Stroke

Continuing or Temporarily Stopping Prestroke Antihypertensive Medication in Acute Stroke

An Individual Patient Data Meta-Analysis

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Abstract—Over 50% of patients are already taking blood pressure–lowering therapy on hospital admission for acute stroke. An individual patient data meta-analysis from randomized controlled trials was undertaken to determine the effect of continuation versus temporarily stopping preexisting antihypertensive medication in acute stroke. Key databases were searched for trials against the following inclusion criteria: randomized design; stroke onset ≤48 hours; investigating the effect of continuation versus stopping prestroke antihypertensive medication; and follow-up of ≥2 weeks. Two randomized controlled trials were identified and included in this meta-analysis of individual patient data from 2860 patients with ≤48 hours of acute stroke. Risk of bias in each study was low. In adjusted logistic regression and multiple regression analyses (using random effects), we found no significant association between continuation of prestroke antihypertensive therapy (versus stopping) and risk of death or dependency at final follow-up: odds ratio 0.96 (95% confidence interval, 0.80–1.14). No significant associations were found between continuation (versus stopping) of therapy and secondary outcomes at final follow-up. Analyses for death and dependency in prespecified subgroups revealed no significant associations with continuation versus temporarily stopping therapy, with the exception of patients randomized ≤12 hours, in whom a difference favoring stopping treatment met statistical significance. We found no significant benefit with continuation of antihypertensive treatment in the acute stroke period. Therefore, there is no urgency to administer preexisting antihypertensive therapy in the first few hours or days after stroke, unless indicated for other comorbid conditions. **(*Hypertension*. 2017;69:933-941. DOI: 10.1161/HYPERTENSIONAHA.116.07982.)**

● **Online Data Supplement**

Key Words: atrial fibrillation ■ blood pressure ■ comorbidity ■ hypertension ■ stroke

Elevated blood pressure (BP) is common in patients presenting with acute stroke, of whom ≈75% have a BP >140/90 mm Hg.[1,2] The natural history is for BP to decline spontaneously during the subsequent several days. Elevated BP is associated with poor outcome, whether defined as recurrent stroke, early death, or death and disability several months after stroke onset.[3–5] There is, however, limited and conflicting evidence on the benefits of BP-lowering treatment in acute stroke, with some large studies reporting near-positive effects on functional outcome[6] but others reporting neutral[7–9] or near-negative results.[10] Thus, current meta-analyses and international guidelines state that the optimal management of elevated BP in acute stroke remains uncertain.[11–15]

An important, and frequently encountered, dilemma faced by clinicians in the management of acute stroke is how to manage preexisting antihypertensive medication. Over 50% of patients presenting with acute stroke are already taking BP-lowering medication not only for the treatment of hypertension but also for the treatment of other comorbidities such as heart failure, ischemic heart disease, atrial fibrillation, and prostatic hypertrophy. Although BP-lowering medication should be continued in the long term for secondary prevention,[16] the effect of its continued use in the immediate poststroke period remains unclear; further, acute stroke may be complicated by dysphagia thereby complicating administration of oral drugs. Continuation of therapy could

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theoretically be beneficial in helping reduce early recurrence, avoiding rebound increases in BP and heart rate with cessation of therapy, and in ensuring that antihypertensives are continued on hospital discharge. Conversely, temporarily stopping treatment may be advantageous: many patients do not regularly take their medication, and, thus, administration in hospital could lead to abrupt and potentially harmful declines in BP; dehydration and hypovolemia are not uncommon after stroke, and further BP lowering may be detrimental; stopping BP-lowering medication may increase blood flow through collateral vessels and increase blood supply to the potentially salvageable ischemic penumbra; administration of oral medication in the presence of dysphagia may lead to aspiration.

Two large randomized controlled trials were undertaken to address this question: COSSACS (Continue or Stop Post-Stroke Antihypertensives Collaborative Study)[17] and ENOS (Efficacy of Nitric Oxide in Stroke trial).[7] Both were neutral for the primary outcome of 2-week death or dependency (COSSACS)[17] and 3-month modified Rankin Scale (mRS) shift (ENOS),[7] although COSSACS was substantially underpowered to detect an effect on primary outcome. Our aim was to perform an individual patient meta-analysis of data from available randomized controlled trials (RCTs) to determine the effect of continuation versus temporarily stopping existing antihypertensive medication in the acute stroke period, an important and common clinical problem. The use of data from individual patients allows analyses to be performed within prospectively determined subgroups, larger than those in individual trials, enhancing statistical power.

Methods

Search Strategy and Selection Criteria

We followed the guidelines for reports of meta-analyses of RCTs according to the PRISMA statement (Table S1 in the online-only Data Supplement) and used a prespecified review protocol.[18] We searched Medline, EMBASE, and the Cochrane library (from inception to October 2015) for RCTs comparing the effect of continuing or temporarily stopping prestroke antihypertensive medications combining text terms, and where appropriate MeSH terms for stroke, and antihypertensive medication. An example search strategy can be found in Table S2. We limited our search to humans, RCTs, meta-analyses, and systematic reviews. We did not apply language restrictions. We also searched reference lists of included articles and systematic reviews, and relevant review articles.

Study Selection and Data Extraction

We defined the following inclusion criteria:

1. Randomized design with a follow-up of ≥2 weeks. Investigating the effect of continuing versus stopping (for at least 1 week) preexisting antihypertensive medication in those with acute stroke (recruited <48 hours of symptom onset).
2. Outcomes of interest including at least one of death; disability (mRS or equivalent); stroke recurrence; neurological deterioration (change in National Institute of Health Stroke Scale [NIHSS] score, or equivalent); and other vascular events.

Two investigators screened the titles and abstracts and excluded all articles not meeting the criteria by consensus. The same investigators evaluated the remaining studies as full articles. Authors of the articles were then contacted to ascertain willingness to be included and agreement to provide necessary data for this individual patient data meta-analysis.

Definitions of risk factors, subgroups at baseline, and outcomes were agreed before analysis of any of the trials. Prespecified subgroups included age (≤70 years, >70); sex; ethnicity (white, Asian, and other); smoking status; atrial fibrillation; diabetes mellitus; previous stroke; BP medications (angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, renin inhibitor, β-receptor antagonist, calcium channel blocker, diuretic, α-receptor antagonist, and centrally acting agent); number of BP medications (1, 2, 3, 4, and >4); feeding status (oral feeding and no oral feeding); systolic BP (SBP; <140, 140–159, 160–180, and >180 mm Hg); NIHSS score (<15 and ≥15); stroke type (ischemic and hemorrhagic); stroke syndrome as per Oxford Community Stroke Project classification (lacunar syndrome, partial anterior circulation syndrome, total anterior circulation syndrome, and posterior circulation syndrome); and time to randomization (≤12, 13–24, 25–36, and >36 hours).

The primary outcome was death or dependency, as measured using the mRS score (0–2 defined as independent, 3–5 dependent, and 6 death) when last measured during trial follow-up. Secondary outcomes at the end of the defined treatment period included death; recurrent stroke (defined as recurrent ischemic stroke or recurrent hemorrhagic stroke and recorded as a safety outcome at 7 days by investigators in ENOS; taken from serious adverse event data in COSSACS); neurological deterioration (adjudicated by local investigators and defined as an increase from baseline NIHSS score of ≥4 points); and death or neurological deterioration. Secondary outcomes at the end of follow-up were collected in both studies by telephone interviews in those who were alive. Those who had died were identified from the National Health Service register, and cause of death was taken from the death certificate. For deaths outside the United Kingdom, information was obtained via individual sites. Secondary outcomes included death; stroke recurrence; cardiovascular events; any vascular events; health-related quality of life (EuroQol [EQ] 5D HUS) and functional outcome (independence or dependence—mRS and Barthel index). If any trial used the Scandinavian Stroke Scale to define baseline severity and neurological impairment, these were transformed into NIHSS scores according to a published algorithm.[19] Because the COSSACS trial defined dependency at 6 months according to 3 categories (based on responses to 3 standardized questions—an approach previously validated for assessment of functional outcome in stroke),[20] rather than individual mRS scores, we used the same approach for ENOS to create a common long-term functional outcome for this analysis. Categories were independent (mRS 0); independent (mRS 1–2); and dependent (mRS 3–5).

The included studies were approved by the relevant ethics committees: COSSACS: Trent Research Ethics Committee (MREC/02/4/051) and ENOS: Trent Regional Ethics Committee (MREC/01/4/046). In both trials, informed consent from the patient, or if the patient lacked capacity, assent from a relative or legal representative (with confirmation of assent from the patient when able) was obtained for all participants.

Statistical Analysis

For the purposes of a 1-stage meta-analysis, individual patient data from both trials were merged in to a single database before further analysis. Data from both trials were checked before and after merging. No imputation was used for missing data. Data are described as mean (standard deviation) for continuous data, median (interquartile range) for ordinal data, or frequency (percentage) for binary data. The effect of continuing prestroke antihypertensive medication (in comparison to temporary stopping) on outcomes was assessed using ANCOVA (BP outcomes), multiple linear regression, ordinal logistic regression, or binary logistic regression (depending on whether data were continuous, ordinal, or binary in nature). For most of the outcomes, our assumption of equal residual variance held true. Nonetheless, to use consistent analysis techniques for outcomes, we applied mixed-effects models to all. The results from these analyses are expressed as odds ratio or mean difference, with 95% confidence intervals. Outcomes analyzed using mean difference were BP, NIHSS score, EQ-5D, EQ visual analogue scale, and Barthel index. The effect of treatment on the primary outcome was assessed in prespecified subgroups in all patients. These subgroup analyses were performed by adding an

interaction term to a mixed-effects ordinal logistic regression model. Analysis of time to death was undertaken using a mixed-effects Cox proportional hazards regression model and a Kaplan–Meier plot used as a visual representation of time to death. All analyses were adjusted using source trial as a random effect. Regression analyses were also adjusted for age, sex, baseline stroke severity (NIHSS score), and mean SBP as fixed effects. All analyses were performed using SAS version 9.3. Statistical significance was set at $P<0.05$.

Results

Results of Search

Figure 1 shows the study selection process. Of 2588 studies identified on the initial search, 2 (COSSACS: ISRCTN89712435 and ENOS: ISRCTN99414122) fulfilled the inclusion criteria. Chief investigators of both studies (T.G.R. and P.M.B., respectively) were collaborators in this review and agreeable for the original data sets to be analyzed. This meta-analysis of individual patient data from the COSSACS and ENOS trials includes data from 2860 patients with acute stroke (within 48 hours of symptom onset), recruited from 222 sites in 23 countries across 5 continents.

Description of Included Studies

COSSACS was a UK multicenter prospective randomized open, blinded end point trial that assigned 763 nondysphagic stroke patients to either continue or stop antihypertensive medication for 14 days using a secure web-based randomization system.[17] Patients and clinicians who randomly assigned patients and administered treatment were unmasked to group allocation. ENOS was a partial factorial international randomized controlled trial where adult patients with acute ischemic stroke or ICH and elevated BP (140–220 mm Hg) were randomized via a secure web-based randomization system to receive a glyceryl trinitrate patch or no glyceryl trinitrate patch for 1 week (administered single blind) and, in a subset of patients on prestroke antihypertensive medication, to continue or stop this medication for 1 week (open label).[21] The primary and main secondary outcomes were collected centrally at day 90 by an assessor in each country who was blinded to treatment. Data from all 2097 ENOS participants were included in this meta-analysis. A summary of characteristics of the 2 studies is shown in Table 1, and details of the primary and secondary outcome measures in Table S3.

Risk of Bias and Quality Assessment

All studies were assessed for quality using the Cochrane Collaboration risk of bias tool, which considers the risk of selection, performance, detection, attrition, and reporting bias[22]; the risk of bias in each domain being low for each study.

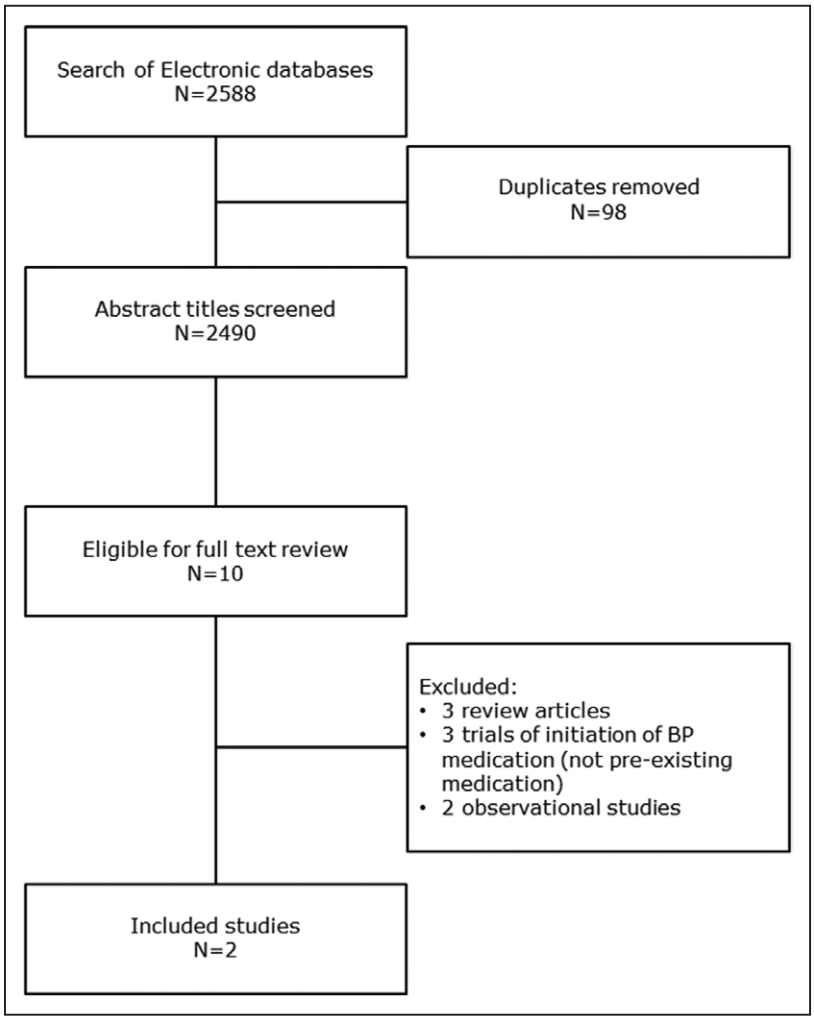

Figure 1. Study selection process.

Patient Characteristics

Across the 2 trials, 1432 patients were randomized to continue prestroke antihypertensive medication, and 1428 were randomized to stop antihypertensive medication temporarily for the acute and subacute stroke periods. Recruited patients were similar to those recruited to stroke services with 52.4% men (mean age: 73 years). Baseline characteristics across the 2 trial cohorts were broadly similar (Table S4). Differences in participants' ethnic origins are to be expected given the geographical location of centers involved in the 2 studies, and the observed differences in stroke type and severity are, at least in part, likely to be a consequence of the COSSACS trial excluding patients with dysphagia (more common in severe strokes). COSSACS did not have blood pressure limits, whereas ENOS included only patients with SBP 140 to 220 mm Hg.

Blood Pressure Profiles

SBP and diastolic BP (DBP) fell in both randomized groups from recruitment to day 7, with a steeper decline seen in those who continued their antihypertensive medication (Figure S1). A significant difference in SBP was present by day 1 and in DBP from day 2; the absolute difference in BP was maximal at day 7.

Effect of Continuation of Antihypertensive Therapy on Outcomes

ENOS and COSSACS recorded outcomes at the end of the treatment at 7 and 14 days, respectively. Logistic and multiple regression analyses adjusted for trial, age, sex, baseline stroke severity, and baseline SBP showed no significant association between continuation of antihypertensive treatment (versus stopping it) and stroke recurrence; neurological impairment, death, or neurological deterioration; or death at the end of the treatment (Table 2). A significant association was observed between continuation of treatment and recurrent ischemic stroke, but no such association was reported with recurrent ICH, nor with recurrent stroke of any type (ICH and ischemic stroke combined). No heterogeneity was observed when assessed by stroke type (ischemic stroke or ICH; Table S5).

With the exception of the Barthel index (measured at 14 days in COSSACS and 90 days in ENOS), end-of-trial outcomes were measured at 180 and 90 days in the COSSACS and ENOS participant cohorts. There was no significant difference in the distribution of scores across mRS categories at the end of the trial, between the continue versus stop groups (Figure 2). In adjusted mixed-effect logistic and multiple regression models, no significant association was found between continuation of antihypertensive treatment and end-of-trial death, death or dependency (mRS>2), or composite vascular events (Table S5). No statistically significant associations were reported between continuation of treatment and health utility scores (EQ 5D HUS), Barthel index scores, or self-reported quality of life using the EQ visual analogue scale (Table S5). Analysis of time to death using a mixed-effects Cox proportional hazards model (visually represented on a Kaplan–Meier plot) showed no difference in mortality in the continue group (Figure S2). An ordinal logistic regression analysis of the mRS, by trial, showed that in both ENOS and COSSACS, there was no significant difference in outcome between the continue versus stop groups (Figure 3). In subgroup analyses, patients who stopped antihypertensives within 12 hours of stroke onset had less death or dependency (Figure 4). No significant association was noted in any of the other prespecified subgroups, although in the majority of subgroups, point estimates of odds ratios favored stopping preexisting antihypertensive therapy.

Table 1. Characteristics of Trials Comparing Continuing Versus Stopping Prestroke Antihypertensive Medication During Acute Stroke

Characteristics	COSSACS	ENOS
Size	763	2097
Recruitment time window, h	<48	<48
Length of treatment, d	14	7
Length of follow-up, d	180	90
SBP range, mm Hg	>100	140–220
Major exclusions	Need for antihypertensive agents	Need for GTN or antihypertensive agents
Countries	1	23
Centers	49	173

COSSACS indicates Continue or Stop Post-Stroke Antihypertensives Collaborative Study; ENOS, Efficacy of Nitric Oxide in Stroke trial; GTN, glyceryl trinitrate; and SBP, systolic blood pressure.

Discussion

Around half of patients presenting with acute stroke are on preexisting antihypertensive medication. Whether to continue or stop this medication in the acute and subacute stroke period is a commonly encountered clinical dilemma and a particular challenge in light of neutral results from previous RCTs and partly conflicting data from other acute stroke BP-lowering trials. The results from this meta-analysis of individual patient data from 2 large RCTs suggest that continuation of preexisting antihypertensive medication, versus temporarily stopping it, confers no significant benefit to patients in terms of short- or long-term outcomes after acute ischemic or hemorrhagic stroke, despite the fact that BP was significantly lower in the continue group from days 1 to 7, and levels of BP declined more steeply. Analyses for the effect of continuing versus stopping antihypertensives on death or dependency, by our predefined subgroups, including effect by drug class, baseline BP, and stroke subtype, showed no obvious effect, with the exception of the subgroup randomized within 12 hours of stroke onset, in which continuation (versus stopping) of antihypertensives was significantly associated with risk of worse outcome. In the absence of any ongoing or planned studies further examining this question, the main implication for clinical practice is that in the acute stroke period, clinicians should not rush to administer preexisting antihypertensive therapy, unless indicated by other comorbid conditions. Indeed, a reasonable approach would be to withhold BP-lowering drugs until patients are medically and neurologically stable, and are

Table 2. Functional Outcome and Vascular Events: Continue vs Stop Prestroke Antihypertensive Medication

Outcomes	Odds Ratio/MD (95% Confidence Interval)	*P* for Significance
End-of-treatment (14 d in COSSACS and 7 d in ENOS)		
Death	1.04 (0.64 to 1.69)	0.87
Recurrence of stroke (ischemic stroke or intracerebral hemorrhage)	1.41 (0.85 to 2.34)	0.19
Recurrence of stroke (ischemic)	2.27 (1.17 to 4.39)	0.015
Recurrence of stroke (hemorrhagic)	0.35 (0.09 to 1.31)	0.12
Death or deterioration	0.86 (0.68 to 1.09)	0.21
Neurological impairment (worsening of scores on the NIHSS score by ≥4 from baseline)*	0.38 (–0.12 to 0.87)	0.75
Death or institutionalization	1.10 (0.93 to 1.30)	0.26
End-of-trial (180 d in COSSACS and 90 d in ENOS)		
Death	1.06 (0.84 to 1.35)	0.63
mRS†	0.94 (0.84 to 1.12)	0.68
Death or dependency (mRS >2)	0.96 (0.80 to 1.14)	0.62
Barthel index‡	–3.20 (–6.08 to –0.33)	0.23
EuroQoL-5D health utility status	–0.03 (–0.06 to 0.00)	0.31
EuroQoL-visual analogue scale	–2.00 (–4.48 to 0.48)	0.31
Vascular events§	0.87 (0.71 to 1.08)	0.21

Percentage for continue versus stop; comparison by mixed-effects logistic regression or mixed-effects multiple regression, adjusted for trial as a random effect and age, sex, severity, and baseline systolic blood pressure as fixed effects. Odds ratios <1 and MD <0 favor continuing prestroke antihypertensive medication. COSSACS indicates Continue or Stop Post-Stroke Antihypertensives Collaborative Study; ENOS, Efficacy of Nitric Oxide in Stroke trial; MD, mean difference; mRS, modified Rankin Scale; and NIHSS, National Institute of Health Stroke Scale.

*In ENOS, NIHSS score derived from Scandinavian Stroke Scale.[20]

‡Measured at 14 d in COSSACS and at 90 d in ENOS.

†Categories derived from the International Stroke Trial questionnaire: independent (mRS 0); independent (mRS 1–2); and dependent (mRS 3 to 5).

§Composite of vascular death, nonfatal stroke, and nonfatal myocardial infarction.

either able to swallow safely or enteral access via feeding tube has been obtained.

This is the first meta-analysis to address the question of whether to continue or temporarily stop prestroke antihypertensive medication, and our study has several strengths: the analysis included a wide range of stroke patients recruited from centers across 23 different countries, albeit predominantly white, with baseline characteristics broadly representative of those recruited to stroke services, thus ensuring generalizability of findings; the large sample size increased precision and reliability of estimates; we used individual patient data, thus allowing us to perform analyses on large predefined subgroups, with higher numbers, and greater statistical power than in the individual trials. However, the power to detect a difference between the 2 groups in the primary outcome is <10%, and any future trial would need to recruit in excess of 10 000 patients.

The neutral results on primary outcome reported in this review are in keeping with the findings of the 2 individual studies when considered separately. Furthermore, our findings are concordant with data from several acute stroke BP-lowering trials that reported no significant effect on functional or neurological outcomes, with initiation of BP-lowering therapy in the acute stroke period.[9,10,23,24] Of course, our data are not directly comparable with such trials given that our study was concerned with preexisting medication, rather than starting new antihypertensive therapy. Nonetheless, this meta-analysis found significantly lower BP profiles with steeper rates of decline in average BP over the first 7 days in the continue versus stop groups. In fact, observed differences in SBP and DBP at day 7 between the 2 randomized groups were greater than has been observed in some acute stroke BP-lowering trials; –9.4 mm Hg for SBP and –5.1 for DBP in the continue versus the stop group. Despite these statistically significant and clinically relevant BP differences, we report no significant evidence of beneficial effect on short- or long-term outcomes with continuation of therapy.

Effects on death and dependency were similar for the majority of our predefined subgroups, including all BP levels, stroke type (ICH or ischemic stroke and Oxford Community Stroke Project Classification), and number and class of prestroke antihypertensive agents. However, in the subgroup randomized within 12 hours of stroke onset, a statistically significant association favoring stop was reported. There is no robust explanation for this result, particularly given that on day 0, the BP differences between continue and stop groups were minimal. It may reflect the play of chance but perhaps in the first few hours after stroke onset, and in the presence of impaired cerebral autoregulation,[25] the penumbral, and potentially salvageable tissue, is particularly vulnerable to the effects of BP lowering, with BP declines increasing risk of further ischemia, especially in the absence of therapeutic or spontaneous reperfusion where collateral blood flow is important. Or early continuation of medications may cause aspiration pneumonia in patients who have, or develop, dysphagia early after their stroke, as seen in ENOS. Conversely, later after onset, the effects of BP lowering on an established ischemic core, with less potentially viable penumbral tissue, may be of less pathological and clinical consequence. Few acute stroke BP-lowering studies have enrolled patients early (within the first few hours) after stroke onset. However, results from a subgroup analysis of ENOS (those receiving BP-lowering treatment with glyceryl trinitrate within 6 hours after stroke onset),[7] and the RIGHT (Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial),[26] where transdermal glyceryl trinitrate was given within 4 hours (median 55 minutes) of stroke onset, are discordant with our findings, each suggesting benefit with early BP lowering. Furthermore, the INTERACT-2 study (Intensive blood pressure reduction in acute cerebral hemorrhage) of BP lowering within 6 hours of ICH showed safety and borderline significant favorable outcomes in early BP lowering.[6]

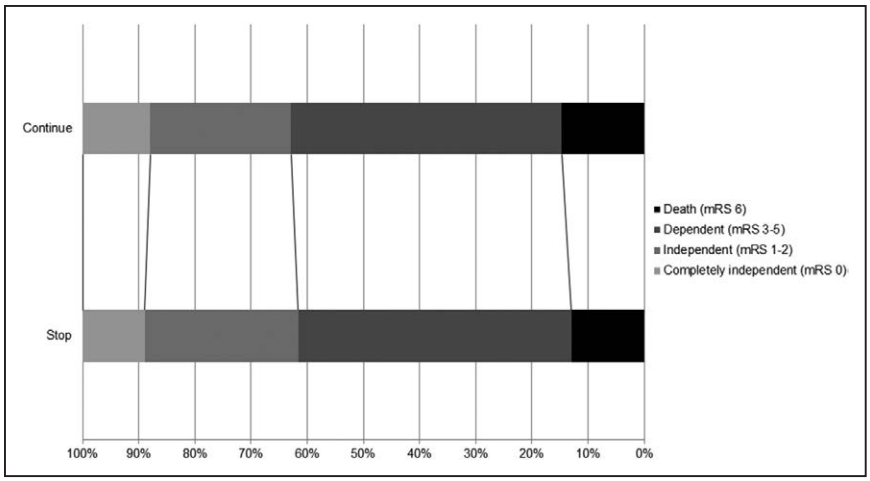

Figure 2. Modified Rankin Scale (mRS) at the end of the trials. Comparison by mixed-effects ordinal logistic regression. odds ratio 0.97 (95% confidence interval, 0.84–1.12; 2*P*=0.68).

Possible explanations for the lack of benefit with continuation of BP-lowering therapy are as follows: first, classes of antihypertensive drug may be important, with some exerting a beneficial and others a detrimental effect. In this meta-analysis, the majority of patients were taking at least one drug-exerting effect on the rennin–angiotensin–system (angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, or β-receptor antagonist). Acute stroke trials have shown harm with angiotensin II receptor antagonist[27] and with β-receptor antagonists.[28] Second, many patients do not regularly take their prescribed medication, and in-hospital administration of BP-lowering medication may lead to abrupt, and potentially hazardous, BP declines. Third, administration of oral medication in those with impaired swallow may lead to aspiration and pneumonia, a hypothesis supported by the ENOS finding of higher rates of pneumonia in the continued group[7] but not in this meta-analysis, potentially because of the COSSACS trial excluding those with dysphagia. Fourth, the effect of continuation of prestroke BP-lowering medication may differ depending on premorbid BP levels or presence or extent of an abrupt BP rise. In a recent observational study in 653 patients with acute ischemic stroke or ICH, Fischer et al[29] found that SBP was substantially raised compared with last premorbid levels in ICH, but in acute ischemic stroke, it was much closer to the accustomed long-term premorbid level. The authors suggested that any benefits of BP-lowering therapy in acute stroke might be greater in those in whom the high postevent level is unaccustomed and postulate that this may help explain the mostly neutral effects of BP lowering on outcome in acute ischemic stroke, compared with potential benefits observed in ICH. Although our subgroup analysis showed no difference in outcome in ischemic stroke and ICH subgroups, the numbers of ICH patients were low (284 patients), and we may, therefore, have not been able to detect an effect. Furthermore, as in most acute stroke BP trials, we do not have data on participant's prestroke BP trends. Finally, BP variability may be of prognostic significance in acute stroke as reported in a recent post hoc analysis of the INTERACT-2 data set.[30] Different antihypertensive agents exert differential effects of BP variability, and, thus, within-individual BP variability (unmeasured in this analysis)[31] and the effect of drug class on BP variability may have had an unmeasured influence on outcome.

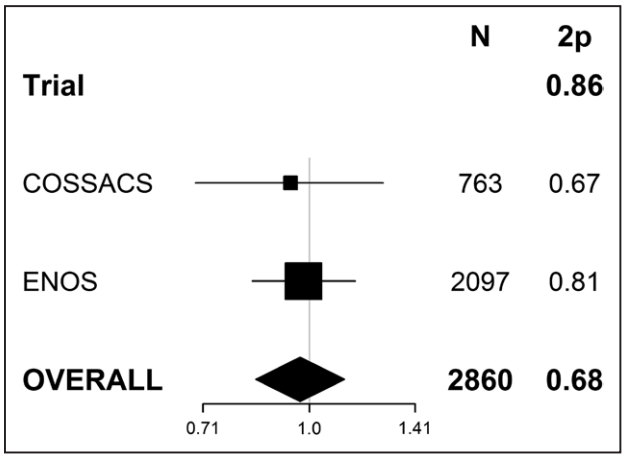

Figure 3. Forest plot of functional outcome (modified Rankin Scale) by trial. Comparison by ordinal logistic regression. COSSACS indicates Continue or Stop Post-Stroke Antihypertensives Collaborative Study; and ENOS, Efficacy of Nitric Oxide and Stroke trial.

Limitations

This study also has potential limitations. The analysis is underpowered; any future trial would need to recruit in excess of 10 000 patients to detect a difference between the 2 groups in the primary outcome. Therefore, applying the conclusions to all subgroups may not be appropriate. For example, detailed information was missing on large vessel occlusions and those who received acute revascularization procedures. In addition, selection bias may have arisen as both trials excluded patients with the following characteristics: high SBP (>200 mm Hg or DBP >120 mm Hg in COSSACS; >220 and >140 mm Hg in ENOS); contraindications to stopping, or indications to continue antihypertensive therapy (plus definite indications or contraindications to nitrate therapy in ENOS); impaired consciousness, premorbid dependency (mRS >3); and patients expected to require surgical intervention (albeit rates of significant carotid artery stenosis were low at 2.6%). In addition, COSSACS excluded those with dysphagia. Although statistical models were adjusted for several covariables, residual confounding may still have occurred. Furthermore, both trials were, out of necessity, open label, and performance bias

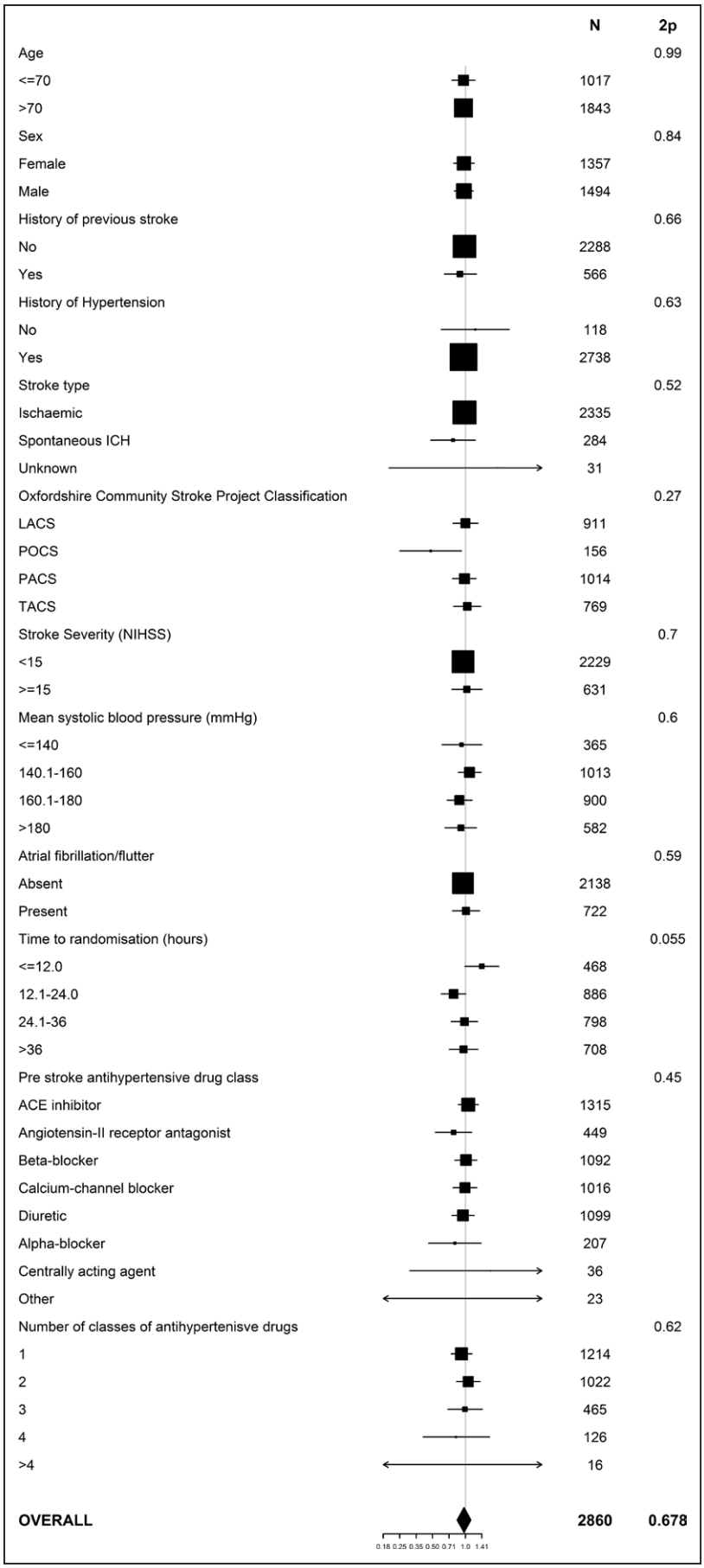

Figure 4. Forest plot of functional outcome (modified Rankin Scale) by prespecified subgroups. Analysis undertaken using a mixed-effects ordinal logistic regression model. ACE indicates angiotensin-converting enzyme; ICH, intracerebral hemorrhage; LACS, lacunar syndrome; NIHSS, National Institute of Health Stroke Scale; PACS, partial anterior circulation stroke; POCS, posterior circulation stroke; and TACS, total anterior circulation stroke.

cannot be excluded, although outcome assessors were masked to treatment allocation in both trials. Finally, there are limited data on patients recruited early from stroke onset, which should be a focus of future acute stroke BP research.

Perspectives

This meta-analysis addresses an important and frequently encountered dilemma for clinicians and represents all available randomized data on the subject. There are unlikely to be further available data in the near future, and our findings are likely to inform future national and international acute stroke guidelines. We found no significant benefit with continuation of treatment in the acute stroke period. Therefore, there is no urgency to administer preexisting antihypertensive therapy in the first few hours or days after stroke and not until the patient is medically stable and has a safe swallow or established enteral access, unless of course indicated by other comorbid conditions. Given recent findings of safety and possible benefit with initiation of BP-lowering therapy within 6 hours of ICH, and recent subgroup analyses in the ischemic stroke population suggesting that early BP lowering may be beneficial, future acute stroke BP studies should aim to recruit patients early after stroke onset, in order to determine the effect of BP lowering in the first few hours.

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Disclosures

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Novelty and Significance

What Is New?

- An individual patient data meta-analysis from randomized controlled trials to determine the effect of continuation versus temporarily stopping preexisting antihypertensive medication in acute stroke.

What Is Relevant?

- No significant association between continuation of prestroke antihypertensive therapy (versus stopping) and risk of death or dependency at final follow-up. Analyses in prespecified subgroups revealed no significant associations with continuation versus temporarily stopping therapy, with the exception of patients randomized ≤12 hours, in whom a difference favoring stopping treatment met statistical significance.

Summary

There is no urgency to administer preexisting antihypertensive therapy in the first few hours or days after stroke, until the patient is medically stable and has a safe swallow or established enteral access, unless indicated by other comorbid conditions.

Hypertension
Journal of the American Heart Association

Continuing or Temporarily Stopping Prestroke Antihypertensive Medication in Acute Stroke: An Individual Patient Data Meta-Analysis

Lisa J. Woodhouse, Lisa Manning, John F. Potter, Eivind Berge, Nikola Sprigg, Joanna Wardlaw, Kennedy R. Lees, Philip M. Bath and Thompson G. Robinson
for the Blood Pressure in Acute Stroke Collaboration

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ONLINE SUPPLEMENT

CONTINUING OR TEMPORARILY STOPPING PRE-STROKE ANTIHYPERTENSIVE MEDICATION IN ACUTE STROKE: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

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Table S1: PRISMA Checklist

Section / topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 (Fig 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9 (Fig 2)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10 (Table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-18 (Tables 2-4; Figures 3-6)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-15 (Figures 4,6)

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	18 (Figure 7)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23-24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	27

Table S2: Example Search Strategy

"Stroke" OR "cerebr* vascular disease" OR "cerebr* ischaemia" OR "intracerebr* haemorrhage" OR "cerebr* haemorrhage" OR "brain isch*" OR "brain haemorrhage" AND "blood pressure" OR "BP" OR "hypertension" OR "antihypertensive" AND "stop" OR "cease" OR "continue" AND "outcome*" OR "prognos*" OR "mortality" OR "death" OR "dependenc*" OR "disability" OR "neurological deterioration" OR "functional depenc*"

Table S3: Primary and secondary outcome measures in the COSSACS and ENOS trials

Continue Or Stop post-Stroke Antihypertensives Collaborative Study		
Primary Outcome	2 weeks	Death and dependency (mRS>3)
Early Secondary Outcomes	2 weeks	NIHSS score increase or decrease by 4 points or more; Barthel Index; EQ-5D; EQ-VAS; Discharge destination; SAEs
Late Secondary Outcomes	6 months	Case fatality; Stroke recurrence; Health-related QoL; Functional status*; Place of residence
Efficacy of Nitric Oxide Study		
Primary Outcome	90 days	mRS shift

Early Secondary Outcomes	7 days	Recurrent stroke; Neurological impairment on Scandinavian Stroke Scale; Death
Late Secondary Outcomes	90 days	Cognition (MMSE); Health related quality of life (EQ-5D), from which the health utility status was calculated [HUS]; EQ-VAS; Mood

mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; EQ-5D: EuroQol-5D; EQ-VAS: EuroQoL- Visual Analogue Scale; SAEs: Serious Adverse Events; QoL: Quality of Life; MMSE: Mini-Mental State Examination.

*functional status (assessed by standardized questions to assess mRS category at telephone interview).

Table S4: Baseline characteristics of trial participants.

Number (percentage) or mean (standard deviation).

Characteristics	COSSACS *	ENOS†	All	Continue	Stop
No. of participants	763	2097	2860	1432	1428
Age (years)	73.95 (10.78)	72.89 (11.18)	73.17 (11.08)	73.49 (11.11)	72.86 (11.05)
Sex, Male (%)	426 (56.5)	1068 (50.93)	1494 (52.4)	738 (51.75)	756 (53.05)
Race-ethnicity (%)					
Caucasian	588 (91.73)	1824 (86.98)	2412 (88.09)	1202 (87.55)	1210 (88.64)
Asia	35 (5.46)	202 (9.63)	237 (8.66)	122 (8.89)	115 (8.42)
Other	18 (2.81)	71 (3.39)	89 (3.25)	49 (3.57)	40 (2.93)
Medical History (%)					
Hypertension	744 (98.02)	1994 (95.09)	2738 (95.87)	1370 (95.87)	1368 (95.87)
Diabetes mellitus	129 (20.12)	484 (23.08)	613 (22.39)	309 (22.51)	304 (22.27)
Hyperlipidemia	350 (46.11)	808 (38.53)	1158 (40.55)	568 (39.75)	590 (41.35)
Atrial fibrillation	156 (20.45)	566 (26.99)	722 (25.24)	382 (26.68)	340 (23.81)

Characteristics	COSSACS *	ENOS†	All	Continue	Stop
Previous stroke	150 (19.76)	416 (19.84)	566 (19.82)	275 (19.24)	291 (20.39)
TIA	140 (18.45)	352 (16.79)	492 (17.23)	255 (17.84)	237 (16.61)
Ischemic heart disease	152 (20.03)	523 (24.94)	675 (23.63)	332 (23.23)	343 (24.04)
Smoking, current	120 (16.06)	363 (18.15)	483 (17.58)	248 (18.09)	235 (17.08)
Rankin scale, pre-morbid 0	497 (65.14)	1413 (67.38)	1910 (66.78)	938 (65.5)	972 (68.07)
Antihypertensive agents pre-stroke					
Angiotensin converting enzyme inhibitor	316 (41.69)	999 (47.64)	1315 (46.06)	697 (48.81)	618 (43.31)
Angiotensin receptor antagonist	112 (14.78)	337 (16.07)	449 (15.73)	207 (14.5)	242 (16.96)
Renin inhibitor	-	4 (0.19)	4 (0.14)	3 (0.21)	1 (0.07)
Beta receptor antagonist	272 (35.88)	820 (39.1)	1092 (38.25)	542 (37.96)	550 (38.54)
Calcium channel blocker	291 (38.44)	725 (34.57)	1016 (35.6)	486 (34.06)	530 (37.14)

Characteristics	COSSACS *	ENOS†	All	Continue	Stop
Diuretic	364 (48.02)	735 (35.05)	1099 (38.49)	552 (38.66)	547 (38.33)
Alpha receptor antagonist	61 (8.04)	146 (6.96)	207 (7.25)	110 (7.7)	97 (6.8)
Centrally acting	4 (0.53)	32 (1.53)	36 (1.26)	22 (1.54)	14 (0.98)
Other	0 (0)	23 (1.1)	23 (0.8)	15 (1.05)	8 (0.56)
Number of antihypertensive agents					
1	299 (39.5)	915 (43.63)	1214 (42.54)	606 (42.47)	608 (42.61)
2	293 (38.71)	729 (34.76)	1022 (35.81)	505 (35.39)	517 (36.23)
3	130 (17.17)	335 (15.98)	465 (16.29)	233 (16.33)	232 (16.26)
4	33 (4.36)	93 (4.43)	126 (4.41)	70 (4.91)	56 (3.92)
> 4	2 (0.26)	14 (0.67)	16 (0.56)	7 (0.49)	9 (0.63)
Medications, other pre-stroke					
Statin	377 (50.07)	882 (42.47)	1259 (44.49)	620 (43.79)	639 (45.19)
Hemodynamic measures					
Systolic BP (mmHg)	149.39 (22.36)	167.08 (18.78)	162.38 (21.28)	161.53 (21.28)	163.22 (21.25)

Characteristics	COSSACS *	ENOS†	All	Continue	Stop
Diastolic BP (mmHg)	80.68 (13.26)	88.3 (13.05)	86.28 (13.53)	85.93 (13.52)	86.62 (13.54)
Pulse pressure (mmHg)	68.71 (17.61)	78.78 (17.65)	76.1 (18.19)	75.6 (17.94)	76.6 (18.43)
Systolic BP, peak (mmHg)	237.67	233.33	237.67	233.33	237.67
Heart rate (bpm)	73.62 (16.33)	77.13 (15.19)	76.21 (15.57)	76.38 (15.83)	76.04 (15.32)
Rate-pressure product (mmHg.bpm)	10988.71 (2861.53)	12880.29 (2899.49)	12385.07 (3006.43)	12354.94 (3039.19)	12415.23 (2974.04)
Stroke severity, NIHSS	5.53 (4.44)	11.55 (5.78)	9.95 (6.07)	10.14 (6.1)	9.77 (6.03)
Stroke type/etiology (%)					
IS	690 (93.12)	1833 (87.41)	2523 (88.9)	1272 (89.45)	1251 (88.35)
ICH	38 (5.13)	246 (11.73)	284 (10.01)	138 (9.7)	146 (10.31)
Non stroke	13 (1.75)	18 (0.86)	31 (1.09)	12 (0.84)	19 (1.34)
Stroke syndrome (%)					
Total anterior circulation	72 (9.56)	697 (33.24)	769 (26.98)	399 (28)	370 (25.96)

Characteristics	COSSACS *	ENOS†	All	Continue	Stop
Partial anterior circulation	312 (41.43)	702 (33.48)	1014 (35.58)	498 (34.95)	516 (36.21)
Posterior circulation	82 (10.89)	74 (3.53)	156 (5.47)	84 (5.89)	72 (5.05)
Lacunar	287 (38.11)	624 (29.76)	911 (31.96)	444 (31.16)	467 (32.77)
Stroke etiology (if ischaemic) (%)					
Small vessel	-	626 (29.85)	626 (29.85)	305 (28.96)	321 (30.75)
Large artery	-	417 (19.89)	417 (19.89)	197 (18.71)	220 (21.07)
Cardioembolic	-	507 (24.18)	507 (24.18)	277 (26.31)	230 (22.03)
Other	-	330 (15.74)	330 (15.74)	170 (16.14)	160 (15.33)
Carotid stenosis, ipsilateral 70-99%	1 (0.13)	74 (3.53)	75 (2.62)	33 (2.3)	42 (2.94)
Time to randomisation (hr) (%)					
<= 12	84 (11.34)	384 (18.35)	468 (16.51)	224 (15.8)	244 (17.23)

Characteristics	COSSACS *	ENOS†	All	Continue	Stop
13-24	315 (42.51)	571 (27.28)	886 (31.26)	444 (31.31)	442 (31.21)
25-48	342 (46.15)	1138 (54.37)	1480 (52.22)	750 (52.89)	730 (51.55)
Oral Feeding	763 (100)	1323 (63.09)	2086 (72.94)	1056 (73.74)	1030 (72.13)

Data presented as mean (SD) or n (%).

BP, blood pressure; ICH, intracerebral hemorrhage; IS, ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack

Table S5: Functional outcome and vascular events.

Percentage for continue versus stop; comparison by mixed-effects ANCOVA (using trial as a random effect, blood pressure outcomes only), mixed-effects logistic regression, or mixed-effects multiple regression. Regression models were adjusted for trial as a random effect and age, sex, severity, systolic blood pressure as fixed effects. Odds ratios below one and mean differences below zero favor continuing pre-stroke antihypertensive medication.

Outcomes	COSSACS		ENOS		All OR/MD (95% CI)	p	IS OR/MD (95% CI)	p	ICH OR/MD (95% CI)	p
	Continue	Stop	Continue	Stop						
Patients	379	384	1053	1044						
End of treatment outcomes (14 days in COSSACS, 7 days in ENOS)										
Death, end of treatment (%)	4 (1.11)	7 (1.97)	34 (3.24)	27 (2.59)	1.04 (0.64, 1.69)	0.87	1.23 (0.73, 2.07)	0.44	0.53 (0.12, 2.42)	0.41
Recurrence, during treatment (%)	8 (2.11)	8 (2.08)	30 (2.86)	18 (1.73)	1.41 (0.85, 2.34)	0.19	1.4 (0.8, 2.46)	0.24	1.33 (0.28, 6.21)	0.72
Ischemic (%)	5 (1.32)	4 (1.04)	25 (2.37)	9 (0.86)	2.27 (1.17, 4.39)	0.015	2.1 (1.05, 4.19)	0.036	-	-
Hemorrhagic (%)	1 (0.26)	0 (0)	2 (0.19)	8 (0.77)	0.35 (0.09, 1.31)	0.12	0.18 (0.02, 1.54)	0.12	0.57 (0.08, 3.77)	0.55
Unknown (%)	2 (0.53)	4 (1.04)	3 (0.28)	1 (0.1)	0.97 (0.28, 3.39)	0.97	0.91 (0.23, 3.68)	0.9		
Death or Deterioration (%)	72 (20.22)	82 (23.43)	108 (10.32)	107 (10.28)	0.86 (0.68, 1.09)	0.21	0.91 (0.7, 1.17)	0.45	0.55 (0.27, 1.14)	0.11
Impairment, NIHSS* (/42)	3.77 (5.34)	3.47 (4.98)	9.17 (6.59)	8.73 (6.47)	0.38 (-0.12, 0.87)	0.75	0.16 (-0.38, 0.7)	0.77	0.45 (-1.17, 2.08)	0.29

Outcomes	COSSACS		ENOS		All OR/MD (95% CI)	p	IS OR/MD (95% CI)	p	ICH OR/MD (95% CI)	p
Systolic BP	140.04 (21.91)	153.48 (23.75)	145.58 (24.52)	155.08 (23.88)	-10.63 (-12.53, -8.72)	< 0.0001	-10.31 (-12.4, -8.22)	< 0.0001	-9.21 (-15.52, -2.9)	0.007
Diastolic BP	76.11 (13.66)	84.11 (13.84)	80.03 (14.72)	85.06 (14.34)	-5.88 (-7.02, -4.73)	< 0.0001	-5.71 (-6.97, -4.46)	< 0.0001	-5.37 (-9.19, -1.55)	0.004
Death or Institution (%)	186 (49.08)	188 (48.96)	662 (62.87)	603 (57.76)	1.1 (0.93, 1.3)	0.26	1.11 (0.92, 1.34)	0.27	1.19 (0.69, 2.05)	0.52
End of trial outcomes (180 days in COSSACS, 90 days in ENOS)										
Death, end of trial (%)	32 (8.79)	30 (8.38)	167 (15.9)	146 (14.02)	1.06 (0.84, 1.35)	0.63	1.18 (0.91, 1.54)	0.22	0.9 (0.46, 1.77)	0.76
4-level mRS‡ mean(SD)	1.31 (1.04)	1.3 (1.01)	1.76 (0.79)	1.74 (0.76)	0.97 (0.84, 1.12)	0.68	0.98 (0.84, 1.16)	0.85	0.77 (0.48, 1.23)	0.27
mRS > 2 (%)	164 (43.27)	163 (42.45)	689 (65.43)	672 (64.37)	0.96 (0.8, 1.14)	0.62	0.97 (0.8, 1.17)	0.74	0.76 (0.41, 1.42)	0.39
Barthel Index ɬ	76.94 (30.56)	78.44 (30.18)	58.1 (40.81)	61.94 (39.4)	-3.2 (-6.08, -0.33)	0.23	-2.93 (-6.12, 0.26)	0.16	-2.35 (-11.64, 6.93)	0.9
Barthel Index < 60 (%) ɬ	82 (23.1)	80 (22.92)	425 (40.83)	365 (35.27)	1.15 (0.95, 1.4)	0.15	1.16 (0.94, 1.43)	0.18	1.18 (0.65, 2.11)	0.59
EQ-5D HUS	0.68 (0.32)	0.7 (0.3)	0.41 (0.4)	0.44 (0.4)	-0.03 (-0.06, 0)	0.31	-0.03 (-0.06, 0.01)	0.31	-0.02 (-0.11, 0.07)	0.81
EQ-VAS	62.64 (22.76)	63.18 (23.57)	51.77 (32.4)	54.2 (31.59)	-2 (-4.48, 0.48)	0.31	-2.54 (-5.31, 0.22)	0.12	3.07 (-4.87, 11)	0.44
Vascular event (%) [6]	39 (10.29)	50 (13.02)	162 (15.38)	167 (16)	0.87 (0.71, 1.08)	0.21	0.94 (0.75, 1.18)	0.6	0.68 (0.35, 1.35)	0.27
Lost to follow-up (%)	18 (4.75)	29 (7.55)	3 (0.28)	3 (0.29)	0.56 (0.31, 1.04)	0.067	0.57 (0.23, 1.39)	0.22	-	-

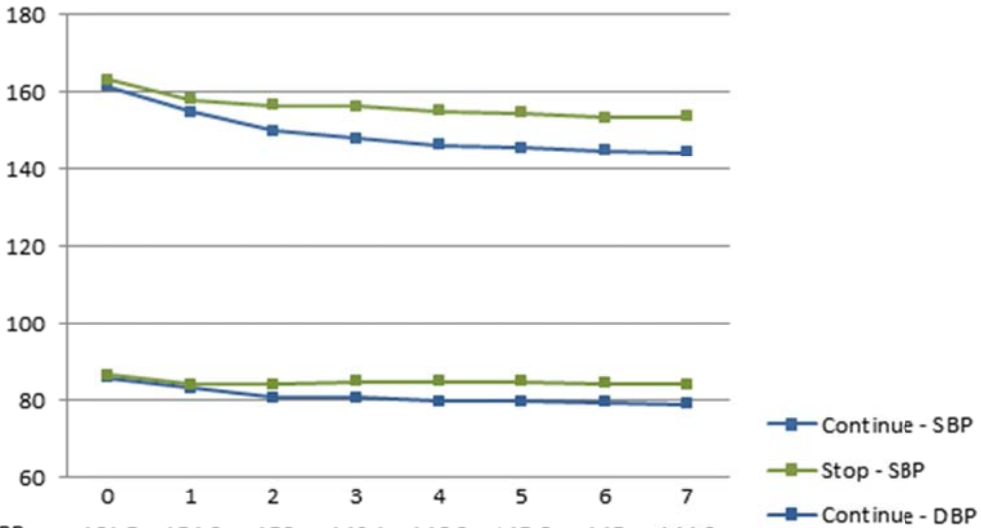
* NIHSS was derived from Scandinavian Stroke Scale scores in ENOS

† Barthel Index measured at 14 days in COSSACS, and 90 days in ENOS

‡ mRS categories derived from the IST questionnaire as follows: Independent (mRS 0); Independent (mRS 1 to 2); dependent (mRS 3 to 5).

ɻ Composite of vascular death, non-fatal stroke, and non-fatal myocardial infarction

EQ-5D HUS: Health utility score calculated form the EuroQoL, health related quality of life questionnaire (EQ-5D); EQ-VAS: self-rated health state, rated from 0 (worst health), to 100 (best imaginable health); ICH: Intracerebral hemorrhage; IS: ischemic stroke; IST: International stroke trial; mRS: modified Rankin scale; OR: odds ratio



	0	1	2	3	4	5	6	7
Continue - SBP	161.5	154.8	150	148.1	146.3	145.6	145	144.3
Continue - SBP SD	21.3	23.2	23.9	24.7	24	24.3	24.3	24.1
Stop - SBP	163.2	158	156.6	156.4	155.2	154.7	153.4	153.7
Stop - SBP SD	21.2	23.7	24.2	23.9	23.9	24.5	23.6	24
Continue - DBP	85.9	83.1	80.7	80.7	79.8	79.7	79.4	79
Continue - DBP SD	13.5	14.2	14.6	14.7	14.5	14.9	14.7	14.6
Stop - DBP	86.6	84.1	84.1	84.9	85	84.9	84.4	84.1
Stop - DBP SD	13.5	14.7	14.8	14.4	14.8	14.6	14.3	14.5
SBP MD	-1.7	-3.2	-6.5	-8.2	-8.9	-9.2	-8.4	-9.4
DBP MD	-0.7	-1.1	-3.4	-4.3	-5.3	-5.2	-5	-5.1
SBP 2p	0.27	0.0039	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
DBP 2p	1	0.5	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Figure S1: Blood pressure profile over the first seven days of treatment.

Comparison by t test with Bonferroni adjustment

DBP: diastolic blood pressure; MD: mean difference between Stop and Continue groups; SBP: systolic blood pressure; SD: standard deviation

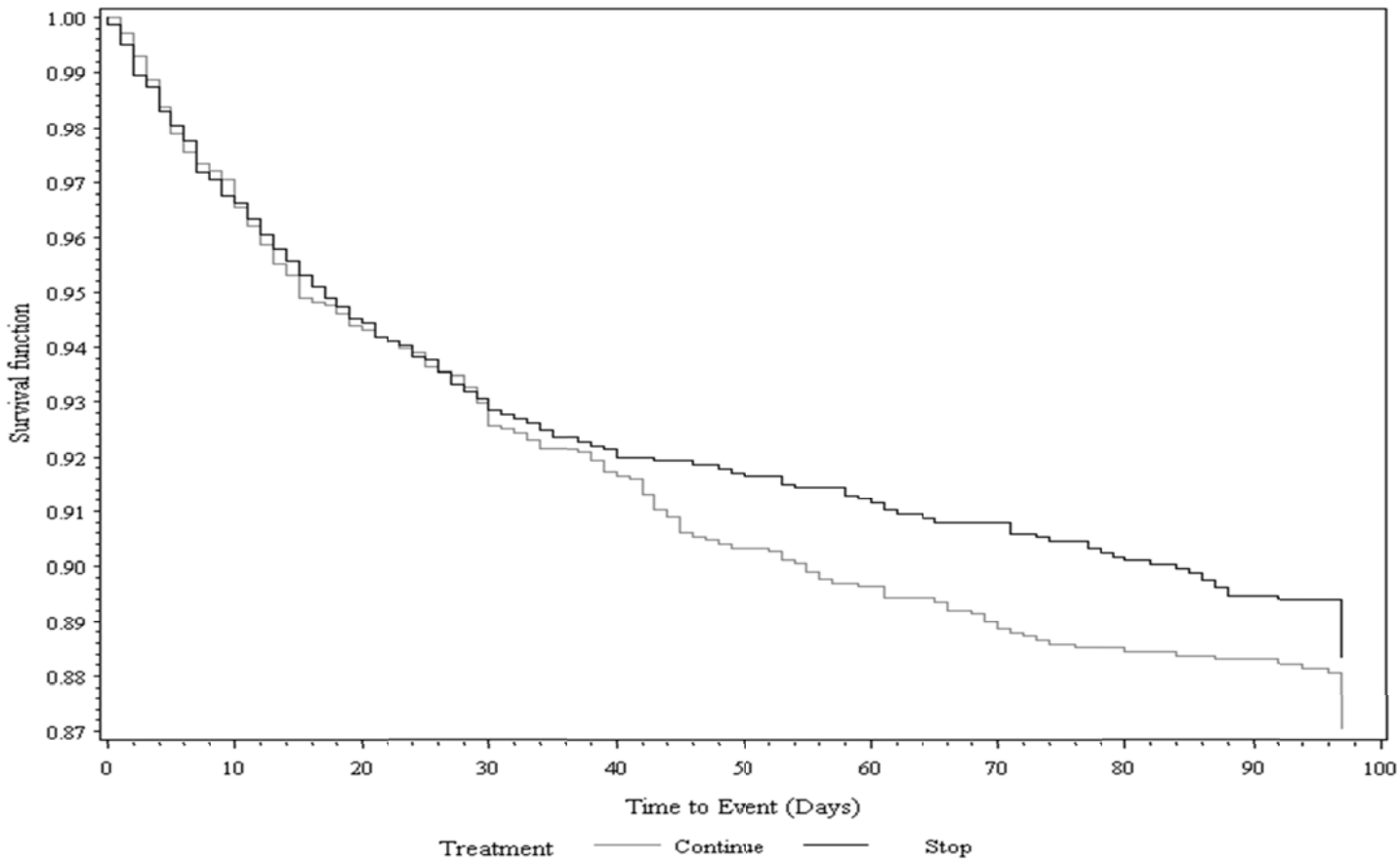


Figure S2. Kaplan-Meier curve for death.

Comparison by mixed-effects Cox regression. HR 1.06 (95% CI 0.86- 1.29, 2p= 0.61). Analysis of time to death undertaken using a mixed-effects cox proportional hazards model; Kaplan-Meier plot used as a visual representation of time to death.