Relationship Between Hyperacute Blood Pressure and Outcome After Ischemic Stroke: Data From the VISTA Collaboration

Gillian M. Sare, Myzoon Ali, Ashfaq Shuaib, Philip M.W. Bath and for the VISTA Collaboration

The online version of this article, along with updated information and services, is
located on the World Wide Web at:
http://stroke.ahajournals.org/cgi/content/full/40/6/2098

Relationship Between Hyperacute Blood Pressure and Outcome After Ischemic Stroke
Data From the VISTA Collaboration

Gillian M. Sare, MRCP; Myzoon Ali, MRes; Ashfaq Shuaib, MD, FRCPC;
Philip M.W. Bath, MD, FRCP; for the VISTA Collaboration

Background and Purpose—High blood pressure (BP) is associated independently with poor outcome after acute ischemic stroke, although in most analyses "baseline" BP was measured 24 hours or more postictus, and not during the hyperacute period.

Methods—Analyses included 1722 patients in hyperacute trials (recruitment <8 hours) from the Virtual Stroke International Stroke Trial Archive (VISTA) Collaboration. Data on BP at enrolment and after 1, 2, 16, 24, 48, and 72 hours, neurological impairment at 7 days (NIHSS), and functional outcome at 90 days (modified Rankin scale) were assessed using logistic regression models, adjusted for confounding variables; results are for 10-mm Hg change in BP.

Results—Mean time to enrolment was 3.7 hours (range 1.0 to 7.9). High systolic BP (SBP) was significantly associated with increased neurological impairment (odds ratio, OR 1.06, 95% confidence interval, 95% CI 1.01 to 1.12), and poor functional outcome; odds ratios for both increased with later BP measurements made at up to 24 hours poststroke. Smaller (versus larger) declines in SBP over the first 24 hours were significantly associated with poor NIHSS scores (OR 1.16, 95% CI 1.05 to 1.27) and functional outcome (OR 1.23, 95% CI 1.13 to 1.34). A large variability in SBP was also associated with poor functional outcome.

Conclusions—High SBP and large variability in SBP in the hyperacute stages of ischemic stroke are associated with increased neurological impairment and poor functional outcome, as are small falls in SBP over the first 24 hours. (***Stroke***. 2009;40:2098-2103.)

Key Words: acute stroke ∎ hypertension ∎ ischemia ∎ outcome

High blood pressure (BP, systolic BP >140 mm Hg as defined by the World Health Organization) is present in approximately 80% of patients with acute ischemic stroke.[1] Multiple studies have shown that high BP is associated independently with poor outcome, including both early death, and late death/dependency.[1–3] Importantly, much of the work examining the relationship between BP and outcome involves the use of observational (nonrandomized) data from acute stroke trials, often with BP measured many hours after stroke onset.[1,2] For example, the first International Stroke Trial (IST) found a "U-shaped" relationship between systolic BP (measured, on average, 24 hours after stroke) and outcome in patients with ischemic stroke such that both high and low systolic BP (SBP) were associated independently with poor outcome.[1] Similarly, data from the Tinzaparin in Acute Ischemic Stroke Trial (TAIST) showed high baseline BP (average 24 hours) to be independently associated with poor outcome.[2]

In contrast, there are few data examining BP in the hyperacute stage of stroke. Analysis of the 303 placebo-treated patients in the ECASS I trial did not find a relationship between higher systolic BP (measured within 5 hours) and outcome; of note, patients with a BP >180/110 mm Hg were excluded from this trial.[3] Similarly, the initial BP measurement (within 6 hours) in placebo-controlled patients from the ECASS II trial was not independently associated with outcome; however, BP measurements made at subsequent time points were predictive of poor functional outcome.[4] Because BP falls naturally over the first week after stroke,[5,6] it is possible that the relationship between BP and outcome may be related to a failure for BP to fall naturally as well as its magnitude at onset. Other hemodynamic measures may also be related to outcome, including BP variability,[4,8,9] pulse pressure, mean arterial pressure, pulse pressure index, and rate pressure product.[2]

We examined the relationships between BP, variability in BP, change in BP over the first 24 hours, and other hemodynamic measures, all recorded in the hyperacute period, and early and late outcome in ischemic stroke, using data from the

© 2009 American Heart Association, Inc.

DOI: 10.1161/STROKEAHA.108.539155

Virtual Stroke International Stroke Trial Archive (VISTA) collaboration.[7]

Methods

Subjects

Data were obtained from patients with hyperacute ischemic stroke (<8 hours) who received placebo treatment in randomized trials from the VISTA collaboration.[7] VISTA is an academic collaboration that aims to aid the planning of clinical trials by collating and providing access to a rich resource of existing patient trial data to perform exploratory analyses. For reasons of confidentiality, the VISTA collaboration does not share information on the identity or number of the trials from which the data set derives (http://www.vista.gla.ac.uk/charter.aspx?sect=pub). Trials that have previously published similar analyses relating BP and outcome were excluded (eg, ECASS I, ECASS II[4,5]) to prevent inclusion bias. We identified placebo-treated patients from VISTA for whom rt-PA was not administered; where demographic data, blood pressure (BP), heart rate measures were available, within the first 10 days; and where impairment (NIH Stroke Scale [NIHSS]) or dependency (modified Rankin Scale [mRS]) information were available at up to 90 days postenrolment.

Hemodynamic Measurement

Systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) were measured in all patients at entry into the trial, and then at 1, 2, 16, 24, 48, and 72 hours. Hemodynamic derivatives of BP and HR were calculated as follows: pulse pressure (PP)=SBP−DBP; mean arterial pressure (MAP)=DBP+PP/3; pulse pressure index (PPI)=PP/MAP; and rate pressure product (RPP, a measure of cardiac workload)=SBP×HR.[8,9]

Change in SBP over the first 24 hours was calculated as SBP at time point−SBP at baseline. BP variability over 24 hours was assessed as the coefficient of variation in BP=SD in SBP/mean SBP, using BP data over the first 24 hours. Similar calculations were performed for variation in SBP over 72 hours, and DBP over both 24 and 72 hours.

Outcome Measurements

Neurological impairment was measured in all subjects at 7 days using the NIHSS. Functional outcome was assessed using the mRS at 90 days. Outcomes were divided into a dichotomous scale, poor versus good outcome; NIHSS scale was divided at its median score, and mRS was divided with scores of 3 to 6 indicating poor outcome, and ≤2 good outcome.

Statistical Methods

The relationship between hemodynamic measures and outcomes were assessed using unadjusted (*t* test) and adjusted (logistic regression) models; adjustments were performed using prognostic and other clinically relevant variables at baseline: age, sex, NIHSS, time from stroke to treatment, history of hypertension, and use of antihypertensive treatment within 7 days of stroke. Relationships involving change in SBP were additionally adjusted for baseline SBP. Odds ratios (OR) refer to a change in BP by 10 mm Hg. Significance was taken at $P<0.05$, and standard deviations or 95% confidence intervals (95% CI) are given. No adjustment for multiple comparisons. All analyses were performed using SPSS (version 11.0 for Mac).

Results

Subjects

The data set included 1722 patients randomized to placebo treatment in hyperacute trials of ischemic stroke from the VISTA collaboration. Baseline characteristics of the patients are shown in Table 1. The mean time from stroke onset to enrolment was 3.7 hours (range 1.0 to 7.9) so that BP

Table 1. Baseline Characteristics for 1722 Patients Included in Analysis

Characteristic	No. (%)/Mean (SD)
Age, y	68.9 (12.1)
Male sex	863 (50.1)
History of hypertension	1,260 (73.2)
History of diabetes	431 (25.0)
Previous stroke	384 (22.3)
Previous TIA	182 (10.6)
History of CHF	181 (10.5)
Atrial fibrillation	471 (27.4)
Time from onset to enrolment, hours	3.7 (1.2)
rt-PA treatment	0 (0)
Baseline NIHSS, median and IQR	11 (8–17)
Baseline systolic BP, mm Hg	154.1 (26.4)
Baseline diastolic BP, mm Hg	83.8 (16.0)
Poor early outcome, NIHSS>median day 7	867 (50.3)
Poor late outcome, mRS 3–6 day 90	994 (57.7)

TIA indicates transient ischemic attack; CHF, congestive cardiac failure; IQR, interquartile range; BP, blood pressure.

measurements at 24 hours occurred approximately 28 hours postictus. Mean baseline SBP 154.1 mm Hg (SD 26.4, range 86 to 250 mm Hg) and DBP 83.8 mm Hg (SD 16.0, range 38 to 180 mm Hg). BP fell significantly over the first 24 hours: SBP mean fall 5.1 mm Hg (SD 24.6 mm Hg, $P<0.0001$); DBP mean fall 3.2 mm Hg (SD 15.7 mm Hg, $P<0.0001$; Figure 1). The baseline median NIHSS at baseline was 11 (interquartile range, IQR 8 to 17); this improved over the first 7 days to 7 (IQR 3 to 15); hence, a "poor" NIHSS at day 7 was defined as NIHSS >7.

Blood Pressure and Other Hemodynamic Variables

Mean hemodynamic measurements and unadjusted and adjusted OR and 95% CI are shown in Tables 2 (baseline) and 3 (24 hours). The relationship between SBP, DBP, and RPP and poor early and late outcome over time are shown in Figure 2. High SBP at baseline was significantly associated with increased impairment at day 7, and the point estimates increased with subsequent measurements up to 24 hours. A similar pattern was seen with SBP and poor functional
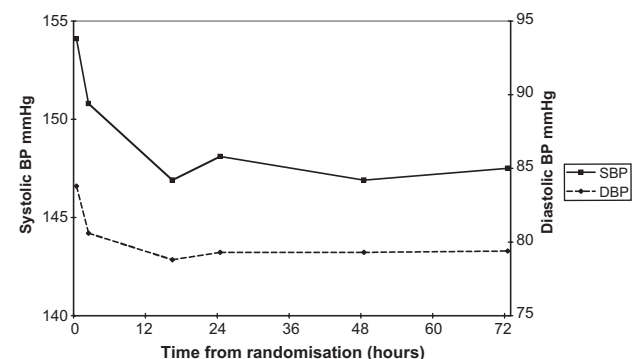
Figure 1. Systolic and diastolic blood pressure profiles over the first 72 hours after entry into the trials.

Table 2.   Hemodynamic Measures at Baseline and Odds of Impairment (NIH Stroke Scale, NIHSS) at Day 7, and Death or Dependency (Modified Rankin Scale, mRS) at Day 90

Hemodynamic Measure	Mean (SD) Poor Outcome	Mean (SD) Good Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Impairment (day 7, NIHSS>median)				
Systolic BP	155.4 (27.2)	152.9 (25.7)	1.04 (1.00–1.07)	**1.06 (1.01–1.12)**
Diastolic BP	83.9 (16.9)	83.6 (15.1)	1.01 (0.95–1.07)	**1.10 (1.01–1.22)**
Mean arterial pressure	107.7 (17.9)	106.7 (16.6)	1.03 (0.98–1.09)	**1.12 (1.02–1.22)**
Pulse pressure	71.4 (22.9)	69.3 (21.1)	**1.05 (1.00–1.09)**	1.03 (0.96–1.12)
Rate pressure product	236.0 (31.4)	231.6 (33.6)	**1.04 (1.01–1.07)**	1.04 (0.99–1.09)
Death or dependency (day 90, mRS 3–6)				
Systolic BP	156.1 (26.3)	151.7 (26.2)	1.06 (1.03–1.11)	1.05 (0.99–1.12)
Diastolic BP	84.1 (16.5)	83.6 (15.2)	1.02 (0.96–1.08)	1.09 (1.00–1.20)
Mean arterial pressure	108.1 (17.4)	106.3 (16.9)	1.06 (1.00–1.12)	**1.09 (1.00–1.19)**
Pulse pressure	72.0 (22.4)	68.1 (21.1)	1.08 (1.04–1.014)	1.02 (0.95–0.1.09)
Rate pressure product	236.5 (33.1)	230.0 (31.2)	1.06 (1.03–1.09)	**1.05 (1.00–1.10)**

Odds ratios per 10-mm Hg change in blood pressure.
Adjusted for age, sex, time to enrollment, baseline NIHSS, history of hypertension, use of antihypertensive treatment in the first 7 days. Bold results $P=<0.05$.

outcome at day 90. DBP was not consistently associated with NIHSS score or functional outcome over the measurement time period and was generally lower in patients who proceeded to have a poor outcome. MAP, PP, and RPP (Figure 2) followed a similar pattern to SBP.

Blood Pressure Variability
Increased SBP variability over 24 hours (OR 0.01, 95% CI 0.00 to 0.36, $P=0.01$) was significantly associated with poor late functional outcome after adjustment. In contrast, SBP variability was not significantly associated with early impairment (OR 0.03, 95% CI 0.00 to 1.91, $P=0.10$); DBP variability was not related to either early NIHSS score or late functional outcome.

Change in Systolic Blood Pressure
Early Impairment
Increased impairment (NIHSS >7) at day 7 was significantly associated with the change in SBP over the first 24 hours (OR 1.16, 95% CI 1.05 to 1.27). Patients with a high NIHSS score (poor early outcome) at day 7 had a mean change in SBP of -4.0 mm Hg (SD 24.8), whereas those with a lower score had a larger change in SBP of -8.2 mm Hg (SD 24.6; $P=0.01$, t test).

Late Functional Outcome
Similarly, the change in SBP by 24 hours was also significantly associated with a poor late functional outcome after adjustment (OR 1.23, 95% CI 1.13 to 1.34); patients with a poor late outcome had a mean change in SBP of -4.8 mm Hg

Table 3.   Hemodynamic Measures at 24 Hours and Odds of Impairment (NIH Stroke Scale, NIHSS) at Day 7, and Death or Dependency (Modified Rankin Scale, mRS) at Day 90

Hemodynamic Measure	Mean (SD) Poor Outcome	Mean (SD) Good Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Poor early NIHSS score (day 7 >median)				
Systolic BP	151.3 (25.8)	145.8 (22.6)	**1.10 (1.05–1.15)**	**1.17 (1.08–1.27)**
Diastolic BP	78.9 (15.9)	79.7 (14.5)	0.96 (0.90–1.04)	1.13 (1.00–1.26)
Mean arterial pressure	103.0 (16.9)	101.7 (15.4)	1.05 (0.98–1.13)	**1.19 (1.07–1.34)**
Pulse pressure	72.4 (21.9)	66.1 (18.1)	**1.17 (1.10–1.24)**	**1.18 (1.06–1.30)**
Rate pressure product	230.9 (32.9)	220.2 (27.8)	**1.13 (1.08–1.17)**	**1.16 (1.08–1.24)**
Poor late outcome (mRS day 90 3–6)				
Systolic BP	151.5 (54.9)	143.9 (22.5)	1.14 (1.09–1.19)	**1.17 (1.07–1.27)**
Diastolic BP	79.3 (15.9)	79.6 (14.1)	0.99 (0.92–1.06)	**1.17 (1.04–1.32)**
Mean arterial pressure	103.4 (16.7)	101.1 (15.1)	1.09 (1.02–1.17)	**1.24 (1.10–1.38)**
Pulse pressure	70.6 (19.5)	64.3 (18.0)	1.021 (1.015–1.31)	**1.18 (1.07–1.31)**
Rate pressure product	230.1 (31.7)	218.1 (27.6)	1.15 (1.10–1.019)	**1.18 (1.10–1.27)**

Odds ratios per 10-mm Hg change in blood pressure.
Adjusted for age, sex, time to enrollment, baseline NIHSS, history of hypertension, antihypertensive treatment in the first 7 days. Bold results $P=<0.05$.
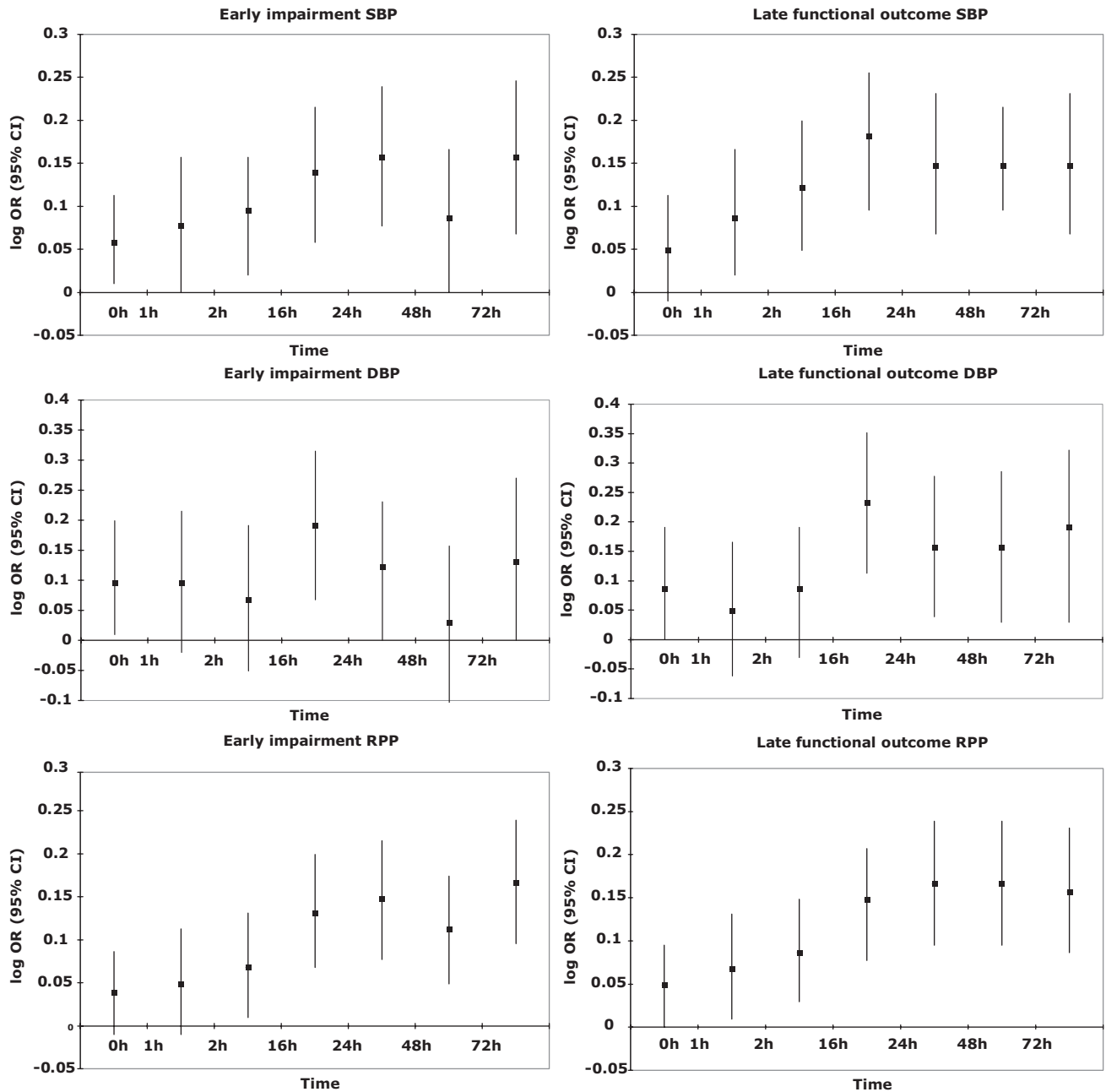
Figure 2. Figure showing log odds ratios (OR) at measurement time points with 95% confidence intervals (CI) for systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate pressure product (RPP). Values >0 represent an increased risk of early neurological impairment (NIHSS >7 at 7 days) or poor late functional outcome (mRS ≥3 at 90 days).

(SD 24.4), whereas those with a good late outcome had a higher mean change in SBP −8.5 mm Hg (SD 25.1; P=0.02, t test).

The proportions of patients with poor early NIHSS scores, or late functional outcome, by different categories of absolute change in SBP are shown in Figure 3. Patients with a very large fall (>75 mm Hg) or a large rise in (>25 mm Hg) in SBP appeared to have a worse outcome than those with a moderate fall; however, the small number of patients with large changes in SBP means the confidence intervals wide are wide.

The Effect of Antihypertensive Medication
532 (31%) patients received antihypertensive intervention during the first 7 days after enrolment and these had a higher BP at baseline: 159.8 (25.8) mm Hg versus 154.6

(26.7) mm Hg (P=0.001). By 72 hours, there was no difference in SBP: 149.6 (21.1) mm Hg versus 151.9 (24.3) mm Hg (P=0.17). Information on the specific agent and timing of administration were not available.

The use of antihypertensive therapy was associated, in an unadjusted model, with a significantly reduced risk of high NIHSS score at day 7 (OR 0.76, 95% CI 0.59 to 0.97); there was no significant relationship with functional outcome at day 90 (OR 0.87, 95% CI 0.68 to 1.12). After adjustment for important covariates, neither outcome was significantly associated with use of antihypertensive treatment during the first 7 days (poor NIHSS score OR 0.84, 95% CI 0.61 to 1.15; poor functional outcome OR 1.04, 95% CI 0.77 to 1.42).
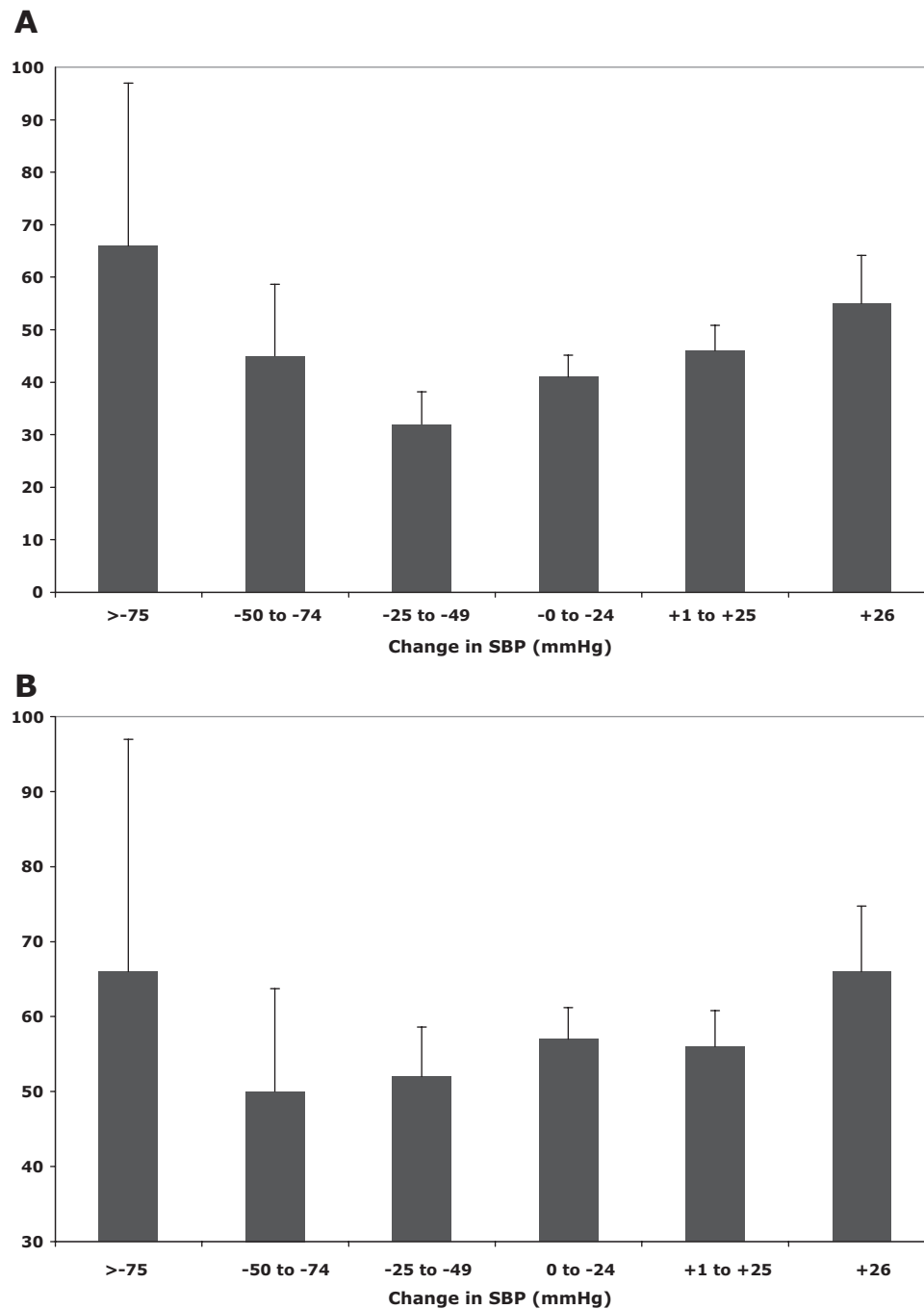
A

B

Figure 3. Histogram showing the proportion (as percentage and 95% CI) of patients with (A) early neurological impairment (NIHSS score >7 at 7 days) and (B) poor late functional outcome (mRS ≥3 at 90 days), by absolute change in systolic blood pressure in the first 24 hours.

Discussion

This analysis of the VISTA database demonstrates that elevations in systolic blood pressure, mean arterial pressure, pulse pressure, and rate-pressure product are each associated with poor outcome in patients with hyperacute ischemic stroke. These findings support earlier studies where BP measurements were measured at an average of 24 hours after stroke onset.[1,2] A new finding is that the strength of these associations appears to increase over the first 24 hours of the acute stroke phase. Higher DBP was not related to poor outcome, an unsurprising finding because DBP is less rele-

vant clinically in older patients. In addition to these conventional hemodynamic measures, the magnitude of change in BP during the first day after stroke onset was also significantly associated with poor early NIHSS score and late functional outcome. In particular, patients having large falls in BP (>75 mm Hg) or rises (>25 mm Hg) in the first 24 hours appeared to have the highest risk of a poor outcome, a finding also seen in the Blood pressure in Acute Stroke Collaboration[10] (Bath P, personal communication).

BP is elevated poststroke in the majority of patients.[1] The present analysis suggests that the strong association between

baseline BP and outcome[1,2] reflects both the level of BP and its rate of fall. Patients in this analysis were not markedly hypertensive at baseline (mean SBP was 154 mm Hg), revealing that the failure of BP to fall naturally may be present in patients with mild as well severe hypertension.

The mechanisms which determine how and when BP falls during the acute phase are unclear but are likely to relate, at least in part, to the cause(s) for the initial rise in BP. Transient causes of hypertension such as the stress of hospitalization and pain (eg, urinary tract)[11] presumably allow high BP to resolve quickly in parallel with the stimulus; in contrast, those causes which are sustained over several days, such as the Cushing reflex which follows intracranial hypertension secondary to cerebral edema, will drive BP to stay elevated for many hours or days.

This analysis also found a significant association between SBP variability and poor late functional outcome, a finding that supports, using a much larger dataset, earlier studies.[3,12,13] Cerebral autoregulation is dysfunctional in acute stroke so cerebral perfusion could become dependent on BP. Interestingly, static changes in BP (such as those seen with antihypertensive induced reductions) may have less effect on cerebral perfusion than dynamic changes.[14]

Possible mechanisms for the independent association between high BP and poor outcome in ischemic stroke include increased recurrence and cerebral edema[1,3]; although animal models have shown an increased risk of hemorrhagic transformation with hypertension,[13–15] this has not been shown in humans in the absence of thrombolysis.[1,16] These relationships, and the finding that a slow reduction in raised BP is also associated with a poor outcome, suggest that trials of BP lowering need to test a wide time-window, both hyperacutely to assess potential effects on the index stroke and its penumbra, and later during the acute phase to determine effects on the rate of fall in BP, variability in BP, stroke recurrence and the development of cerebral edema.

This analysis has several caveats and limitations. First, the data are taken from placebo-treated patients in various hyperacute stroke trials; performing "observational" analysis on data from randomized controlled trials has the disadvantage that patients are selected according to predefined inclusion criteria, thus the results might not be applicable to a more unselected population of patients. Because the VISTA collaboration does not share the identity of the trials,[7] we cannot be certain what particular inclusion criteria were used to select patients. However, the heterogeneity between trials in the inclusion/exclusion means the results are more likely to have external validity. Second, this analysis is tertiary (retrospective), although the data were collected prospectively from high-fidelity trials. Third, a substantial number of patients received nonrandomized antihypertensive medication in the first 7 days after enrolment. Treated patients were more likely to be hypertensive at baseline than those not so treated. Fourth, the methodology for measuring BP is not available. Finally, the data set lacks information on stroke subtype (anterior or posterior circulation; large or small vessel) and therefore lacks the sensitivity to detect whether individual subgroups respond differently to BP.

This analysis provides important novel information on the effect of raised BP in the hyperacute phase of stroke on outcome.

High BP, other hemodynamic variables, increased variability in BP, and failure for BP to fall rapidly were each related to poor outcome. Ongoing randomized trials into the effect of antihypertensive treatment in acute stroke (ENOS,[15] INTERACT, and SCAST) may help to answer questions about the timing of intervention and the magnitude of BP reduction.

References

1. 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.
2. Sprigg N, Gray LJ, Bath PMW, Boysen G, De Deyn PP, Friis P, Leys D, Marttila R, Olsson J-E, O'Neill D, Ringlestein B, van der Sande J-J, Lindenstrom E, for the TAIST investigators. Relationship between outcome and baseline blood pressure and other haemodynamic measures in acute ischaemic stroke: Data from the TAIST trial. *J Hypertens*. 2006;24:1413–1417.
3. 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.
4. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. *Stroke*. 2008;39:366–372.
5. Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. *Stroke*. 1986;17:861–864.
6. Wallace JD, Levy LL. Blood pressure after stroke. *JAMA*. 1981;246:2177–2180.
7. Ali M, Bath PM, Curram J, Davis SM, Diener HC, Donnan GA, Fisher M, Gregson BA, Grotta J, Hacke W, Hennerici MG, Hommel M, Kaste M, Marler JR, Sacco RL, Teal P, Wahlgren NG, Warach S, Weir CJ, Lees KR. The virtual international stroke trials archive. *Stroke*. 2007;38:1905–1910.
8. *Textbook of Hypertension*. Oxford: Blackwell Scientific Press; 1994.
9. Rashid P, Weaver C, Leonardi-Bee JA, Fletcher S, Bath FJ, Bath PMW. The effects of transdermal glyceryl trinitrate, a nitric oxide donor on blood pressure, cerebral and cardiac haemodynamics and plasma nitric oxide levels in acute stroke. *J Stroke Cerebrovasc Dis*. 2003;13:143–151.
10. Blood pressure in Acute Stroke Collaboration. The effect of vasoactive drugs on blood pressure and outcome in acute stroke (Cochrane review). Oxford: Update Software; 2001.
11. Carlberg B, Asplund K, Hagg E. Factors influencing admission blood pressure levels in patients with acute stroke. *Stroke*. 1991;4:527–530.
12. Dawson DA. Nitric oxide and focal cerebral ischemia: Multiplicity of actions and diverse outcome. *Cerebrovasc Brain Metab Rev*. 1994;6:299–324.
13. 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.
14. Dawson SL, Blake MJ, Panerai RB, Potter JF. Dynamic but not static cerebral autoregulation is impaired in acute ischaemic stroke. *Cerebrovasc Dis*. 2000;10:126–132.
15. The ENOS Trial Investigators. Glyceryl trinitrate vs control, and continuing vs stopping temporarily prior antihypertensive therapy, in acute stroke: rationale and design of the efficacy of nitric oxide in stroke (ENOS) trial (ISRCTN99414122). *Int J Stroke*. 2006;1:245–249.
16. Sare GM, Bath PM, Gray LJ, Moulin T, Woimant F, England T, Geeganage C, Christensen H, De Deyn PP, Leys D, O'Neil D, Ringlestein EB; for the TAIST Investigators. The relationship between baseline blood pressure and computed tomography findings in acute stroke: data from the tinzaparin in acute ischaemic stroke trial (TAIST). *Stroke*. 2009;40:41–46.