Prognostic Significance of Short-Term Blood Pressure Variability in Acute Stroke

Systematic Review

Lisa S. Manning, MBChB; Peter M. Rothwell, FMedSci; John F. Potter, DM; Thompson G. Robinson, MD

Background and Purpose—Blood pressure variability (BPV) may be an important prognostic factor acutely after stroke. This review investigated the existing evidence for the effect of BPV on outcome after stroke, also considering BPV measurement techniques and definitions.

Methods—A literature search was performed according to a prespecified study protocol. Two reviewers independently assessed study eligibility and quality. Where appropriate, meta-analyses were performed to assess the effect of BPV on poor functional outcome.

Results—Eighteen studies from 1359 identified citations were included. Seven studies were included in a meta-analysis for the effect of BPV on functional outcome (death or disability). Systolic BPV was significantly associated with poor functional outcome: pooled odds ratio per 10-mm Hg increment, 1.2; confidence interval (1.1–1.3). A descriptive review of included studies also supports these findings, and in addition, it suggests that systolic BPV may be associated with increased risk of intracranial hemorrhage in those treated with thrombolytic therapy.

Conclusions—This systematic review and meta-analysis suggest that greater systolic BPV, measured early from ischemic stroke or intracerebral hemorrhage onset, is associated with poor longer-term functional outcome. Future prospective studies should investigate how best to measure and define BPV in acute stroke, as well as to determine its prognostic significance. **(*Stroke*. 2015;46:2482-2490. DOI: 10.1161/STROKEAHA.115.010075.)**

Key Words: blood pressure ■ meta-analysis ■ odds ratio ■ prospective studies ■ stroke

Elevated blood pressure (BP) is an established prognostic factor after acute stroke,[1,2] although evidence as to the effect of BP lowering on outcome is partly conflicting, with some large studies reporting near positive effects on functional outcome[3] but others, including the recent Efficacy of Nitric Oxide in Stroke (ENOS) trial,[4] reporting neutral[5] or near negative results.[6] BP variability (BPV) may be important in the acute stroke period. Within-individual systolic BPV (SBPV) is a risk factor for stroke and cardiovascular events, independent of mean absolute BP level.[7,8] Furthermore, there are highly consistent drug class effects on interindividual and intraindividual variability in BP.[9,10] The variable efficacies of different antihypertensive agents on stroke risk reduction cannot be explained purely by effects on mean BP reduction alone, and thus, BPV may provide a potentially modifiable therapeutic target.[8] Available evidence on the effect of BPV on outcome after acute stroke is scarce, and data are lacking as to the natural history of BPV in acute stroke, its definition, and the most appropriate measurement technique. There are currently no available systematic reviews on BPV in the acute-stroke setting.

This systematic review addresses the above points by investigating the existing evidence of the effect of SBPV on outcome after stroke, including mortality, functional dependency, and adverse neuroimaging outcomes. In addition, we consider the BP measurement techniques used, including casual cuff measurements, and beat-to-beat and 24-hour or ambulatory monitoring. Statistical techniques to derive BPV are also considered. This review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[11]

Methods

Search Strategy and Selection Criteria

A prespecified study protocol was followed. A literature search in the bibliographic databases MEDLINE (1948 to present), Web of Science (1970 to present), EMBASE (1980 to present), AMED (1985 to present), The Cochrane Library, Cochrane Stroke Group

Received May 13, 2015; final revision received July 1, 2015; accepted July 2, 2015.

From Department of Cardiovascular Sciences and NIHR Biomedical Research Unit in Cardiovascular Disease, University of Leicester, Leicester, United Kingdom (L.S.M., T.G.R.); Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, United Kingdom (P.M.R.); and Faculty of Medicine and Health Sciences, Norfolk and Norwich Medical School, University of East Anglia, Norwich, United Kingdom (J.F.P.).

Guest Editor for this article was Kazunori Toyoda, MD, PhD.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.010075/-/DC1.

Correspondence to Lisa S. Manning, MBChB, University of Leicester, Room 228, RKCSB, PO Box 65, LE2 7LX, Leicester, United Kingdom. E-mail lm313@le.ac.uk

Trials Register, Cochrane Central Register of Controlled Trials, SCOPUS (1966 to present), and Index to UK theses was performed independently by 2 researchers. Databases of ongoing trials were also searched: ClinicalTrials.gov, Current Controlled Trials Stroke Trials Register, and WHO International Clinical Trials Registry. Combinations of search terms used were "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 "blood pressure variability" or "BPV" and "outcome*" or "prognos*" or "predict*" or "mortality" or "death" or "dependenc*" or "disability" or "neurological deterioration" or "functional depenc*". MeSH terms and groupings were adapted as appropriate, for each database. The search was limited to studies involving humans and adults. The references of selected studies and relevant reviews were hand searched for additional relevant articles.

Randomized controlled trials, controlled trials, cohort studies, and observational studies that assessed the effect of BPV on outcome after acute ischemic stroke or primary intracerebral hemorrhage (ICH) were included. Eligibility was assessed by reading abstracts and, if necessary, whole articles. Studies in which BPV was not reported within the first 7 days of stroke onset were excluded, as were those which did not report clinical outcome measures of interest, namely death, disability, dependency, neurological deterioration, recurrent vascular events, or radiological mechanisms for poor outcomes (hemorrhagic transformation, cerebral edema, and hematoma expansion). Disability was measured as the modified Rankin Scale (mRS). Neurological deterioration was defined as worsening on a stroke neurological impairment scale (National Institute of Stroke Scale Score) or equivalent. Studies that gave insufficient detail on BP measurements or BPV calculations were excluded. Full study inclusion and exclusion criteria can be found in the study protocol (online-only Data Supplement). Study quality and risk of bias were assessed using a checklist adapted from authors, editors, and reviews of meta-analyses of observational studies[12] (Table I in the online-only Data Supplement).

Statistical Analysis

Given the potential heterogeneity of included studies, we exercised caution in deciding whether a meta-analysis was appropriate. We used consensus opinion (L.M., T.G.R., and P.M.R.) to determine whether meta-analysis was appropriate for each of our outcomes of interest, and if so, which studies were suitable for inclusion, based on common methodology, BPV parameters and definitions, definitions of outcome, and the reporting of results. In the event of uncertainty surrounding study inclusion, further statistical advice and opinion was sought from statisticians at the University of Oxford, United Kingdom. Where meta-analysis was not deemed appropriate, we describe results in a descriptive manner.

Our primary analyses were based on studies reporting the effect of BPV on poor functional outcome, defined as death or major disability (mRS or equivalent), and secondary analyses were based on studies reporting the effect on predefined radiological outcomes and the effect on early neurological outcome. Studies were included only if authors reported odds ratios (OR) and 95% confidence intervals (CIs) for the effect of a defined increment (eg, per 10-mm Hg increase or 1-SD increase) in either SD of SBP (SD SBP) or coefficient of variation of SBP (CV SBP), on outcome. Studies using BPV parameters other than SD or CV were not included as such indices (eg, successive variation [SV] and average real variability are not directly comparable with SD or CV, and equivalent values cannot be accurately derived. Where ORs were adjusted for potentially confounding factors in multivariable analyses, the adjusted OR and 95% CI were used in the meta-analysis. In-house software (a previously validated macro within Microsoft EXCEL 2003) was used to calculate pooled ORs, 95% CIs, P values for significance, and Cochran Q statistic for heterogeneity, assuming a fixed effects model (Mantel–Haenszel–Peto method) with effect sizes weighted according to the reciprocal of their variance. Statistical significance was set at $P<0.05$.

Results

Eighteen articles of 1359 originally identified citations were included (Figure I in the online-only Data Supplement). No randomized controlled trials were identified. Seven studies were of a prospective observational nature,[13–19] 5 were observational analyses of prospective stroke registry data,[20–24] and 6 were observational analyses of previous randomized controlled trial data.[25–30] Study sample size varied from 71 to 2645 participants. Eight studies were deemed suitable to include in the meta-analysis for effect of BPV on functional outcome.[14,15,17,18,20,22,26,27] The remaining 10 studies were excluded from this analysis because of heterogeneity in methodology and reporting (Table II in the online-only Data Supplement).[13,16,19,21,23–25,28–30] One further study was later excluded from the meta-analysis on the basis that it was a small study with an extreme effect,[15] leaving 7 studies in the final analysis. We provide results for the meta-analysis including and excluding this extreme outlier.

The median checklist quality score was 12 (range, 7–15), highlighting the heterogeneity in study methodology reporting and incomplete reporting of key criteria in many studies (Table III in the online-only Data Supplement). Fifteen studies included patients with acute ischemic stroke only,[13–18,20–25,28–30] 1 study included both patients with ischemic stroke and ICH,[27] and 2 included only those with primary ICH.[19,26] Study characteristics are shown in the Table.

Fifteen studies measured BP using casual BP cuffs[13,15,18–30]; 1 study used 24-hour ambulatory BP monitors[17]; and 2 used beat-to-beat BP monitors.[14,16] Thirteen studies enrolled patients and started BP measurements within 24 hours of stroke onset,[13,15,17–21,23,24,26,28–30] 10 of these within the first 6 hours.[15,18–21,23,26,28–30] Of the remaining studies, 2 recruited patients within 48 hours,[25,27] 1 within 72 hours,[14] 1 at 72 hours,[22] and the remaining study within the first 7 days.[16] The duration of time over which BPV was calculated varied from 10 minutes to ≈137 hours. A variety of parameters were used to define BPV (outlined in Figure II and Table IV in the online-only Data Supplement). The Table shows BP measurement techniques, timings, and parameters used.

Fifteen studies reported functional status (death or disability) as an outcome measure; all used dichotomized mRS scores. Thirteen studies reported functional outcome at 90 days,[13,15–22,26,28–30] 1 at 30 days,[14] and 1 at 14 days.[27] Six studies reported neurological improvement or deterioration as an outcome measure.[15,16,18,19,25,28] Eight studies reported outcome data relating to neuroimaging findings: 7 studies used hemorrhage or hematoma expansion on repeat imaging within 14 days of onset as an outcome measure (with heterogeneity in definitions and timing of scans).[18–21,23,26,29] Further details can be found in Table V in the online-only Data Supplement.

Thirteen studies used logistic regression models to investigate associations between BPV parameters and outcome, reporting ORs, and 95% CIs.[14,15,20–30] Three studies used other forms of multivariable analyses,[17–19] and 2 simply compared BPV parameters between good and poor outcome groups.[13,16] Although most studies adjusted analyses for baseline prognostic variables, only 7 studies adjusted for baseline BP level or mean BP.[18,19,22,23,26–28]

To assess the effect of BPV on functional outcome, we report the results of our meta-analyses and provide a descriptive analysis of our findings. Heterogeneity in study methodology precluded a formal meta-analysis for the effect of BPV on radiological outcomes or on short-term neurological outcome, although several nonstatistically significant trends are apparent, as discussed below. Table VI in the online-only Data Supplement summarizes the effect of BPV on outcome in all studies.

Seven studies were deemed eligible for inclusion in meta-analyses to assess the pooled effect of SBPV on functional outcome.[14,17,18,20,22,26,27] All used dichotomized mRS scores to define poor versus favorable outcomes. Where studies reported ORs for the effect on favorable mRS scores,[18,20] ORs were inverted, to provide OR for poor outcome. All studies used either SD or CV SBP as their key variability parameter. Three studies quoted ORs and 95% CIs per 10-mm Hg increment in BPV parameter,[17,18,20] 3 reported ORs and 95% CIs for each 1-SD increment in BPV parameter,[22,26,27] and 1 reported ORs and 95% CIs for each 1-mm Hg increment in SBPV.[14] Using the mean SBPV for the study populations, we converted all ORs to ORs for the effect per 10-mm Hg increment in SBPV. The analysis showed nonsignificant heterogeneity between trials; so, we used a fixed effects model. SBPV was significantly associated with poor functional outcome: pooled OR, 1.2; CI (1.1–1.3); P_{sig}=0.0004; P_{het}=0.1 (Figure). Pooled OR estimates were similar for the same meta-analysis using random effects models, although they did not meet statistical significance (Table VII in the online-only Data Supplement). For the analysis including the study with the extreme result (Delgado-Mederos et al[15]), pooled OR estimates were similar and remained significant for the fixed effects model, although they did not meet statistical significance for the random effects model: fixed effect model pooled OR 1.2, CI (1.1–1.3), P_{sig}=0.0004, P_{het}=0.01; random effects model pooled OR 1.2, CI (0.9–1.5), P_{sig}=0.15.

On descriptive review of all studies that investigated associations between SBPV and longer-term (≥3 months) functional outcome after acute ischemic stroke, results are partly conflicting. Although some studies reported significant relationships between greater SBPV and poor outcomes[15,20–22,28,29] and significantly greater SBPV indices in poor outcome groups,[13,22] others did not.[16–18,24,27,30] Five retrospective observational analyses of large datasets reported SBPV to independently predict functional outcome in acute ischemic stroke: Kang et al[22] reported that systolic variability parameters were significantly associated with poor functional outcome in 2271 patients; Sare et al[28] reported a significant relationship between greater CV SBP and poor outcome in a post hoc analysis of 1722 patients; Endo et al[20] reported a significant relationship between all included SBPV parameters (SD, CV, and SV) and death at 90 days, and a nonsignificant trend toward improved functional outcome with lower SBPV indices, in an analysis of stroke registry data. A post hoc analysis of data from the European Cooperative Acute Stroke Study 2 (ECASS2) reported significant inverse associations between SV SBP and favorable 90-day functional outcome in tissue-type plasminogen activator and placebo-treated groups.[29] Kellert et al[21] reported a significant relationship between lower SBPV (SV SBP only) and favorable functional outcome in 427 patients receiving thrombolytic therapy. In contrast to the findings reported in the above studies, a post hoc analysis of 592 patients from the ECASS collaboration, using SV SBP as the sole variability parameter, revealed no significant relationship between SBPV and functional outcome.[30]

In smaller study cohorts in acute ischemic stroke, significant relationships with functional outcome were reported less frequently or were found in subgroups only: Tomii et al[18] reported no significant associations between SBPV (CV SBP only) and functional outcome in a prospective study of 130 patients; Stead et al[24] reported no association between SBPV and death at 90 days; Delgado-Mederos et al[15] found a significant relationship between SD SBP and outcome only in the subgroup of patients with persistent middle cerebral artery occlusion and in 80 patients thrombolyzed for ischemic stroke. Buratti et al[13] found significantly higher SD SBP and CV SBP in those with poor functional outcome in a prospective cohort of patients with ischemic stroke and ipsilateral internal carotid artery occlusion. Graff et al[16] found no differences in SBPV or diastolic BPV (DBPV) derived from beat-to-beat monitoring in 75 patients with ischemic stroke. In the one included study that used ambulatory BP monitoring (during 24 hours), no significant associations were found between SBP variability (defined as CV) and functional outcome.[17]

Two studies assessed the effect of BPV on 90-day functional outcome in patients with acute ICH and elevated BP. Manning et al[26] reported significant associations between SD SBP in the hyperacute phase (first 24 hours) and poor functional outcome and between SD SBP in the acute phase (day 2 to day 7) and outcome. Furthermore, in sensitivity analyses, all SBPV parameters (SD, CV, residual SD, average real variability, and maximum SBP) were significantly associated with outcome. More recently, Tanaka et al[19] reported a significant association between SV SBP during 24 hours and poor functional outcome in a prospective cohort of 205 patients with ICH, although they found no significant association with SD SBP.[19]

Three studies investigated the effects of BPV on functional outcomes (death alone, disability alone, or death and disability combined) early after stroke (≤30 days).[14,25,27] Although 1 study found SD SBP to be an independent predictor of death and neurological deterioration at 10 days,[25] the other 2 studies found no association between SBPV and outcome at ≤1 month.[14,27] Of 4 studies investigating the effect of BPV on neurological deterioration <7 days of ischemic stroke onset, none reported significant associations with outcome.[15,16,19,28]

Heterogeneity in BPV parameters, outcome definitions, and reporting of results precluded a formal meta-analysis for the effect on neuroimaging outcomes, although certain nonstatistically significant trends were apparent (detailed in Table VIII in the online-only Data Supplement). One study found SD SBP to be an independent predictor of ischemic lesion growth on repeat magnetic resonance imaging scan in patients with acute ischemic stroke and persistent middle cerebral artery occlusion post thrombolysis but found no such association in those with middle cerebral artery recanalization.[15] Five studies investigated the effect of BPV on hemorrhagic complications (on repeat brain imaging) after ischemic stroke in patients eligible for thrombolysis.[18,20–22,28] In studies where

100% of participants received thrombolytic therapy, 3 (of 4) reported significant associations between greater SBPV and hemorrhage on repeat brain imaging.[18,20,21] A further 2 studies, recruiting those with ischemic stroke (in which 51% and 64% received thrombolytic therapy), reported positive associations between at least 1 reported SBPV parameter and hemorrhagic transformation on repeat imaging (Table VIII in the online-only Data Supplement).[23,29] In acute ICH, neither of the 2 included articles found significant associations between SBPV and hematoma growth on repeat imaging.[19,26]

Although the primary focus of this review was on SBPV, DBPV was also considered (Tables VI and IX in the online-only Data Supplement). The effects of DBPV indices on outcome were considered in 16 studies, SD DBP being the most frequently used parameter.[13–15,17–28,30] Reporting of results was often incomplete, and therefore, it precluded meta-analyses. DBPV parameters were significantly associated with outcome in 8 studies: 4 reported associations with radiological outcome,[15,20,21,23] 2 with death,[20,24] 4 with poor longer-term functional outcome,[15,22,26,30] and 1 with poor functional outcome at 30 days.[14] The associations were often of borderline significance or for some but not all parameters. DBPV was not significantly associated with radiological or short-term functional or neurological outcomes in any included study.[19–21,25,28,29] In acute ICH, 1 study reported mean arterial pressure and DBPV parameters to be weak but significant predictors of outcome,[26] although another found no association between DBPV and outcome.[19]

Discussion

This is the first systematic review to investigate the prognostic significance of BPV in acute stroke and to bring together the current evidence about the measurement and definition of BPV in the acute-stroke setting. Pooled estimates for the effect of BPV suggest that greater SD SBP and CV SBP early after acute stroke may be associated with an increased risk of death and disability. Although these results must be interpreted with caution, nonstatistically significant trends described in our qualitative review support this finding, and in addition, they suggest that SBPV, measured early after acute stroke, is often associated with the risk of ICH in those treated with thrombolytic therapy. Conversely, SBPV does not seem to be associated with short-term functional or neurological outcomes in acute ischemic stroke, and the prognostic significance of DBPV is uncertain.

Most studies (9 of 12), reporting the effect of BPV on longer-term functional outcome, found SBPV to be independently associated with death or dependency.[15,19–22,26–29] Studies reporting such associations were more often those with higher numbers of patients (n>500), although those reporting neutral or nonsignificant results had smaller sample sizes (n<150)[14,17,18,24] and recruited a population with a noticeably lower average stroke severity.[17,27] These findings are not based on quantitative analysis and are merely hypothesis generating. Publication bias may have played a role in the former observation, with larger studies reporting positive results more likely to be published. We aimed to minimize the risk of this as much as possible through our exhaustive approach to the literature review.

Interestingly, most studies in which BP measurements commenced early from stroke onset[15,19–21,26,28,29] reported positive associations between SBPV and poor longer-term functional outcomes or hemorrhagic complications on repeat brain imaging, whereas studies in which BP measurements commenced later (>12 hours from stroke onset) more often reported no, or weaker, associations with outcome.[14,16,17,23,24,27] All studies that assessed the relationship between SBPV and risk of intracranial hemorrhage post thrombolysis for acute ischemic stroke reported significant associations, with greater SBPV being associated with increased risk.[18,20,21,23,30] In acute ICH, both included studies found associations between SBPV and functional outcome but not hematoma growth.[19,26] We found limited and conflicting data on associations between DBPV and functional, neurological, or radiological outcomes, and because of a combination of heterogeneity and incomplete reporting of results cannot draw firm conclusions as to its potential prognostic significance.

The findings of this review must be interpreted with caution. In particular, reverse causality, whereby larger strokes, with a poorer prognosis may give rise to greater variability in BP, cannot be excluded. However, there are other plausible hypotheses to explain the observed relationship between BPV and outcomes, most of which relate to the effects of BP fluctuations, on an increasingly pressure-dependant cerebral circulation. Cerebral autoregulation is impaired in acute stroke,[31] and dynamic BP fluctuations, in the context of greater BPV, may lead to increased cerebral edema, or risk of hemorrhagic transformation, in this pressure-dependent cerebral circulation. Indeed in those receiving thrombolytic therapy, greater fluctuations or sudden BP increases may exacerbate the deleterious effects of reperfusion injury on salvageable ischemic tissue, which may in part explain the reported associations between greater BPV and poor outcome in studies of this patient group.

The pathophysiological effects of greater BPV on brain tissue may vary depending on the degree of impairment in cerebral autoregulation, which is influenced by factors such as infarct size.[32,33] Thus, in those with more severe strokes with greater cerebral dysautoregulation, BPV may exert greater pathophysiological effects than in those with milder disease. Another hypothesis relates to the potential difference in pathophysiological effects of BPV on potentially viable brain tissue (the ischemic penumbra) versus effects on the irreversibly damaged ischemic core and may help explain why studies commencing BP measurements earlier more often found associations with outcome. Perhaps in the first few hours after onset, the potentially salvageable penumbral tissue is particularly vulnerable to the effects of BP fluctuations, with sudden BP declines increasing the risk of further ischemia and reducing the chances of reperfusion, and abrupt BP rises increasing the risk of hemorrhage.

Greater SBP fluctuations may contribute to ongoing bleeding and hematoma growth in ICH, and hypotensive episodes associated with greater BPV may lead to secondary cerebral ischemia or enhance the formation of cerebral edema. Indeed, a significant correlation between BP instability (and baroreceptor sensitivity) and relative edema after ICH was reported

Table. Study Characteristics

Study	Patient Numbers	Study Design	Stroke Type*	Thrombolytic Therapy Given?†	Average Initial Stroke Severity‡§
Buratti et al,[13] 2014	89	Prospective observational analysis	AIS	No	Good outcome 8; poor outcome 9.5
Dawson et al,[14] 2000	92	Prospective observational analysis	AIS	No	Not reported
Delgado-Mederos et al,[15] 2008	80	Prospective observational analysis	AIS	Yes (100%)	15 (10–19)
Endo et al,[20] 2013	527	Observational analysis (stroke registry)	AIS	Yes (100%)	12 (7–18)
Geeganage et al,[25] 2011	1479	Observational analysis (RCT data)	AIS	No	Not stated
Graff et al,[16] 2013	75	Prospective observational analysis	AIS	Not stated	5
Kang et al,[22] 2012	2271	Observational analysis (stroke registry)	AIS	Yes (12.9%)	3 (2–7)
Kellert et al,[21] 2012	427	Observational analysis (stroke registry)	AIS	Yes (all)	ICH negative 10.5 (9), ICH positive 14 (8) (quoted as mean [SD])
Ko et al,[23] 2010	792	Observational analysis (stroke registry)	AIS	Yes (64.3%)	HT negative 4 (2–8); HT positive 13 (7–18)
Manning et al,[26] 2014	2645	Observational analysis (RCT data)	ICH	No	10 (6–15)
Manning et al,[27] 2015	934	Observational analysis (RCT data)	ICH and AIS	No	COSSACS: 4 (3–8); CHHIPS 9 (5–16)
Sare et al,[28] 2009	1722	Observational analysis (RCT data)	AIS	No	11 (8–17)
Stead et al,[24] 2006	71	Observational analysis (stroke registry)	AIS	Not stated	11.8 (10.4) (quoted as mean [SD])
Tanaka et al,[19] 2014	205	Prospective observational analysis	ICH	No	13 (8–17)
Tomii et al,[17] 2011 (24-h BP)	104	Prospective observational analysis	AIS	Yes (15%)	4 (1–8)
Tomii et al,[18] 2011	125	Prospective observational analysis	AIS	Yes (100%)	13 (7–18)
Yong et al,[25] 2005	791	Observational analysis (RCT data)	AIS	Yes (50.4%)	SSS categorized into groups: 0–14, 12.3%; 15–25, 26.5%; 26–35, 32.03%; >36, 26.17%
Yong et al,[29] 2008	592	Observational analysis of RCT data	AIS	Yes (51.3%)	SSS by SBP group (mean SD): SBP≤140, 27.4 (11.1); SBP≥140, 31.5 (11.3)

Functional outcome: measured on the modified Rankin scale or equivalent. Further information on timing and exact definitions of outcome measures can be found in Table V in the online-only Data Supplement. ABPM indicates ambulatory blood pressure monitoring; AIS, acute ischemic stroke; ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; CHHIPS, Controlling Hypertension and Hypotension Immediately Post Stroke; COSSACS, Continue or Stop Post-Stroke Antihypertensives Collaborative Study; CV, coefficient of variation; END, early neurological deterioration; HT, hemorrhagic transformation of infarct on brain imaging; ICH, intracerebral hemorrhage; IQR, interquartile range; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NIHSS, National Institute of Health Stroke Scale; PP, pulse pressure; RCT, randomized controlled trial; RSD, residual standard deviation; SBP, systolic blood pressure; SSS, Scandinavian Stroke Scale; SV, successive variation; and VIM, variation independent of the mean.

*Stroke type described as ischemic only/ICH only/both ischemic and ICH included.

†Where thombolytic therapy given, % of participants receiving therapy given in brackets.

‡Given for the whole cohort, unless reported by outcome group only in the original article, in which case, reported by outcome group.

§NIHSS given unless otherwise stated. Quoted as median (IQR where reported) unless otherwise stated.

‖Identified on repeat brain imaging.

Antihypertensives Given?	Time From Stroke Onset to Recruitment	BP Measurement Technique and Duration of Monitoring	No. of BP Measures From Which BPV Calculated	BPV Parameters Included in Analyses	Outcome Measures
Yes, as per normal clinical practice	≤9 h	Casual cuff BP for 48 h	≥10	SD, CV	Functional outcome
No	<72 h	Beat-to-beat BP for 10 min	Beat-to-beat	SD	Functional outcome
Yes, as per normal clinical practice	<6 h	Casual cuff BP for 24 h	52	SD	Functional outcome, END, infarct volume on MRI
Yes, as per normal clinical practice	<6 h	Casual cuff BP for 24 h	6	SD, SV, CV	Functional outcome, ICH*
Not stated	<48 h	Casual cuff BP (duration unknown)	Not stated	SD	Functional outcome, END
Yes, as per normal clinical practice	<7 d (median, 2 d)	Beat-to-beat BP (duration unknown)	Beat-to-beat	SD	Functional outcome, END
Yes, as per normal clinical practice	72 h	Casual cuff BP for median duration 8.7 days (IQR, 6.8–11.9) from stroke onset; BPV calculated from 72 h post stroke to hospital discharge	Median 34	SD, CV	Functional outcome
Yes, as per normal clinical practice	<6 h	Casual cuff BP for 24 to 36 h (no median quoted)	Median 21.5 (IQR, 9.5)	SV	Functional outcome, ICH*
Yes, as per normal clinical practice	<24 h	Casual cuff BP for 72 h	Median 18 (IQR, 14–57)	SD, SV, maximum SV	ICH‖
Yes, trial protocol	< 6 h	Casual cuff BP for the first 24 h and from day 2 to day 7	5 in day 1, 12 from day 2 to day 7	SD, CV, VIM, ARV, RSD	Functional outcome, hematoma growth*
Yes, trial protocol	<48 h	Casual cuff BP for 10 min	6	SD, CV, ARV, VIM	Functional outcome
Yes, dependant on trial	<6 h	Casual cuff BP for 24 h	7	CV	Functional outcome, END
No	<24 h	Casual cuff BP for 3 h	Median 9 (range, 2–30)	Slope (fitting linear regression to curve), % change from baseline SBP	Death
Yes, IV Nicardipine as per study protocol	<3 h	Casual cuff BP for 24 h	24	SD, SV	Functional outcome
Yes, as per normal clinical practice	<24 h	ABPM for 24 h on day 2 and day 7 post stroke	48 in each 24-h period	CV	Functional outcome
Yes, as per normal clinical practice	<3 h	Casual cuff for 24 h	28	CV	Functional outcome, ICH*
Not stated	<6 h	Casual cuff for 24 h	37	SV	Functional outcome,
Not stated	<6 h	Casual cuff for 72 h	23	SV	Functional outcome, ICH*

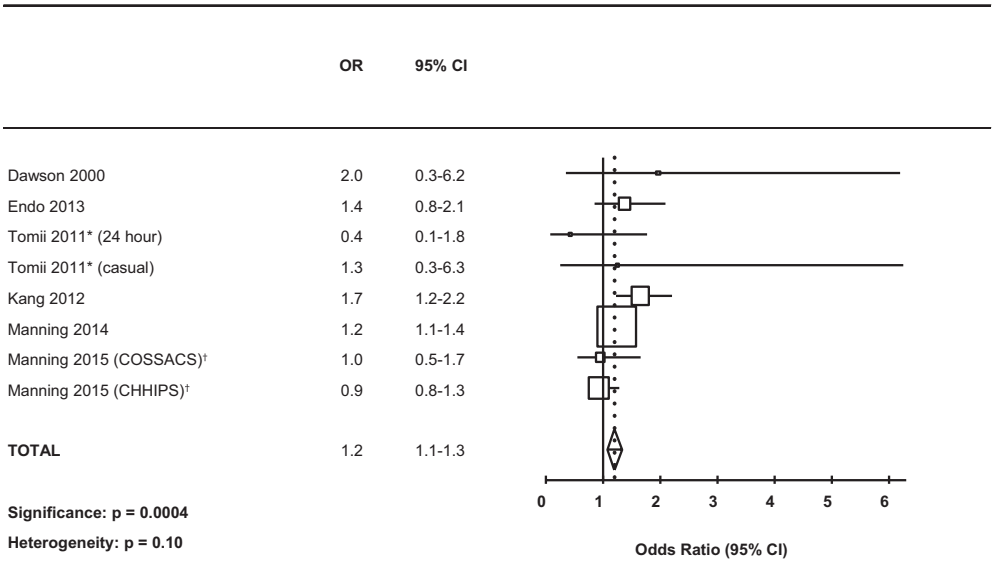

Figure. Forrest plot of the association between systolic blood pressure variability (SBPV) and poor functional outcome (death or disability). Included studies quoted odds ratio (OR) for the effect of SD SBP on outcome unless otherwise indicated. OR quoted for the effect per 10-mm Hg increment in SBPV. *Reported OR (95% confidence interval [CI]) for the effect per 10-mm Hg coefficient of variation (CV) SBP, where CV=(SD/mean)×100 mm Hg.[17,18] ORs are likely to be overestimates compared with those studies quoting OR per 10-mm Hg increment in SD SBP. †Separate ORs provided for Hypertension and Hypotension Immediately Post Stroke (CHHIPS) and Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) cohorts in the original article[27]; therefore, 2 ORs also used for the purposes of meta-analysis.

in a recent observational study.[34] All of the above hypotheses remain speculative at present, given the lack of prospective studies investigating the effect of BPV on the blood supply to the ischemic penumbra and surrounding tissue in acute stroke.

The pathophysiological mechanisms responsible for the observed associations between BPV and longer- but not shorter-term functional or neurological outcomes remain unclear, and given the lack of available data on the natural history of BPV after stroke, it is difficult to suggest robust hypotheses. Perhaps BPV in the acute stroke period correlates with BPV several weeks or months from the event, in which case, the effects of BPV on large and small artery remodeling and associated changes in arterial function may be relevant.[35] These uncertainties should be addressed in future prospective studies, which in the first instance should determine the course of BPV in the short and longer term after stroke.

There is currently no consensus as to the best parameter to use to estimate BPV in acute stroke. A variety of parameters were used to define BPV across the studies in this review. Only 1 study performed discriminatory analyses to determine the most useful outcome predictors.[26] In most studies using >1 variability parameter, either all included SBP parameters were associated with outcome or no associations were found. No one parameter was consistently associated with outcome and another, consistently not. Furthermore, no study used >1 BP measurement technique in the same cohort of patients; so, no direct comparisons between techniques can be made in terms of ability to capture BP variations or acceptability to participants. Therefore, we cannot comment on the most useful BPV parameter, or the most appropriate BP measurement technique for the purposes of BPV estimation in acute stroke.

This study has several limitations. Our meta-analysis was limited to only 7 studies because of the heterogeneity in methodology and reporting of results, thus, limiting the statistical power and precision of results. Furthermore, the analyses were based on adjusted ORs from each trial rather than on more sensitive actuarial analysis of individual patient data. BPV increases proportionally to mean BP in hypertensive individuals, and some studies did not adjust for BP level in their analyses; of studies included in the meta-analysis, 4 studies adjusted for mean SBP[18,22,26,27]; and 1 study did not adjust the reported OR but reported no heterogeneity in the effect of BPV on outcome across groups depending on mean BP level.[14] The relationship between the BP level and outcome after stroke is complex and nonlinear; adjustment for BP level between studies was heterogeneous; and thus, any attempt to adjust for this in the meta-analysis would be complicated and may even cause artifact. The meta-analysis included studies of both acute ICH and acute ischemic stroke combined. As BP management strategies, target BP level, and evidence for the effect on BP lowering on outcome is different in acute ischemic stroke compared with ICH, our results may not reflect the relationship between BPV and the stroke subtypes when considered as 2 separate entities. However, we are limited by the small number of studies eligible for inclusion in the analysis, with only 1 study recruiting patients with acute ICH only and 1 enrolling a cohort including both stroke subtypes but predominantly ischemic stroke. Most of the larger included studies were post hoc analyses and thus, prone to selection bias. Furthermore, reverse causality cannot be excluded, as discussed previously. Finally, many studies included patients receiving antihypertensive therapy, although few described drugs, or doses used, or reported on the potential effect of such drugs on BPV and outcome.

A main finding of this review was heterogeneity in currently available data. In future studies, to create a homogenous

set of data amenable to meta-analysis and to find from which robust conclusions can be drawn about the most appropriate definition and measurement of BPV, and its effects on outcome after acute stroke, we would recommend the following as a minimum: authors should provide a detailed description of the study population, in particular, the number and class of preexisting antihypertensive medications; the timing and duration of BP measurements should be clearly stated, as should the time from stroke onset and the time from which outcome events were included; analyses should include at least 2 BPV parameters and should include SD or CV; mean SD for the population should be stated; BPV should be measured during the short (minutes) and longer terms (hours to days); a description of the relationship between BP level and outcome should be provided, and authors should state if and how any adjustment for BP level was performed in their analyses; authors should report the effect of both SBPV and DBPV; investigators should use a range of BP measurement techniques to capture BPV; acceptability and failure rates of BP measurement devices should be assessed.

Nonetheless, this review brings together the current evidence about the potential prognostic significance of BPV in acute stroke, and although we cannot make recommendations for clinical practice based on our findings, the present review will inform future research. Given the variable efficacies of different antihypertensive agents on stroke risk reduction that cannot be explained purely by effects on mean BP reduction alone (with calcium-channel blockers being most protective)[9] and the highly consistent and significant drug class effects on interindividual BPV,[9,10] where calcium-channel blockers and nonloop diuretics reduce variation although angiotensin receptor and β-blockers increase it, BPV may represent a modifiable therapeutic target in acute stroke. Future research aimed at determining the feasibility and effect of reducing BPV in acute stroke is justified, although first, prospective studies of the minimum standard described above should aim to address how best to measure and define BPV.

Conclusions

This systematic review and meta-analysis suggest that greater SBPV, measured early from ischemic stroke or ICH onset, is associated with poor longer-term functional outcome. In addition, in those with acute ischemic stroke eligible for thrombolytic therapy, increased BPV is frequently associated with increased risk of hemorrhage on repeat brain imaging. Although robust conclusions cannot be drawn because of limitations in the quality of included studies and heterogeneity in study methodology, this is the first review to investigate the prognostic significance of BPV in acute stroke, and our results will inform future studies. In addition, our results have potential implications for clinical practice, whereby clinicians should aim for smooth and sustained control of BP in acute stroke and not solely focus on absolute or average BP values.

A paucity of data directly comparing the predictive value of different BPV parameters, the timing and duration of BPV measurements, and the practicality and acceptability to patients of the various BP measurement techniques, in the acute stroke population, means that we cannot firmly conclude how best to measure or define BPV. Further prospective work is needed before embarking on larger studies to determine the feasibility and efficacy of reducing BPV after acute stroke and to assess its effect on outcome.

Sources of Funding

This systematic review is the first output of a programme grant from the British Heart Foundation and United Kingdom Stroke Association (TSA BHF 2012/01). L.S. Manning was supported by a programme grant from the British Heart Foundation and UK Stroke Association (TSA BHF 2012/01).

Disclosures

None.

References

1. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, et al; 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. doi: 10.1161/STROKEAHA.109.548602.
2. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension*. 2004;43:18–24. doi: 10.1161/01.HYP.0000105052.65787.35.
3. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368:2355–2365. doi: 10.1056/NEJMoa1214609.
4. Bath PM, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, Bereczki D, et al; 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. doi: 10.1016/S0140-6736(14)61121-1.
5. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol*. 2009;8:48–56. doi: 10.1016/S1474-4422(08)70263-1.
6. Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, et al; 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. doi: 10.1016/S0140-6736(11)60104-9.
7. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905. doi: 10.1016/S0140-6736(10)60308-X.
8. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010;375:938–948. doi: 10.1016/S0140-6736(10)60309-1.
9. 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. doi: 10.1016/S0140-6736(10)60235-8.
10. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al; ASCOT-BPLA and MRC Trial Investigators. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol*. 2010;9:469–480. doi: 10.1016/S1474-4422(10)70066-1.
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336–341. doi: 10.1016/j.ijsu.2010.02.007.
12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
13. Buratti L, Cagnetti C, Balucani C, Viticchi G, Falsetti L, Luzzi S, et al. Blood pressure variability and stroke outcome in patients with internal carotid artery occlusion. *J Neurol Sci*. 2014;339:164–168. doi: 10.1016/j.jns.2014.02.007.

14. Dawson SL, Manktelow BN, Robinson TG, Panerai RB, Potter JF. Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? *Stroke*. 2000;31:463–468.
15. Delgado-Mederos R, Ribo M, Rovira A, Rubiera M, Munuera J, Santamarina E, et al. Prognostic significance of blood pressure variability after thrombolysis in acute stroke. *Neurology*. 2008;71:552–558. doi: 10.1212/01.wnl.0000318294.36223.69.
16. Graff B, Gąsecki D, Rojek A, Boutouyrie P, Nyka W, Laurent S, et al. Heart rate variability and functional outcome in ischemic stroke: a multiparameter approach. *J Hypertens*. 2013;31:1629–1636. doi: 10.1097/HJH.0b013e328361e48b.
17. Tomii Y, Toyoda K, Suzuki R, Naganuma M, Fujinami J, Yokota C, et al. Effects of 24-hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. *Stroke*. 2011;42:3511–3517. doi: 10.1161/STROKEAHA.111.628586.
18. Tomii Y, Toyoda K, Nakashima T, Nezu T, Koga M, Yokota C, et al. Effects of hyperacute blood pressure and heart rate on stroke outcomes after intravenous tissue plasminogen activator. *J Hypertens*. 2011;29:1980–1987. doi: 10.1097/HJH.0b013e32834a764e.
19. Tanaka E, Koga M, Kobayashi J, Kario K, Kamiyama K, Furui E, et al. Blood pressure variability on antihypertensive therapy in acute intracerebral hemorrhage: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-intracerebral hemorrhage study. *Stroke*. 2014;45:2275–2279. doi: 10.1161/STROKEAHA.114.005420.
20. Endo K, Kario K, Koga M, Nakagawara J, Shiokawa Y, Yamagami H, et al. Impact of early blood pressure variability on stroke outcomes after thrombolysis: the SAMURAI rt-PA Registry. *Stroke*. 2013;44:816–818. doi: 10.1161/STROKEAHA.112.681007.
21. Kellert L, Sykora M, Gumbinger C, Herrmann O, Ringleb PA. Blood pressure variability after intravenous thrombolysis in acute stroke does not predict intracerebral hemorrhage but poor outcome. *Cerebrovasc Dis*. 2012;33:135–140. doi: 10.1159/000334186.
22. Kang J, Ko Y, Park JH, Kim WJ, Jang MS, Yang MH, et al. Effect of blood pressure on 3-month functional outcome in the subacute stage of ischemic stroke. *Neurology*. 2012;79:2018–2024. doi: 10.1212/WNL.0b013e3182749eb8.
23. Ko Y, Park JH, Yang MH, Ko SB, Han MK, Oh CW, et al. The significance of blood pressure variability for the development of hemorrhagic transformation in acute ischemic stroke. *Stroke*. 2010;41:2512–2518. doi: 10.1161/STROKEAHA.110.595561.
24. Stead LG, Gilmore RM, Vedula KC, Weaver AL, Decker WW, Brown RD Jr. Impact of acute blood pressure variability on ischemic stroke outcome. *Neurology*. 2006;66:1878–1881. doi: 10.1212/01.wnl.0000219628.78513.b5.
25. Geeganage C, Tracy M, England T, Sare G, Moulin T, Woimant F, et al; 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. doi: 10.1161/STROKEAHA.110.596163.
26. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, et al; INTERACT2 Investigators. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. *Lancet Neurol*. 2014;13:364–373. doi: 10.1016/S1474-4422(14)70018-3.
27. Manning LS, Mistri AK, Potter J, Rothwell PM, Robinson TG. Short-term blood pressure variability in acute stroke: post hoc analysis of the controlling hypertension and hypotension immediately post stroke and continue or stop post-stroke antihypertensives collaborative study trials. *Stroke*. 2015;46:1518–1524. doi: 10.1161/STROKEAHA.115.009078.
28. Sare GM, Ali M, Shuaib A, Bath PM; VISTA Collaboration. Relationship between hyperacute blood pressure and outcome after ischemic stroke: data from the VISTA collaboration. *Stroke*. 2009;40:2098–2103. doi: 10.1161/STROKEAHA.108.539155.
29. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. *Stroke*. 2008;39:366–372. doi: 10.1161/STROKEAHA.107.492330.
30. Yong M, Diener HC, Kaste M, Mau J. Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. *Stroke*. 2005;36:2619–2625. doi: 10.1161/01.STR.0000189998.74892.24.
31. Dawson SL, Panerai RB, Potter JF. Serial changes in static and dynamic cerebral autoregulation after acute ischaemic stroke. *Cerebrovasc Dis*. 2003;16:69–75. doi: 10.1159/000070118.
32. Reinhard M, Rutsch S, Lambeck J, Wihler C, Czosnyka M, Weiller C, et al. Dynamic cerebral autoregulation associates with infarct size and outcome after ischemic stroke. *Acta Neurol Scand*. 2012;125:156–162. doi: 10.1111/j.1600-0404.2011.01515.x.
33. Guo Z, Liu J, Xing Y, Yan S, Lv C, Jin H, et al. Dynamic cerebral autoregulation is heterogeneous in different subtypes of acute ischemic stroke. *PLoS One*. 2014;9:93213. doi: 10.1371/journal.pone.0093213.
34. Sykora M, Diedler J, Rupp A, Turcani P, Rocco A, Steiner T. Impaired baroreflex sensitivity predicts outcome of acute intracerebral hemorrhage. *Crit Care Med*. 2008;36:3074–3079. doi: 10.1097/CCM.0b013e31818b306d.
35. Laurent S, Briet M, Boutouyrie P. Large and small artery cross-talk and recent morbidity-mortality trials in hypertension. *Hypertension*. 2009;54:388–392. doi: 10.1161/HYPERTENSIONAHA.109.133116.