

Low blood pressure and adverse outcomes in acute stroke: HeadPoST study explanations

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Objective: As uncertainties exist over underlying causes, we aimed to define the characteristics and prognostic significance of low blood pressure (BP) early after the onset of acute stroke.

Methods: Post hoc analyzes of the international Head Positioning in acute Stroke Trial (HeadPoST), a pragmatic cluster-crossover randomized trial of lying flat versus sitting up in stroke patients from nine countries during 2015–2016. Associations of baseline BP and death or dependency [modified Rankin scale (mRS) scores 3–6] and serious adverse events (SAEs) at 90 days were assessed in generalized linear mixed models with adjustment for multiple confounders. SBP and DBP was analysed as continuous measures fitted with a cubic spline, and as categorical measures with low (<10th percentile) and high (≥ 140 and ≥ 90 mmHg, respectively) levels compared with a normal range (≥ 10 th percentile; 120–139 and 70–89 mmHg, respectively).

Results: Among 11 083 patients (mean age 68 years, 39.9% women) with baseline BP values, 7.2 and 11.7% had low SBP (<120 mmHg) and DBP (<70 mmHg), respectively. Patients with low SBP were more likely to have preexisting cardiac and ischemic stroke and functional impairment, and to present earlier with more severe neurological impairment than other patients. Nonlinear ‘J-shaped’ relationships of BP and poor outcome were apparent: compared with normal SBP, those with low SBP had worse functional outcome (adjusted odds ratio 1.27, 95% confidence interval 1.02–1.58) and more SAEs, particularly cardiac events, with adjustment for potential confounders to minimize reverse causation. The findings were consistent for DBP and were stronger for ischemic rather than hemorrhagic stroke.

Conclusion: The prognostic significance of low BP on poor outcomes in acute stroke was not explained by reverse causality from preexisting cardiovascular disease, and propensity towards greater neurological deficits and cardiac events. These findings provide support for the hypothesis that low BP exacerbates cardiac and cerebral ischemia in acute ischemic stroke.

Keywords: acute stroke, blood pressure, hypotension, outcome, trial

Abbreviations: AIS, acute ischemic stroke; BP, blood pressure; CI, confidence interval; GLM, generalized linear mixed model; HeadPoST, Head Positioning in acute Stroke Trial; ICH, intracerebral hemorrhage; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SAE, serious adverse events

INTRODUCTION

Blood pressure (BP) is often altered in acute stroke [1–3], typically as an acute hypertensive (physiological) response (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg within 24 h of symptom onset), presumably related to cerebral ischemia and/or elevated intracranial pressure. Observational studies are consistent in showing that high BP is positively associated with adverse clinical outcomes [4,5]. However, randomized controlled trials of blood pressure lowering have produced mixed results [6,7],

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although any benefits on functional recovery appear more likely for intracerebral hemorrhage (ICH) [7] than acute ischemic stroke (AIS) [8]. Although the prognostic significance of the less frequent situation of low presentation BP (variously defined by SBP <120, <130, or <155 mmHg) in an acute stroke is well recognized [9–14], uncertainties exist over whether this represents a risk factor or risk marker in relation to premorbid factors in final few years of life [15] or critical cerebral injury from impaired perfusion pressure in acute stroke. Herein, we report post hoc secondary analyses of the Head Positioning in acute Stroke Trial (HeadPoST) dataset, where the systematic assessment of a large and broad range of relatively unselected patients provided us with an opportunity to determine relationships of low baseline BP and the patterns of functional recovery and serious adverse events (SAEs), overall and by major pathological subtype of acute stroke.

METHODS

Study design

HeadPoST was an international, pragmatic, multicenter, cluster crossover, clinical trial involving 11 093 adults (≥ 18 years) with acute stroke who were randomly allocated to the lying flat or sitting up head position at a median time of 14 h (interquartile range 5–35 h) after symptom onset at 114 hospitals in nine countries between March 2015 and November 2016 [16].

Standard protocol approvals, registrations, and patient consents

Relevant hospital ethics committees or institutional review boards approved the study, which included the use of a cluster guardian consent to allow implementation of the randomized intervention as a policy of usual service delivery for a predefined patient cluster; patients only provided written consent for use of their medical record data and release of personal information to allow centralized telephone interview for follow-up at 90 days. The study is registered at ClinicalTrials.gov (NCT02162017).

Procedures

Demographic information, clinical data, including the severity of neurological impairment according to the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is a measure of neurological impairment caused by a stroke, composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score, ranging from 0 to 42. Baseline BP were collected at the time of presentation/admission to hospital. Trained and certified staff, blind to treatment allocation, contacted patients not known to have died by telephone to assess their functional status on the modified Rankin scale (mRS) at 90 days. The mRS is a global, seven-level assessment of disability, in which scores of 0 or 1 indicate good function without or with symptoms but no disability, scores of 2 indicates slight disability, 3 to 5 indicate increasing levels of disability (and

dependency), and a score of 6 indicates death. The primary outcome for these analyses was death or dependency (mRS scores 3–6), and secondary outcomes were all-cause and cause-specific SAEs, as reported by site investigators and coded centrally according to standard definitions.

Statistical analysis

Descriptive statistics were reported across categories with ANOVA for normally distributed data, Kruskal–Wallis test for skewed continuous variables, and chi-squared test for categorical variables. Generalized linear mixed (GLM) models were built with initial adjustment for the study design of the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and cross-over period; and then adjusted for clinical risk factors with *P* less than 0.1 (listed in Table 1 and Supplemental Table e-1, <http://links.lww.com/HJH/B455>) to determine the estimates of low SBP and DBP on outcomes, respectively. Restricted cubic splines was used to visualize the relationships of baseline SBP and DBP as continuous variables and outcomes in the models, fitted with three to five knots with placement recommended by Harrell [17] and optimal knots selected according to the likelihood ratio test and Akaike information classification (AIC). The point of lowest odds ratio (OR) was used as the optimal reference. To explore associations of categorical BP and clinical outcomes, the first decile of BP (121 mmHg for SBP and 68 mmHg for DBP) were used to define the ranges of low BP in the study population (<120 mmHg in SBP and <70 mmHg in DBP being considered for meaningful interpretability). High BP was defined as at least 140 and at least 90 mmHg in SBP and DBP, respectively, according to guidelines [18]. The primary analysis were according to the intention-to-treat population, with stratified analyses conducted by final diagnoses of AIS or ICH. Prespecified subgroup analyses were performed by ethnicity (Asian vs. non-Asian), use of intensive BP-lowering treatment, preuse of antihypertensive agents, and randomized head position. In view of the high proportion (12%) of missing 90-day mRS data, multiple imputation was conducted as a sensitivity analysis with all missing covariates and outcome variable imputed [19] in a mixed model for analysis of the main results (see Supplemental Appendix, <http://links.lww.com/HJH/B455>). Data are reported with OR and 95% confidence intervals (CI), with a two-sided *P* less than 0.05 considered statistically significant. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina, USA) and STATA version 15 (StataCorp, College Station, Texas, USA).

Data availability

Individual de-identified participant data used in these analyses may be shared by request from any qualified investigator via the Research Office of The George Institute for Global Health, Australia.

RESULTS

A total of 11 083 patients (mean age 68 years, 39.9% women) had baseline BP recorded, of whom 64.7% had a history of hypertension and 85.6% had a final diagnosis of AIS (Table 1

TABLE 1. Baseline characteristics by categories of SBP

Variable	Overall	SBP (mmHg)			P value
		<120	120–139	≥140	
Number of patients	11083	795 (7.2)	2393 (21.6)	7895 (71.2)	
Age (years)	68 (13.8)	65 (15.5)	66 (14.6)	69 (13.2)	<0.0001
Female	4423 (39.9)	300 (37.7)	888 (37.1)	3235 (41.0)	0.0012
Region					<0.0001
Australia and UK	4754 (42.9)	390 (49.1)	971 (40.6)	3393 (43.0)	
China and Taiwan	4652 (42.0)	245 (30.8)	1056 (44.1)	3351 (42.4)	
South America	910 (8.2)	83 (10.4)	179 (7.5)	645 (8.2)	
India and Sri Lanka	770 (6.9)	77 (9.7)	187 (7.8)	506 (6.4)	
Clinical features					
Final pathological type of stroke					<0.0001
AIS	9467 (85.6)	675 (85.1)	2086 (87.4)	6701 (85.1)	
ICH	930 (8.4)	39 (4.9)	123 (5.1)	768 (9.8)	
Uncertain	696 (6.0)	79 (10.0)	178 (7.5)	405 (5.1)	
Severity of neurological impairment, NIHSS score ^a					
Score ≥15	4 (2–8)	5 (2–10)	4 (2–8)	4 (2–8)	0.0002
Score <15	1207 (11.1)	112 (14.3)	240 (10.2)	855 (11.0)	0.0079
SBP (mmHg)	151 (136–171)	110 (105–116)	130 (125–134)	162 (150–180)	<0.0001
DBP (mmHg)	85 (76–97)	70 (61–75)	80 (70–84)	90 (80–100)	<0.0001
Time from onset (h)	7.5 (2.3–26.8)	6.4 (2.0–25.3)	8.9 (2.5–31.8)	7.2 (2.3–25.9)	<0.0001
Medical history					
Hypertension	7148 (64.7)	382 (48.2)	1310 (54.8)	5456 (69.3)	<0.0001
Current treatment	5616 (50.7)	322 (40.6)	1055 (44.1)	4238 (53.7)	0.0007
Number of antihypertensive agents	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.0030
Diabetes mellitus	2650 (24.0)	159 (20.1)	546 (22.9)	1945 (24.7)	0.0054
Atrial fibrillation	1189 (10.8)	112 (14.1)	287 (12.0)	790 (10.1)	0.0002
Coronary disease	1540 (14.0)	141 (17.8)	361 (15.1)	1038 (13.2)	0.0003
Heart failure	413 (3.8)	53 (6.7)	105 (4.4)	255 (3.3)	<0.0001
Previous stroke	2605 (23.6)	189 (23.9)	571 (23.9)	1845 (23.4)	0.8779
Smoking	2124 (19.4)	177 (22.7)	519 (21.9)	1428 (18.3)	<0.0001
High level of premorbid function (mRS 0–1) ^b	8733 (78.9)	603 (75.9)	1860 (77.8)	6270 (79.5)	0.0205
Hypercholesterolemia	2731 (24.6)	215 (27.3)	591 (24.8)	1925 (24.5)	0.2175
COPD/emphysema	406 (3.7)	37 (4.7)	78 (3.3)	291 (3.7)	0.1809
Medications					
Aspirin/other antiplatelet	5398 (48.7)	387 (48.7)	1249 (52.2)	3762 (47.7)	0.0005
Anticoagulation	951 (8.6)	87 (11.0)	223 (9.3)	641 (8.1)	0.0088
Statin/other lipid lowering	2295 (20.7)	188 (23.6)	501 (20.9)	1606 (20.3)	0.2219

Data are mean (SD), median (IQR), and n (%). Analyses were ANOVA test for normally distributed variables, Kruskal–Wallis test for skewed continuous variables, and chi-squared test for categorical variables. AIS, acute ischemic stroke; COPD, chronic obstructive pulmonary disease; ICH, intracerebral hemorrhage; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; UK, United Kingdom.

^aNIHSS is a measure of neurological impairment caused by a stroke, composed of 11 items, each of which scores a specific ability from 0 up to 4. For each item, a score of 0 typically indicates normal function in that specific ability, whereas a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient’s total NIHSS score, ranging from 0 to 42.

^bThe mRS represents a global, seven-level assessment of disability, in which score of 0 or 1 indicate good function without or with symptoms but no disability, score of 2 indicates slight disability, scores of 3–5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death.

and Table e-1, <http://links.lww.com/HJH/B455>). Overall, their mean baseline SBP and DBP were 155 and 87 mmHg, respectively, and 7.2% were defined as having low SBP (<120 mmHg). Compared with other patients, those with low SBP were younger, less likely to have history of hypertension, and more likely to have comorbid heart disease and functional impairment, and greater neurological impairment and strokes without brain imaging confirmation (Table 1). In multivariable analysis, history of atrial fibrillation, coronary disease, heart failure and current smoking were related to increased risk of low BP at presentation (Table e-2, <http://links.lww.com/HJH/B455>).

Low SBP and clinical outcomes

After adjustment for study design and various potential confounding baseline factors, restricted cubic splines regression curves show a nonlinear ‘J-shaped’ relationship

between baseline SBP and death or dependency, with the odds increasing for SBP levels less than 130 mmHg (Fig. 1a) and in those with a final diagnosis of AIS rather than ICH (Fig. 2). Patients with low SBP had an increased risk of death or dependency in the main analysis (adjusted OR 1.27, 95% CI 1.02–1.58; Fig. 3), which was consistent after multiple imputation (adjusted OR 1.26, 95% CI 1.02–1.56; Fig. 3). Risks of death and any SAE were also higher in patients with low SBP, with the latter related to an increased risk of cardiac events (Table 2). Similar J-shaped relationships were found for SBP and SAEs, with adjusted OR increasing with SBP less than 140 mmHg (Fig. 1b). Compared with those with AIS, ICH patients were more likely to present with high SBP (≥140 mmHg; Table 1), which significantly increased the risk of SAEs compared with those with normal SBP (adjusted OR 2.31, 95% CI 1.16–4.60; Figure e-1A, <http://links.lww.com/HJH/B455>).

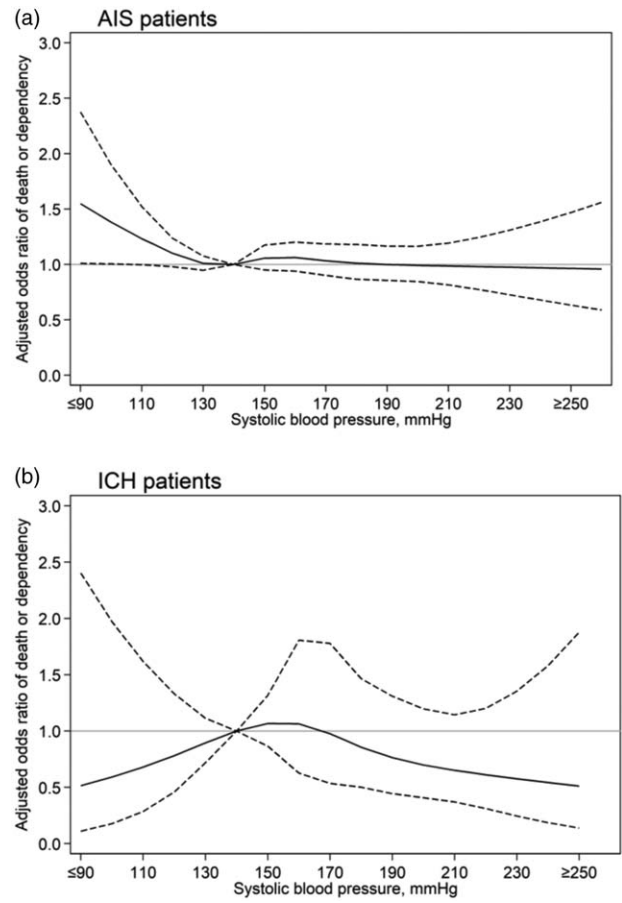
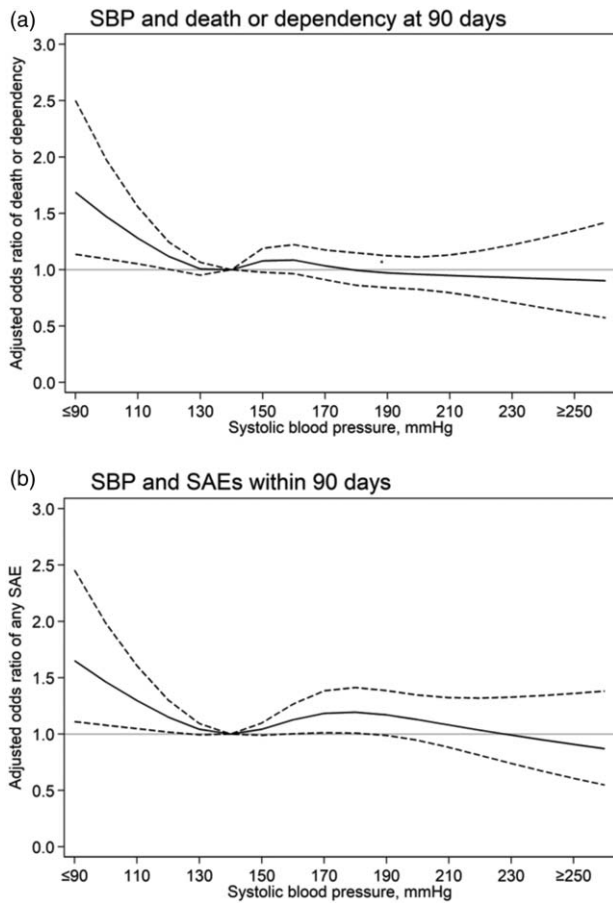


FIGURE 1 Restricted cubic spline of baseline SBP and clinical outcomes at 90 days. Generalized linear mixed models were used with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and potential baseline confounders of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale score, pathological stroke type, premorbid score 0–1 on the modified Rankin scale, aspirin/other antiplatelet treatment, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. (a) Spline fitted with five knots (percentiles 5th, 27.5th, 50th, 72.5th, 95th) for SBP; (b) Spline fitted with four knots (percentiles 5th, 35th, 65th, 95th) for SBP. Reference SBP 140 mmHg. Solid line indicates odds ratios; dotted line indicates 95% confidence intervals. SAE, serious adverse events.

FIGURE 2 Restricted cubic spline of baseline SBP and 90-day death or dependency, by stroke subtype. Generalized linear mixed model fitted were used with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and potential baseline confounders of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale score, pathological stroke type, premorbid score 0–1 on the modified Rankin scale, aspirin/other antiplatelet treatment, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. Splines fitted with five knots (percentiles 5th, 27.5th, 50th, 72.5th, 95th) for SBP. Reference SBP 140 mmHg. Solid line indicates odds ratios; dotted line indicates 95% confidence intervals. AIS, acute ischemic stroke; ICH, intracerebral hemorrhage.

Low DBP and clinical outcomes

A similar relationship applied for DBP, with odds of poor outcome increasing with DBP levels less than 90 mmHg, overall and in those with AIS and ICH (Figures e-2A, <http://links.lww.com/HJH/B455> and e-3, <http://links.lww.com/HJH/B455>). Similar associations were identified for low DBP and poor outcome, where patients with low DBP had an increased risk of death or dependency in the main analysis (adjusted OR 1.25, 95% CI 1.06–1.48), which was consistent after multiple imputation (adjusted OR 1.20, 95% CI 1.03–1.40) (Figure e-4, <http://links.lww.com/HJH/B455>). There was a nonlinear relationship between DBP and SAE (Figure e-2B, <http://links.lww.com/HJH/B455>), but this association was not significant when compared with a normal range (70–89 mmHg) of DBP (Figure e-1B, <http://links.lww.com/HJH/B455>).

Subgroup analysis

Heterogeneity was found in the association between low BP and outcome, comparing Asian ($n = 4947$) and non-Asian ($n = 4428$) patients, with the former having a significantly higher risk of poor outcome at 90 days (SBP, adjusted OR 1.53, 95% CI 1.11–2.11, Figure e-5, <http://links.lww.com/HJH/B455>; DBP, adjusted OR 1.38, 95% CI 1.05–1.81, Figure e-6, <http://links.lww.com/HJH/B455>). However, for non-Asian patients, high BP was associated with lower risk of poor outcome (SBP, adjusted OR 0.78, 95% CI 0.65–0.94, Figure e-5, <http://links.lww.com/HJH/B455>; DBP, adjusted OR 0.80, 95% CI 0.68–0.94, Figure e-6, <http://links.lww.com/HJH/B455>). No heterogeneity was found in subgroup analysis by use of intensive BP lowering during hospitalization, prior use of antihypertensive treatment, or randomized head positioning, and death or

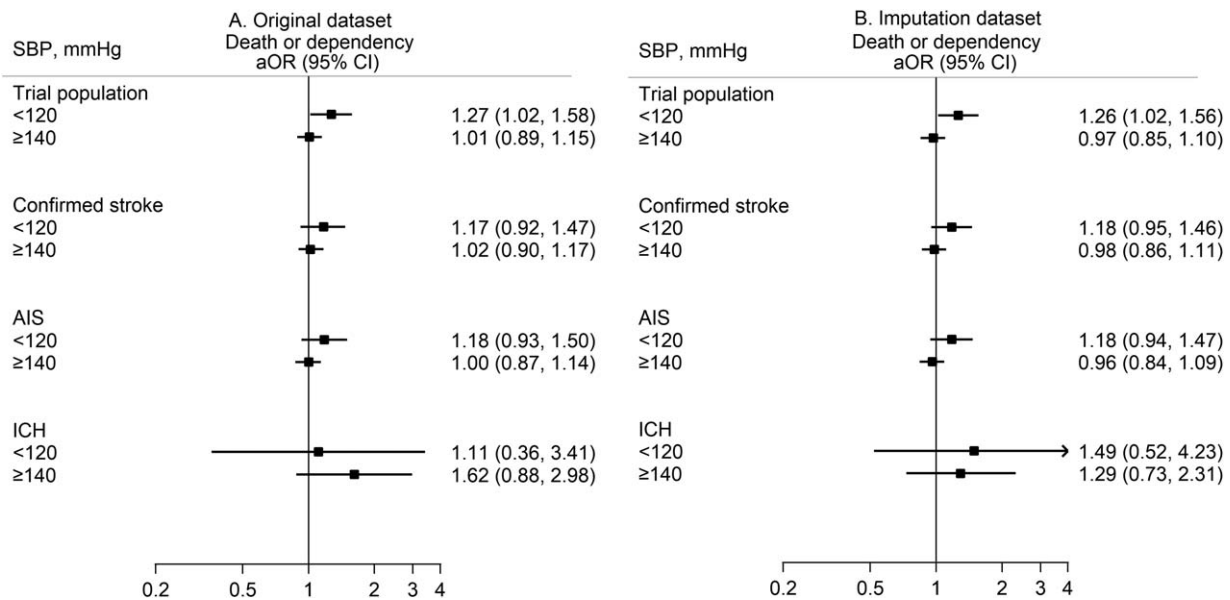


FIGURE 3 Association of categorical baseline SBP and 90-day death or dependency, by dataset. Generalized linear mixed model fitted were used with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and potential baseline confounders of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale score, pathological stroke type, premorbid score 0–1 on the modified Rankin scale, aspirin/other antiplatelet treatment, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. Reference SBP 120–139 mmHg. Boxes indicate point estimate of odds ratios, solid line indicates 95% confidence intervals. AIS, acute ischemic stroke; aOR, adjusted odds ratio; CI, confidence interval; ICH, intracerebral hemorrhage; OR, odds ratio.

dependency (Figures e-5, <http://links.lww.com/HJH/B455> and e-6, <http://links.lww.com/HJH/B455>).

DISCUSSION

In these secondary analyzes of a large and heterogenous international clinical cohort, low BP early after hospital presentation for acute stroke was associated with increased odds of poor clinical outcome after full adjustment for many potential confounding factors. The findings of consistency in the association for both SBP and DBP on functional recovery and cardiac SAEs, and being greater for AIS than ICH, provides support for the common concern for an interaction between low BP and cardiac and cerebral hypoperfusion and ischemia [1].

Most guidelines provide recommendations on the management of BP in AIS [20] and particularly ICH [20,21], principally as hypertension is a commonly observed phenomenon [22–24] with a well documented relation to increased adverse outcomes [25]. Although less frequently observed, low BP is also clearly not a benign phenomenon. Previous observational studies have found J-curve relationships between BP and adverse outcomes in relation to various heart diseases [26–28], and proposing ‘reverse causation’ as the basis for the progression of heart failure with premorbid comorbidities and frailty [29]. Similarly for stroke, one study has shown that low SBP (<120 mmHg) after recent AIS is related to increased recurrent stroke and vascular death [30], whereas another showed that diastolic hypotension increased the risks of death, myocardial

TABLE 2. Outcomes at 90 days by baseline SBP

Outcome	SBP (mmHg)			P value
	<120	120–139	≥140	
Death or dependency (mRS ^a 3–6)	296/669 ^b (44.2)	778/2084 ^b (37.3)	2746/6986 ^b (39.3)	0.0060
Disability (mRS ^a 3–5)	228/669 (34.1)	607/2084 (29.1)	2189/6986 ^b (31.3)	0.0349
Death	68/669 (8.7)	171/2084 (7.3)	557/6986 (7.2)	0.3308
SAE	138/795 ^c (17.4)	303/2393 ^c (12.7)	1098/7895 ^c (13.9)	0.0040
Recurrent stroke	43/795 (5.4)	104/2393 (4.4)	380/7895 (4.8)	0.4289
Cardiac or other vascular events	26/795 (3.3)	40/2393 (1.7)	169/7895 (2.1)	0.0247
Pneumonia	23/795 (2.9)	54/2393 (2.3)	215/7895 (2.7)	0.4103
Other infection	11/795 (1.8)	28/2393 (1.2)	79/7895 (1.0)	0.1326
Other SAE	28/795 (3.5)	60/2393 (2.5)	197/7895 (2.5)	0.2134

Data are n/N (%); P value from chi-squared test. mRS, modified Rankin scale; SAE, serious adverse event.
^aThe mRS represents a global, seven-level assessment of disability, in which scores of 0 or 1 indicate good function without or with symptoms but no disability, score of 2 indicates slight disability, scores of 3–5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death.
^bN is according to total number of patients at 90-day follow-up.
^cN is according to total number of patients randomized.

infarction [31], and recurrent vascular events including stroke [32]. There is a strong argument that a reduction in systematic BP may worsen cerebral ischemia in relation to altered cerebral autoregulation in the vulnerable penumbra region of AIS [33], whereas comorbidity and greater neurological severity in those presenting with hypotension, may partly explain the increase in SAEs shown in previous acute stroke trials [34]. Although low BP in frail older patients might be a harbinger of preterminal decline [35], we found the increased risk of adverse events in stroke patients with low BP persisted after adjustment for pre-morbid disability and comorbid heart disease.

Our study also found that the prognostic significance of low BP was modified by ethnicity, with Asian patients having a worse outcome irrespective of BP than non-Asians, who had a comparably lower odds of death or dependency from low BP. Although some studies have also shown poorer functional outcome in Asian compared with European stroke patients [36], there are limited data specifically pertaining to ethnicity and low BP. Yet, ethnic disparities in cardiovascular risk factor control, as well as acute stroke care, and regional differences in rehabilitation, might explain some of this variation [37].

In addition to the large sample size and systematic recording of outcomes, key strengths of our study were the steps taken to adjust for many potential confounding factors and to minimize potential reverse causation. Moreover, the generalizability of the results is enhanced by the use of broad inclusion criteria applied to AIS and ICH patients recruited in multiple countries. However, as the HeadPoST study was a pragmatic clinical trial focused on different head positions after stroke, there were limited in-hospital BP measures recorded for the study or these were measured BP according to local protocols, although any effect of BP misclassification would be to attenuate the strength of associations. In addition, we did not have data concerning dose of prior antihypertensive therapy nor use of other cardiac medications, although the frequency of hypertension and number of antihypertensive agents were greater in those patients presenting with elevated BP. Other limitations related to these being secondary analyses with relatively small number of patients in subgroups, variable cut-points to define BP categories, and missing or misclassification of confounding covariates.

In conclusion, our study has shown that low presenting BP, both SBP and DBP, are associated with poor outcome after acute stroke, even after taking account of these patients being a particularly high-risk group from having preexisting cardiac or cerebral cardiovascular comorbidity and dependency/frailty; and of the severity of neurological injury. As well as alerting clinicians to the care of these vulnerable patients, there may be merit in further studies being undertaken to better define the mechanisms of low BP on the cerebral circulation, and the most appropriate management strategies for low BP.

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undertook statistical analyses with assistance from L.B. and X.W. M.O. wrote the first draft of manuscript with input from C.S.A., T.R., and P.M.V. All authors commented upon and approved the final version of the manuscript for publication.

Conflicts of interest

P.M.V. reports grants from The George Institute for Global Health and Clínica Alemana de Santiago, during the conduct of the study; and research grants from CONICYT, outside the submitted work. P.M.L. reports grants from The George Institute for Global Health and Clínica Alemana de Santiago, during the conduct of the study; and non-financial support from Boehringer Ingelheim, grants and personal fees from Bayer and AstraZeneca, and grants from CONICYT, outside the submitted work. X.W. receiving National Heart Foundation (102117) and New South Wales Health grants. M.L.H. holds a National Health and Medical Research Council of Australia (NHMRC) Career Development Fellowship. V.V.O. reports grants from The George Institute for Global Health and Clínica Alemana de Santiago, during the conduct of the study; and research grants from Boehringer Ingelheim and CONICYT outside the submitted work. A.B. reports grants from Clínica Alemana de Santiago. S.M. was a member of the NHMRC Research Committee during 2015–2018. O.M.P.N. received grants for the Brazilian Stroke Research Network by DECIT/MS and CNPQ (402388/2013–5) for conduct this study. C.L.W. is a National Institute for Health Research (NIHR) Senior Investigator (Emeritus), and holds a number of grants from NIHR. The views expressed in this article are not necessarily those of the NIHR or the Department of Health and Social Care. T.G.R. is a National Institutes for Health Research (NIHR) Senior Investigator, whose views expressed in this article are his and not necessarily those of the NIHR or the Department of Health and Social Care. C.S.A. holds an NHMRC Senior Investigator Fellowship, and reports honoraria and travel reimbursement, and grants, from Takeda China. The other authors have no disclosures to report.

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