Full Title

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

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Short Title

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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 pre-existing 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 pre-stroke antihypertensive medication; follow up of ≥2 weeks. Two randomized controlled trials were identified and included in this meta-analysis of individual patient data from 2860 patients ≤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 pre-stroke antihypertensive therapy (versus stopping) and risk of death or dependency at final follow-up: Odds Ratio 0.96 (95% Confidence Intervals 0.80 to 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 pre-specified subgroups revealed no significant associations with continuation versus temporarily stopping therapy, with the exception of patients randomised ≤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 pre-existing antihypertensive therapy in the first few hours or days following stroke, unless indicated for other comorbid conditions.

Keywords

Stroke, Hypertension, Antihypertensive therapy, Blood pressure, Individual patient data meta-analysis, Randomized controlled trials

Introduction

Elevated blood pressure (BP) is common in patients presenting with acute stroke, of whom approximately 75% have a BP >140/90 mmHg [1,2]. The natural history is for BP to decline spontaneously over 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 regarding 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 [7,8,9], 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 pre-existing antihypertensive medication. Over 50% of patients presenting with acute stroke are already taking BP lowering medication, usually for the treatment of hypertension, but also for other co-morbidities 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 post stroke period remains unclear; further, acute stroke may be complicated by dysphagia thereby complicating administration of oral drugs. Continuation of therapy could 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 following 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) [7]. Both were neutral for the primary outcome of 2-week death or dependency (COSSACS) [17] and 3-month modified Rankin scale (mRS) shit (ENOS) [7], though 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) and used a pre-specified 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 pre stroke 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 papers 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
2) Investigating the effect of continuing versus stopping (for at least 1 week) pre-existing anti-hypertensive medication in those with acute stroke (recruited <48 hours of symptom onset)
3) Outcomes of interest including at least one of: death; disability (mRS or equivalent); stroke recurrence; neurological deterioration (change in National Institute of Health Stroke Severity score (NIHSS), or equivalent); other vascular events.

Two investigators screened the titles and abstracts and excluded all papers not meeting the criteria by consensus. The same investigators evaluated the remaining studies as full papers. Authors of the papers 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, sub-groups at baseline, and outcomes were agreed prior to analysis of any of the trials. Pre-specified subgroups included: age (≤70 years, >70); sex; ethnicity (Caucasian, Asian, other); smoking status; atrial fibrillation (AF); diabetes; previous stroke; BP medications (angiotensin converting enzyme inhibitor (ACE-I), angiotensin two receptor antagonist (ARA), renin inhibitor, beta receptor antagonist, calcium channel blocker (CCB), diuretic, alpha receptor antagonist, centrally acting agent); number of BP medications (1, 2, 3, 4, >4); feeding status (Oral feeding, No oral feeding); Systolic BP (SBP; <140, 140 to 159, 160 to 180, >180mmHg); NIHSS (<15, ≥15); stroke type (ischemic, hemorrhagic); stroke syndrome as per Oxford Community Stroke Project classification (OCSP) (lacunar syndrome – LACS, partial anterior circulation syndrome - PACS, total anterior circulation syndrome – TACS, posterior circulation syndrome – POCS); and time to randomization (≤12 hours, 13 to 24, 25 to 36, >36).

The primary outcome was death or dependency, as measured using the mRS (0-2 defined as independent, 3-5 dependent, 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 stroke ischemic" or "recurrent stroke hemorrhagic" 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 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 (NHS) 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]. Since the COSSACS trial defined dependency at six months according to three categories, (based on responses to three 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 in order to create a common long-term functional outcome for this analysis. Categories were: Independent (mRS 0); Independent (mRS 1 to 2); dependent (mRS 3 to 5).

The included studies were approved by the relevant ethics committees: COSSACS – Trent Research Ethics Committee MREC/02/4/051); 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 one-stage meta-analysis, individual patient data from both trials were merged in to a single database prior to further analysis. Data from both trials were checked prior to and post 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 pre stroke antihypertensive medication (in comparison to temporary stopping) on outcomes was assessed using ANCOVA (BP outcomes), multiple linear regression, ordinal logistic regression (OLR) 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, in order 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) or mean difference (MD), with 95% confidence intervals. Outcomes analysed using mean difference were BP, NIHSS, EQ-5D, EQ-VAS and Barthel Index. The effect of treatment on the primary outcome was assessed in pre-specified subgroups in all patients. These subgroup analyses were performed by adding an interaction term to a mixed-effects OLR 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) 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, two (COSSACS – ISRCTN89712435, and ENOS – ISRCTN99414122) fulfilled the inclusion criteria. Chief investigators of both studies (TGR and PMB, respectively) were collaborators in this review and agreeable for the original datasets to be analysed. 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 endpoint trial that assigned 763 non-dysphagic stroke patients to either continue or stop antihypertensive medication for 14 days using a secure web-based randomisation 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 to 220mmHg) were randomized via a secure web-based randomization system to receive a GTN patch or no GTN patch for one-week (administered single blind), and in a subset of patients on pre-stroke antihypertensive medication, to continue or stop this medication for one 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 was included in this meta-analysis. A summary of characteristics of the two 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.

Patient Characteristics

Across the two trials, 1432 patients were randomized to continue pre-stroke antihypertensive medication, and 1428 were randomized to stop antihypertensive medication temporarily for the acute and sub-acute stroke periods. Recruited patients were similar to those recruited to stroke services with 52.4% male, a mean age of 73 years. Baseline characteristics across the two trial cohorts were broadly similar (Table S4). Differences in participants' ethnic origins are to be expected given the geographical location of centres involved in the two 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 140-220 mmHg.

Blood Pressure Profiles

SBP and Diastolic BP (DBP) fell in both randomized groups from recruitment to day seven, with a steeper decline seen in those who continued their anti-hypertensive 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 end of treatment at seven 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 end of 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 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 VAS (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 OLR 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 pre-specified subgroups, though in the majority of subgroups, point estimates of odds ratios favored stopping pre-existing antihypertensive therapy.

Discussion

Around half of patients presenting with acute stroke are on pre-existing anti-hypertensive medication. Whether to continue or stop this medication in the acute and sub-acute 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 two large RCTs suggest that continuation of pre-existing antihypertensive medication, versus temporarily stopping it, confers no significant benefit to patients in terms of short- or long-term outcomes following acute ischemic or hemorrhagic stroke, despite the fact that BP was significantly lower in the Continue group from days one to seven, and levels of BP declined more steeply. Analyses for the effect of continuing versus stopping antihypertensives on death or dependency, by our pre-defined 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 pre-existing 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 with a safe swallow or once enteral access is obtained.

This is the first meta-analysis to address the question of whether to continue or temporarily stop pre-stroke antihypertensive medication, and our study has several strengths: the analysis included a wide range of stroke patients recruited from centres across 23 different countries, albeit predominantly Caucasian, 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 pre-defined subgroups, with higher numbers, and greater statistical power than in the individual trials. However, the power to detect a difference between the two groups in the primary outcome is less than 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 two 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 pre-existing 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 seven days in the continue versus stop groups. In fact, observed differences in SBP and DBP at day seven between the two randomized groups were greater than has been observed in some acute stroke BP lowering trials; -9.4mmHg 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 pre-defined subgroups, including all BP levels, stroke type (ICH or ischemic stroke, and OCSP class), and number and class of pre-stroke 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 very early (within the first few hours) from stroke onset. However, results from a subgroup analysis of ENOS (those receiving BP-lowering treatment with GTN within six hours from stroke onset) [7], and the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT) [26], where transdermal GTN was given within four hours (median 55 minutes) of stroke onset, are discordant with our findings, each suggesting benefit with very early BP lowering. Furthermore, the Intensive blood pressure reduction in acute cerebral hemorrhage (INTERACT-2) study of BP lowering within 6 hours of ICH showed safety and borderline significant favorable outcomes in early BP lowering [6].

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 effects on the renin angiotensin system (ACE-I, ARA, or ß-receptor antagonist). Acute stroke trials have shown harm with ARA [27], and with ß-receptor antagonists [28]. Secondly, 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. Thirdly, 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 due to the COSSACS trial excluding those with dysphagia. Fourthly, the effect of continuation of pre-stroke

BP-lowering medication may differ depending on pre-morbid 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, Rothwell and colleagues found that SBP was substantially raised compared with last premorbid levels in ICH, but in acute ischemic stroke was much closer to the accustomed long-term pre-morbid level [29]. The authors suggested that any benefits of BP-lowering therapy in acute stroke might be greater in those in whom the high post-event 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. Though 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 pre-stroke BP trends. Finally, BP variability (BPV) may be of prognostic significance in acute stroke as reported in a recent *post-hoc* analysis of the INTERACT 2 dataset [30]. Different antihypertensive agents exert differential effects of BPV, and thus, within individual BPV (unmeasured in this analysis) [31] and the effect of drug class on BPV may have had an unmeasured influence on outcome.

Limitations

This study also has potential limitations. The analysis is under-powered; any future trial would need to recruit in excess of 10,000 patients to detect a difference between the two groups in the primary outcome is less than 10%. Therefore, applying the conclusions to all sub-groups 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: very high SBP (> 200mmHg, or DBP >120 in COSSACS; >220 and >140 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 co-variables, residual confounding may still have occurred. Furthermore, both trials were, out of necessity, open label and performance bias cannot be excluded, although outcome assessors were masked to treatment allocation in both trials. Finally, there are limited data on patients recruited very 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 pre-existing antihypertensive therapy in the first few hours or days following 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 sub-group analyses in the ischemic stroke population suggesting that very early BP lowering may be beneficial, future acute stroke BP studies should aim to recruit patients very early from stroke onset, in order to determine the effect of BP lowering in the first few hours.

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Conflict of Interest/ Disclosure

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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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 pre-existing antihypertensive medication in acute stroke.

What Is Relevant?

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

Summary

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

Figure Legends

Figure 1: Study Selection Process

Figure 2. Modified Rankin scale at end of trials. Comparison by mixed-effects ordinal logistic regression. OR 0.97 (95% CI 0.84-1.12, 2p=0.68).

Figure 3. Forest plot of functional outcome (mRS) by trial

Comparison by ordinal logistic regression.

Figure 4. Forest plot of functional outcome (mRS) by pre-specified subgroups

ICH, Intracerebral Hemorrhage; LACS, lacunar syndrome; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke; ACEI, angiotensin converting enzyme inhibitor. Analysis undertaken using a mixed-effects ordinal logistic regression model.

Table 1. Characteristics of trials comparing continuing versus stopping pre-stroke antihypertensive medication during acute stroke

Characteristics	COSSACS	ENOS
Size	763	2097
Recruitment time window (hrs)	< 48	< 48
Length of treatment (days)	14	7
Length of follow-up (days)	180	90
SBP range (mmHg)	> 100	140 - 220
Major exclusions	Need for antihypertensive agents	Need for GTN or antihypertensive agents
Countries	1	23
Centres	49	173

COSSACS: Continue Or Stop post-Stroke Antihypertensives Collaborative Study; ENOS: Efficacy of Nitric Oxide and Stroke trial; GTN: glyceryl trinitrate; SBP: systolic blood pressure

Table 2. Functional outcome and vascular events: continue versus stop pre-stroke antihypertensive medication. 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 below one and mean differences below zero favor continuing pre-stroke antihypertensive medication.

Outcomes	Odds ratio/MD (95% Confidence Interval)	P for significance
End-of-treatment (14 days in COSSACS, 7 days in ENOS)		
Death	1.04 (0.64, 1.69)	0.87
Recurrence of stroke (ischemic stroke or intracerebral hemorrhage)	1.41 (0.85, 2.34)	0.19
Recurrence of stroke (ischemic)	2.27 (1.17, 4.39)	0.015
Recurrence of stroke (hemorrhagic)	0.35 (0.09, 1.31)	0.12
Death or Deterioration	0.86 (0.68, 1.09)	0.21
Neurological Impairment (worsening of scores on the NIHSS by ≥4 from baseline)*	0.38 (-0.12, 0.87)	0.75
Death or Institutionalization	1.10 (0.93, 1.30)	0.26
End-of-trial (180 days in COSSACS, 90 days in ENOS)		
Death	1.06 (0.84, 1.35)	0.63
Modified Rankin Scale (mRS) ‡	0.94 (0.84, 1.12)	0.68

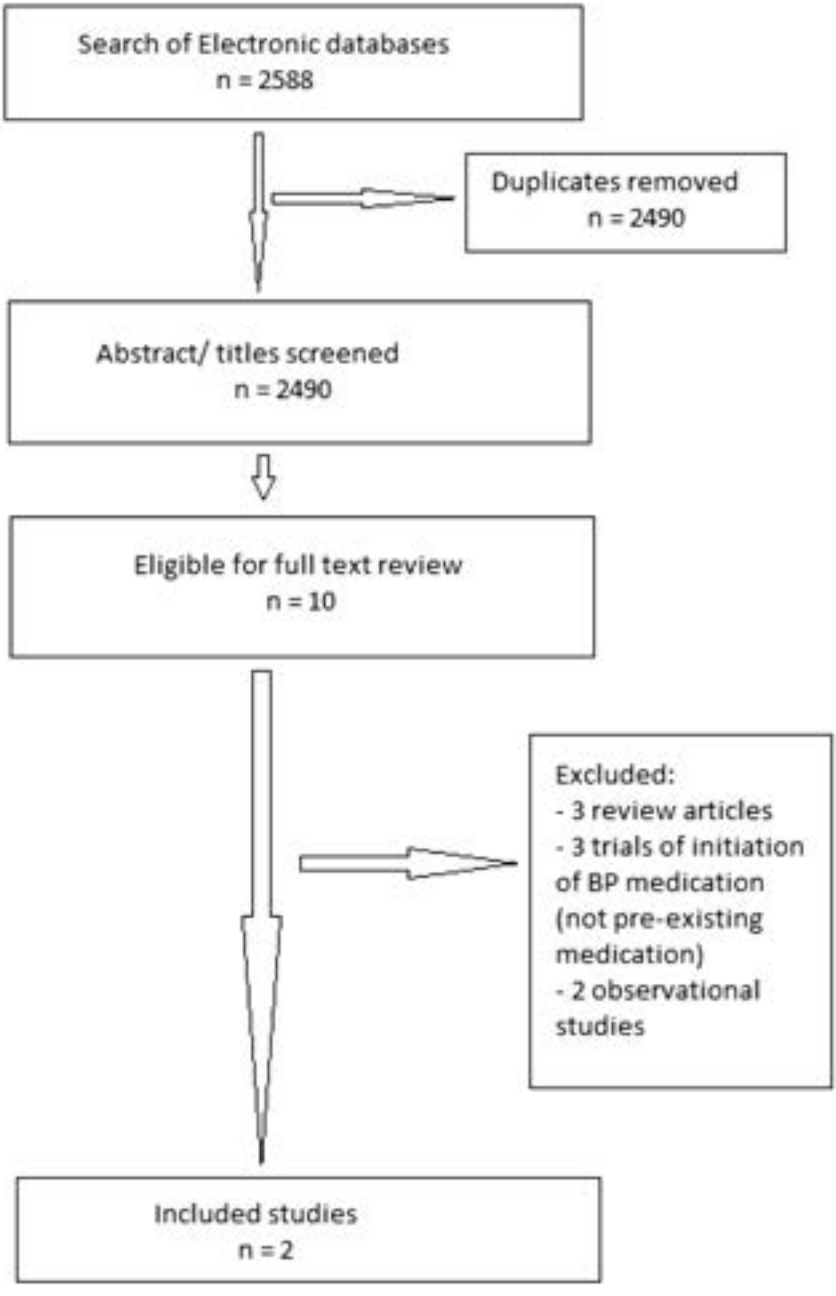
Outcomes	Odds ratio/MD (95% Confidence Interval)	P for significance
Death or dependency (mRS > 2)	0.96 (0.80, 1.14)	0.62
Barthel Index †	-3.20 (-6.08, -0.33)	0.23
EuroQoL-5D health utility status	-0.03 (-0.06, 0.00)	0.31
EuroQoL-visual analogue scale	-2.00 (-4.48, 0.48)	0.31
Vascular events ɬ	0.87 (0.71, 1.08)	0.21

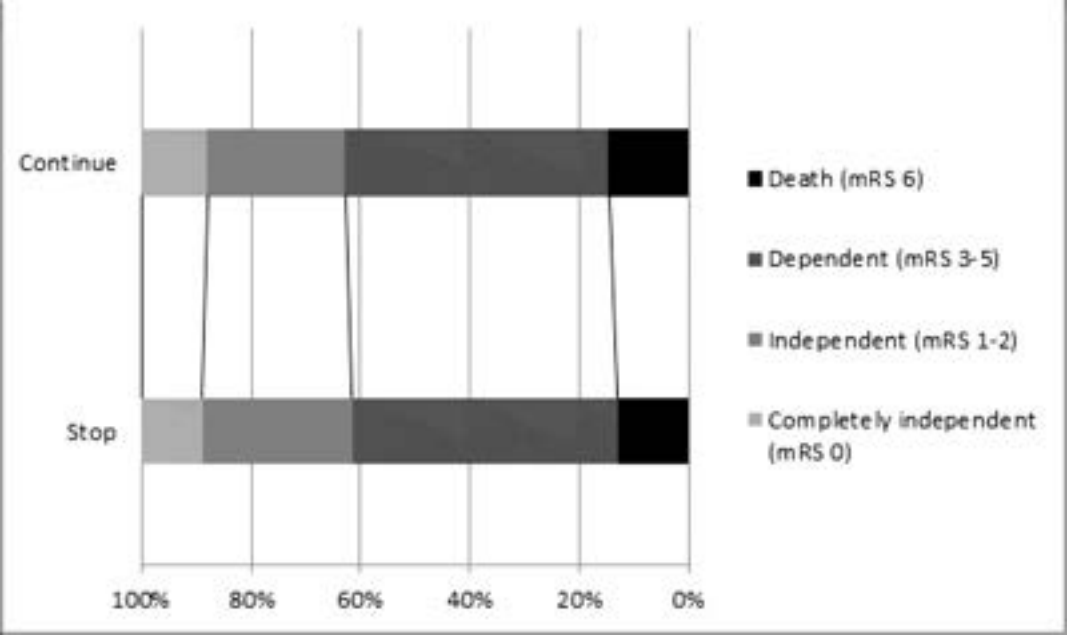
* In ENOS, NIHSS derived from Scandinavian Stroke Scale [20]

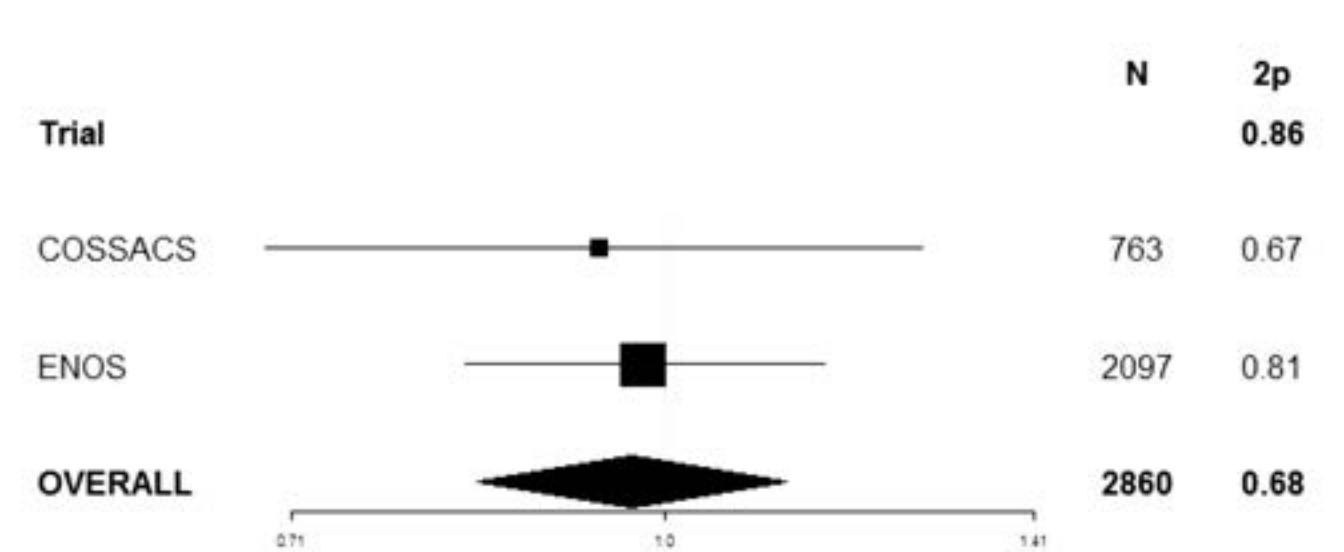
† Measured at 14 days in COSSACS, and 90 days in ENOS

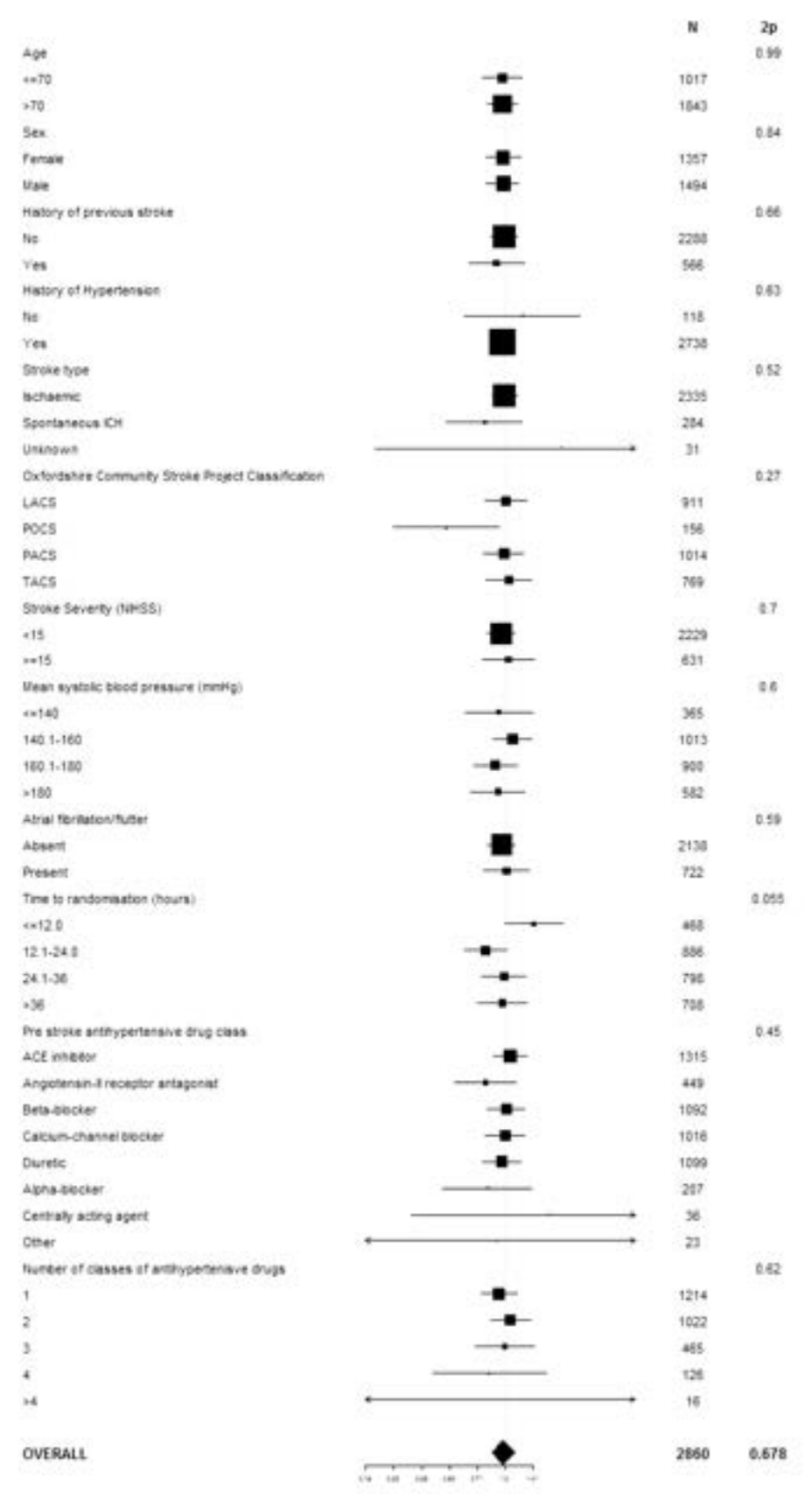
‡ Categories derived from the International Stroke Trial questionnaire: Independent (mRS 0); Independent (mRS 1 to 2); Dependent (mRS 3 to 5).

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


Search of Electronic databases
n = 2588
Duplicates removed
n = 2490
Abstract/ titles screened
n = 2490
Eligible for full text review
n = 10
Excluded:
- 3 review articles
- 3 trials of initiation of BP medication (not pre-existing medication)
- 2 observational studies
Included studies
n = 2


Continue
Stop
100%
80%
60%
40%
20%
0%
Death (mRS 6)
Dependent (mRS 3-5)
Independent (mRS 1-2)
Completely independent (mRS 0)


N
2p
Trial
0.86
COSSACS
763
0.67
ENOS
2097
0.81
OVERALL
2860
0.68
0.71
1.0
1.41


N
2p
Age
0.99
<=70
1017
>70
1843
Sex
0.84
Female
1357
Male
1494
History of previous stroke
0.66
No
2288
Yes
566
History of Hypertension
0.63
No
118
Yes
2736
Stroke type
0.52
Ischaemic
2335
Spontaneous ICH
284
Unknown
31
Oxfordshire Community Stroke Project Classification
0.27
LACS
911
POCS
156
PACS
1014
TACS
769
Stroke Severity (NIHSS)
0.7
<15
2229
>=15
631
Mean systolic blood pressure (mmHg)
0.6
<=140
365
140.1-160
1013
160.1-180
900
>180
582
Atrial fibrillation/flutter
0.59
Absent
2138
Present
722
Time to randomisation (hours)
0.055
<=12.0
468
12.1-24.0
886
24.1-36
796
>36
786
Pre stroke antihypertensive drug class
0.45
ACE inhibitor
1315
Angiotensin-II receptor antagonist
449
Beta-blocker
1092
Calcium-channel blocker
1016
Diuretic
1099
Alpha-blocker
287
Centrally acting agent
36
Other
23
Number of classes of antihypertensive drugs
0.62
1
1214
2
1022
3
465
4
126
>4
16
OVERALL
2860
0.678

ONLINE SUPPLEMENT

Contents:

Members of the Blood pressure in Acute Stroke Collaboration (BASC):

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ENCHANTED: Craig Anderson

ENOS: Philip M Bath, Nikola Sprigg, Joanna M Wardlaw

FAST-Mag: Jeff Saver, Nerses Sanossian

GTN-1/2/3, RIGHT: Philip M Bath

ICH ADAPT: Ken Butcher

IMAGES: Kennedy R Lees, Keith W Muir

INTERACT: Craig Anderson

INTERACT-2: Craig Anderson, Hisatomi Arima, Emma Heeley

PILFAST: Gary Ford

SCAST: Eivind Berge, Else Charlotte Sandset

STAR: Nikola Sprigg, Philip Bath

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 ɻ	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 (%) ɻ	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	-	-

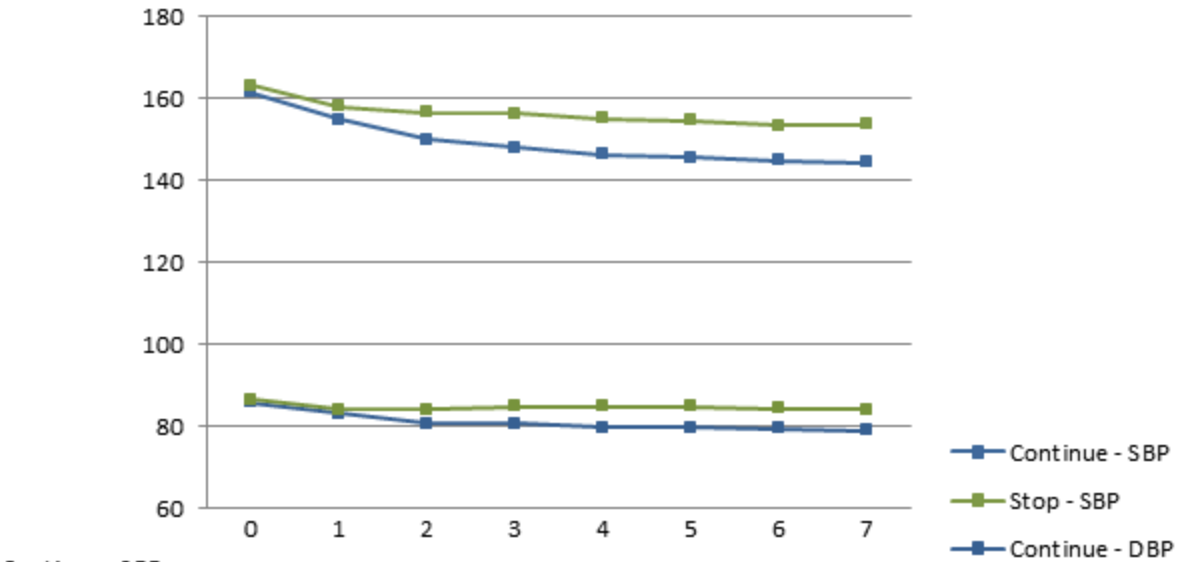
* NIHSS was derived from Scandinavian Stroke Scale scores in ENOS

† 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

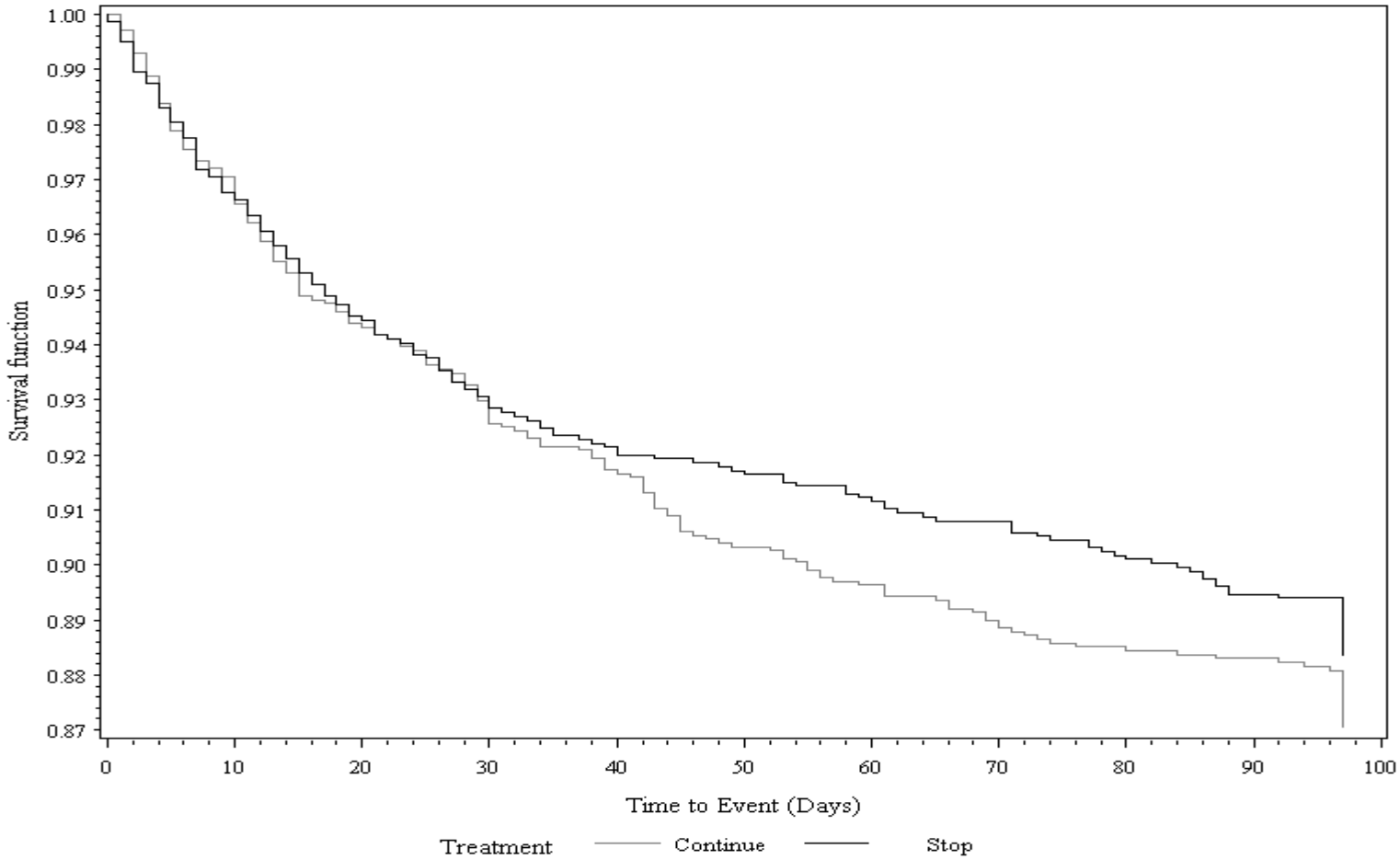


Figure S2. Kaplan-Meier curve for death.

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.