



The University of  
**Nottingham**

UNITED KINGDOM · CHINA · MALAYSIA

Woodhouse, Lisa J. and Manning, Lisa and Potter, John F. and Berge, Eivind and Sprigg, Nikola and Wardlaw, Joanna and Lees, Kennedy R. and Bath, Philip M. and Robinson, Thompson G. (2017) Continuing or temporarily stopping prestroke antihypertensive medication in acute stroke: an individual patient data meta-analysis. *Hypertension*, 69 (5). pp. 933-941. ISSN 0194-911X

**Access from the University of Nottingham repository:**

<http://eprints.nottingham.ac.uk/42032/1/Continuing%20or%20Temporarily%20Stopping%20Prestroke%20Antihypertensive%20Medication%20in%20Acute%20StrokeNovelty%20and%20Significance.pdf>

**Copyright and reuse:**

The Nottingham ePrints service makes this work by researchers of the University of Nottingham available open access under the following conditions.

This article is made available under the University of Nottingham End User licence and may be reused according to the conditions of the licence. For more details see:  
[http://eprints.nottingham.ac.uk/end\\_user\\_agreement.pdf](http://eprints.nottingham.ac.uk/end_user_agreement.pdf)

**A note on versions:**

The version presented here may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the repository url above for details on accessing the published version and note that access may require a subscription.

For more information, please contact [eprints@nottingham.ac.uk](mailto:eprints@nottingham.ac.uk)

**Full Title**

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

**Authors**

†Lisa Woodhouse MSc. Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham, NG5 1PB, UK.

†Dr Lisa Manning MBChB. Consultant Stroke Physician. University Hospitals of Leicester NHS Trust, Leicester, LE5 1WW, UK.

Prof John F Potter DM. Professor of Ageing and Stroke Medicine. Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, Norfolk, UK.

Prof Eivind Berge MD, Oslo University Hospital, Department of Internal Medicine, Kirkeveien 166, NO-0407 Oslo, Norway

Dr Nikola Sprigg MD. Associate Professor of Stroke Medicine. Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham, NG5 1PB, UK.

Prof Joanna Wardlaw FMedSci. Professor of Applied Neuroimaging. Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, EH4 2XU, UK

Prof Kennedy R Lees FRCP. Professor of Cerebrovascular Medicine. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow G11 6NT, UK

‡ Prof Philip M Bath DSc FMedSci. Stroke Association Professor of Stroke Medicine. Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham, NG5 1PB, UK.

‡ Prof Thompson G Robinson FRCP MD. Professor of Stroke Medicine. University of Leicester, Department of Cardiovascular Sciences and NIHR Biomedical Research Unit in Cardiovascular Disease, Leicester, LE2 7LX, UK.

for the Blood Pressure in Acute Stroke Collaboration (BASC)

† These authors contributed equally

‡ These authors contributed equally

### **Short Title**

Continue or Stop BP Lowering Therapy Post Stroke

### **Counts**

Full title: 117 characters

Short title: 48 characters (including spaces)

Total (including references, figures, legends): 6053 words

Abstract: 237 words

Figures: 4

### **Corresponding Author**

Prof Philip M Bath DSc FMedSci. Stroke Association Professor of Stroke Medicine. Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham, NG5 1PB, UK. Telephone: +44 (0)115 823 1765; Fax: +44 (0)115 823 1767; Email: [philip.bath@nottingham.ac.uk](mailto:philip.bath@nottingham.ac.uk)

**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  $\leq 48$  hours; investigating the effect of continuation versus stopping pre-stroke antihypertensive medication; follow up of  $\geq 2$  weeks. Two randomized controlled trials were identified and included in this meta-analysis of individual patient data from 2860 patients  $\leq 48$  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  $\leq 12$  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) shift (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  $\geq 2$  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 ( $\leq 70$  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,  $> 180$ mmHg); NIHSS ( $< 15$ ,  $\geq 15$ ); 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 ( $\leq 12$  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  $\geq 4$  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  $\beta$ -receptor antagonist). Acute stroke trials have shown harm with ARA [27], and with  $\beta$ -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 pre-morbid 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, pre-morbid 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.

## **Acknowledgements**

The paper is written on behalf of the Blood pressure in Acute Stroke Collaboration (BASC, convener P Bath). For details of membership see Online Supplement.

## **Sources of Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The COSSACS trial was funded by The Health Foundation and The Stroke Association. The ENOS trial was funded by BUPA Foundation and the Medical Research Council (UK). PB is Stroke Association Professor of Stroke Medicine.

## **Conflict of Interest/ Disclosure**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://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.

**References**

- (1) Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Hussein. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *American Journal of Emergency Medicine*. 2007;25:32-38.
- (2) Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, Lees KR, Toni D, SITS Investigators. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis. retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke*. 2009;40:2442-2449.
- (3) Ahmed N, Wahlgren N. High initial blood pressure after acute stroke is associated with poor functional outcome. *Journal of Internal Medicine*. 2001;249:467-473.
- (4) Leonardi-Bee J, Bath PMW, Phillips SJ, Sandercock PAG, for the IST Collaborative Group. Blood Pressure and Clinical Outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315-1320.
- (5) Geeganage C, Tracy M, England T, Sare G, Moulin T, Woimant F, Christensen H, De Deyn PP, Leys D, O'Neill D, Ringelstein EB, Bath PMW, and for TAIST Investigators. Relationship Between Baseline Blood Pressure Parameters (Including Mean Pressure, Pulse Pressure, and Variability) and Early Outcome After Stroke: Data From the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST). *Stroke*. 2011;42:491-493.
- (6) Anderson CS, Heeley E, Huang Y, et al. Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage. *N Engl J Med*. 2013;368:2355-2365.

(7) The ENOS Trial Investigators. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): A partial-factorial randomised controlled trial. *Lancet*. 2015;385:617-628.

(8) Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for Treatment of Acute Lacunar Stroke Syndromes. *Lancet*. 2004;363:439-445.

(9) He J, Zhang Y, Xu T, et al, for the CATIS investigators. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischaemic stroke. *JAMA*. 2014;311:479-489.

(10) Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, Murray GD, Richter PS, Roine RO, Terent A, Thijs V, Berge E, on behalf of the SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741-750.

(11) Jauch EC, Saver JL, Adams HP et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870-947.

(12) Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the Early Management of Adults With Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation*. 2007;115:e478-e534.

- (13) Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, Mayberg M, Morgenstein L, Ogilvy CS, Vespa P, Zuccarello M. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults: 2007 Update: A Guideline From the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38:2001-2023.
- (14) NICE. Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). *NICE guidelines* [CG68] 2008;1(1).
- (15) Bath PMW, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke (Review). *Cochrane Collaboration*. 2014;10.
- (16) Rashid P, Leonardi-Bee J, Bath P. Blood Pressure Reduction and Secondary Prevention of Stroke and Other Vascular Events: A Systematic Review. *Stroke*. 2003;34:2741-2748.
- (17) Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, James MA, Knight J, Markus HS, Mistri AK, Poulter NR. Effects of antihypertensive treatment after acute stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurology*. 2010;9:767-775.
- (18) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *International Journal of Surgery*. 2010;8:336-341.
- (19) Gray LJ, Ali M, Lyden PD, Bath PM, Virtual International Stroke Trials Archive Collaboration. Interconversion of the National Institutes of Health Stroke Scale and Scandinavian Stroke Scale in acute stroke. *Journal of Stroke and Cerebrovascular Disease*. 2009;18:466-468.

- (20) Dennis M, Wellwood I, Warlow C. Are simple questions a valid measure of outcome? *Cerebrovasc Dis.* 1997;7:22-27.
- (21) Bath PMW. Efficacy of Nitric Oxide in Stroke (ENOS) trial. Summary of protocol (version 1.5). 2007; Available at: <http://www.enos.ac.uk/enossummaryv15.htm>. Accessed 21/10, 2013.
- (22) Higgins JPT, Green S. The Cochrane handbook for Systematic Reviews of Interventions. 5.1.0 ed.: *Cochrane Library*; 2011.
- (23) Rosenfield HY, Scott PA, Summers DR, Wang DZ, Wintermark M, Demaerschalk BM, Khatri P, McMullan PW, Qureshi AI. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2013;44:870-947.
- (24) Diener H, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurology.* 2008;7:875-884.
- (25) Aries MJH, Elting JW, De Keyser J, Kremer BPH, Vroomen PCAJ. Cerebral Autoregulation in Stroke: A Review of Transcranial Doppler Studies. *Stroke.* 2010;41:2697-2704.
- (26) Ankolekar S, Fuller M, Cross I, Renton C, Cox P, Sprigg N, Siriwardena N, Bath PM. Feasibility of an Ambulance-Based Stroke Trial, and Safety of Glyceryl Trinitrate in Ultra-Acute Stroke: The Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT, ISRCTN66434824). *Stroke.* 2013;44:3120-3128.

- (27) Schrader J, Lüders S, Kulschewski A, Berger J, Zidek W, Treib J, Einhaupl K, Diener HC, Dominiak P, on behalf of the ACCESS Study Group. The ACCESS Study: Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke*. 2003;34:1699-1703.
- (28) Barer DH, Cruickshank JM, Ebrahim SB, Mitchell JR. Low dose beta blockade in acute stroke ("BEST" trial): an evaluation. *British Medical Journal*. 1988;296:737-741.
- (29) Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, Mehta Z, Rothwell PM. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. *Lancet Neurology*. 2014;13:374-384.
- (30) Manning L, Hirakawa Y, Arima H, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. *Lancet Neurology*. 2014;13:364-373.
- (31) Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet*. 2010;375:906-915.

## **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  $\leq 12$  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
<b>End-of-treatment (14 days in COSSACS, 7 days in ENOS)</b>		
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 $\geq 4$ from baseline)*	0.38 (-0.12, 0.87)	0.75
Death or Institutionalization	1.10 (0.93, 1.30)	0.26
<b>End-of-trial (180 days in COSSACS, 90 days in ENOS)</b>		
Death	1.06 (0.84, 1.35)	0.63
Modified Rankin Scale (mRS) ‡	0.94 (0.84, 1.12)	0.68
Death or dependency (mRS > 2)	0.96 (0.80, 1.14)	0.62

Outcomes	Odds ratio/MD (95% Confidence Interval)	P for significance
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 ‡	0.87 (0.71, 1.08)	0.21

\* In ENOS, NIHSS derived from Scandinavian Stroke Scale <sup>(20)</sup>

† 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).

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