simple questions a valid measure of outcome? Cerebrovascular Diseases 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: 1883-1887.

26. Geeganage CM, Bath PMW. Relationship between therapeutic changes in blood pressure and outcomes in aucute stroke. A metaregression. Hypertension 2009; 54: 775-781.

27. Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. Lancet 2004; 363: 439-445.

28. 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. Journal of Hypertension 2008; 26: 1058-1064.

29. 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 01 Apr 2010).

30. Rothwell P, Warlow C. Timing of transient ischaemic attacks preceding ischaemic stroke. Neurology 2005; 64: 817-820

~~30. 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 (9).~~

31. ~~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. International Journal of Stroke 2006; 1: 245-249.~~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 (9).

~~31.~~32. The ENOS Investigators. Glyceryl trinitrate vs. control, and continuing vs. stopping temporarily antihypertensive therapy in acute stroke: rationale and design

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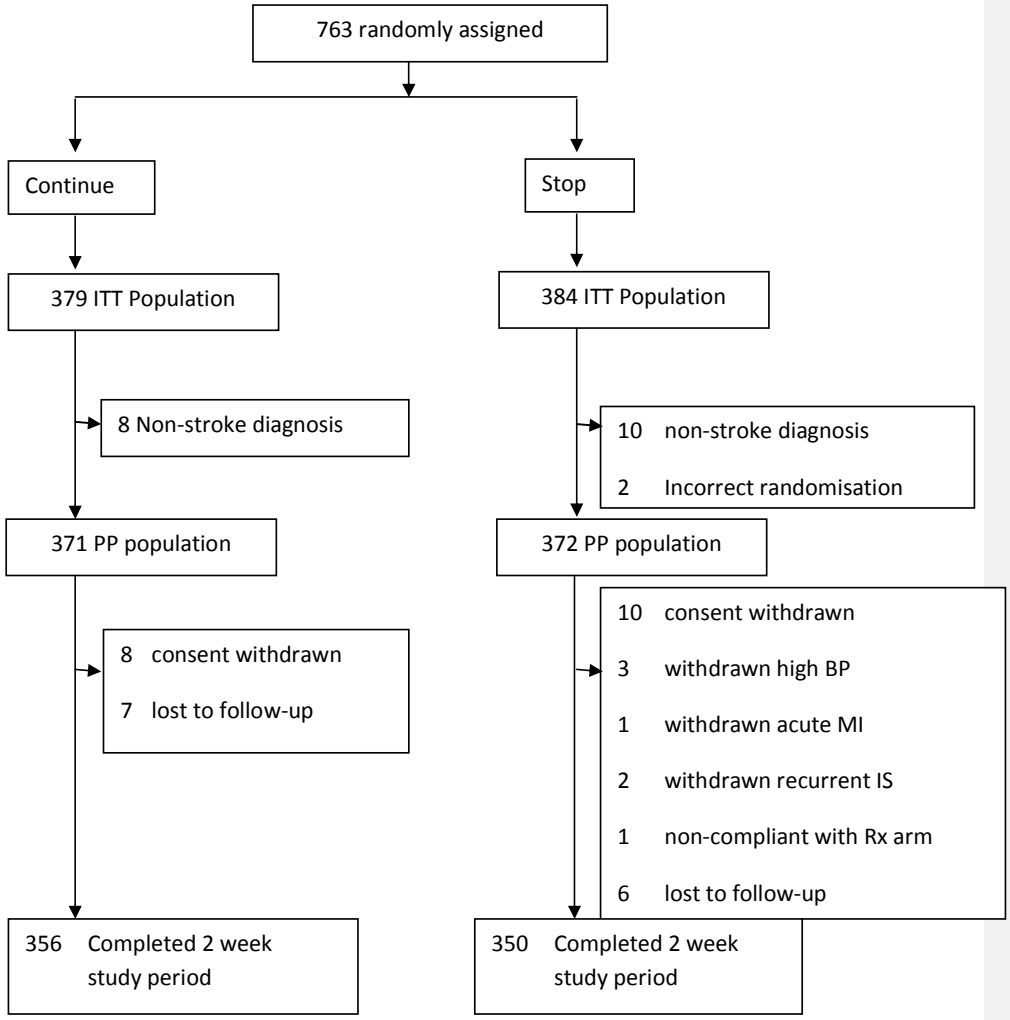
of the Efficacy of Nitric Oxide in Stroke (ENOS) trial. International Journal of Stroke 2006; 1: 245-249.

Figure 1: Trial Protocol



MI: myocardial infarction, IS: ischaemic stroke, Rx: treatment.

Table 1: Baseline characteristics of the COSSACS patients at randomisation (Intention To Treat Population)

	Continue (n=379)	Stop (n=384)
Gender, n (%)		
Male	210 (56)	216 (57)
Age in years, mean (SD)	74 (11)	74 (11)
Ethnicity, n (%)		
Caucasian	288 (89)	300 (93)
Non-Caucasian	32 (11)	21 (7)
SBP mmHg, mean (SD)	149 (23)	150 (22)
DBP mmHg, mean (SD)	80 (13)	81 (14)
OCSP, n (%)		
Total anterior	38 (10)	34 (9)
Partial anterior	149 (40)	163 (43)

Lacunar	143 (39)	144 (38)
Posterior	42 (11)	40 (10)
Stroke type (Neuroimaging)		
Acute ischaemic	243 (67)	211 (58)
HTI	5 (1)	4 (1)
PICH	19 (6)	19 (5)
Non relevant*	86 (24)	121 (33)
Non-stroke	8 (2)	10 (3)
NIHSS, median (IQR)	4 (3-8)	4 (2-7)
Premorbid mRS, n (%)		
0	250 (66)	247 (64)
1	71 (19)	66 (17)
2	43 (11)	54 (14)
3	15 (4)	17 (4)
Baseline BI, median (IQR)	13 (8-19)	13 (8-19)
Time since last antihypertensive taken (hour), median (IQR)	19.5 (7.0-29.6)	13.1 (6.7-28.3)
Time since stroke onset (hour), median (IQR)	23.6 (18.6-35.8)	23.4 (17.5, 34.2)
Past Medical History, n (%)		

Stroke	63 (17)	87 (23)
TIA	74 (20)	66 (17)
Hypertension	369 (96)	375 (98)
Diabetes	69 (22)	60 (19)
Hypercholesterolaemia	173 (49)	177 (49)
IHD	77 (20)	75 (20)
Atrial Fibrillation	72 (19)	78 (20)
PVD	20 (5)	22 (6)
Smoking, n (%)		
Current	63 (17)	57 (15)
Ex-smoker	145 (39)	142 (38)
Alcohol (units/week), median (IQR)	0.5 (0-8)	0 (0-6)
Family history, n (%)		
Present	78 (21)	73 (19)
Baseline number of BP-lowering agents, n (%)		
1	153 (41)	147 (38)
2	135 (36)	159 (42)
≥3	88 (23)	77 (20)

Data presented as mean (SD) for symmetrically distributed variables if not stated otherwise. Denominators vary due to missing data. OCSP=Oxford Community Stroke Project classification. SBP=systolic blood pressure. DBP=diastolic blood pressure. mRS=modified Rankin scale. BI=Barthel Index. NIHSS=National Institutes of Health stroke scale. IHD=ischaemic heart disease. TIA=transient ischaemic attack. PVD=peripheral vascular disease. IQR=interquartile range. *Non relevant=no evidence or acute ischaemic or haemorrhagic stroke or non-stroke diagnoses (e.g. non-acute stroke, normal).

Table 2. Means and differences (95% confidence intervals) in BP, neurological and functional parameters between continue and stop arms at 2 weeks (Intention To Treat Population)

	Continue (n=379)	Stop (n=384)	Difference (95% CI)	p-value
SBP (mmHg)	140 (138, 142)	153 (151, 156)	13 (10, 17)	<0.001
DBP (mmHg)	76 (75, 76)	84 (83, 86)	8 (6, 10)	<0.001
NIHSS	3.8 (3.2, 4.3)	3.5 (2.9, 4.0)	0.3 (-0.5, 1.1)	0.46
BI	15.6 (15.0, 16.2)	16.0 (15.4, 16.6)	-0.5 (-1.3, 0.4)	0.30

Data are mean (95% CI). SBP=systolic blood pressure. DBP=diastolic blood pressure.

NIHSS=National Institutes of Health Stroke Scale. BI=Barthel Index.

Figure 2: Death or dependency at 2 weeks (Intention To Treat Population)

Primary outcome shown as differences in modified Rankin Scale (mRS) between continue and stop groups. mRS score of 0=no residual disability; 5=bedbound and requiring 24-hour care; 6=death. Figures refer to absolute numbers.

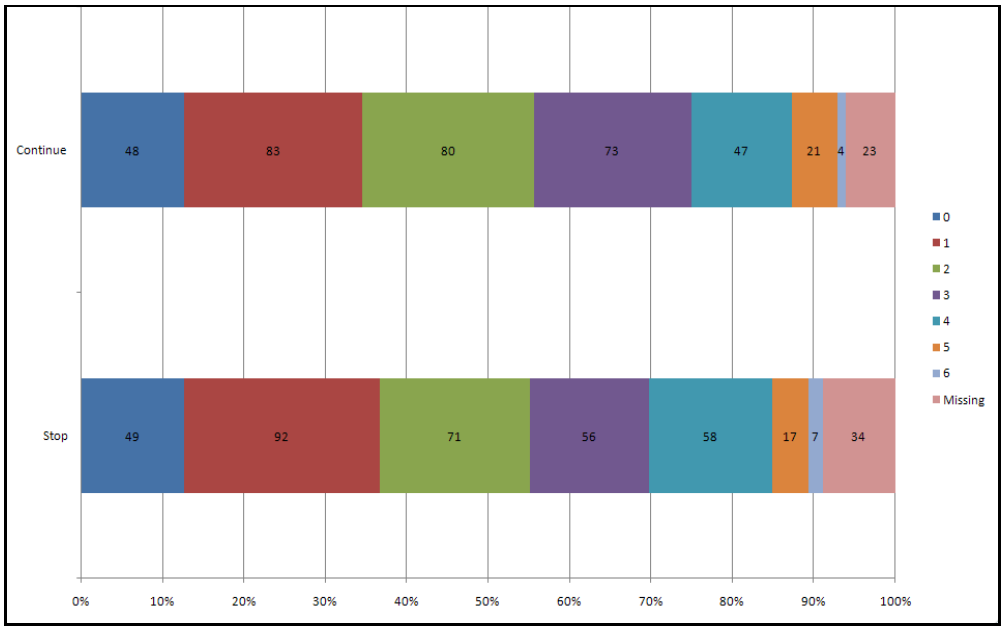
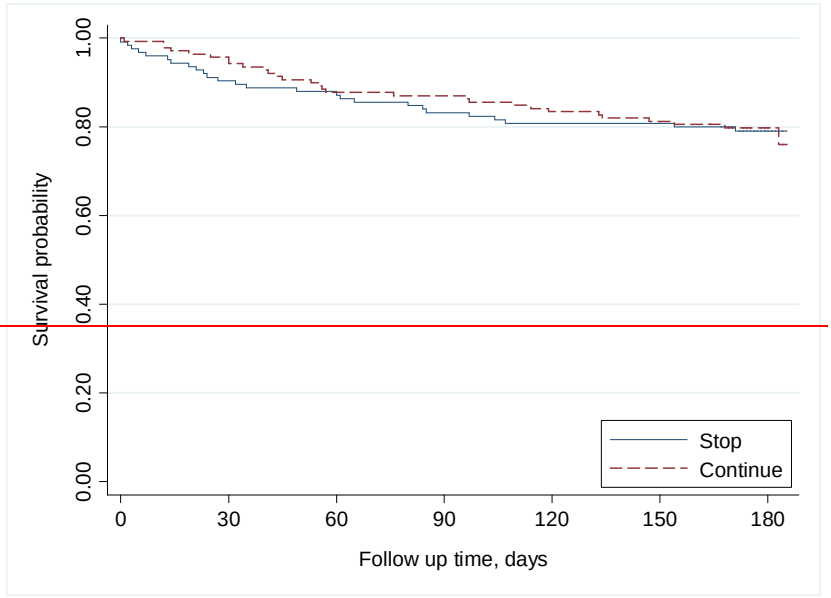


Table 3: Mortality and functional outcomes at 6 months (Intention To Treat Population)

	Continue (n=379)	Stop (n=384)
Alive	332 (87.6%)	331 (86.1%)
Independent (mRS 0)	124	118
Independent (mRS 1-2)	42	53
Dependent (mRS 3-5)	110	112
Dead	32 (8.4%)	29 (7.6%)
Within 2 weeks	4	7
Between 2 weeks and 6 months	28	22
Missing	15 (4.0%)	24 (6.3%)

Data are numbers (%). mRS=Modified Rankin Scale. Dependency categories were derived from the responses to the International Stroke Trial telephone-administered questionnaire with an answer yes to the question 'do you need help from another person for everyday activities' indicating dependency (mRS 3 to 5), and an answer of yes (mRS 0) or no (mRS 1 to 2) to the question 'do you feel that you have made a complete recovery from your stroke' indicating independence.

Figure 3: Kaplan-Meier survival estimates for continue and stop groups for the 6-month post-randomisation period (Intention To Treat Population)



Numbers at risk							
Stop	353	341	338	332	332	329	263
Continue	362	356	345	344	339	336	271