Relationship Between Therapeutic Changes in Blood Pressure and Outcomes in Acute Stroke
A Metaregression

Chamila M. Geeganage, Philip M.W. Bath

Abstract—Both low and high blood pressures (BPs) during the acute phase of stroke are associated independently with a poor outcome. Several small clinical trials have involved the alteration of BP, and this study assessed the relationship between change in BP and functional outcome. Randomized, controlled trials of interventions that would be expected, on pharmacological grounds, to alter BP in patients within 1 week of the onset of acute ischemic or hemorrhagic stroke were sought using electronic searches. Data were collected on BP and clinical outcome. The relationship between the differences in on-treatment BP and odds ratios for outcomes was assessed using meta-regression. Thirty-seven trials involving 9008 patients were included. A U- or J-shaped relationship was found among on-treatment BP difference and early death, death at the end of 90-day follow-up, and combined death or dependency at the end of follow-up. Although outcomes were not significantly reduced at any level of change in BP, the lowest odds occurred at the following times: early death (odds ratio: 0.87; 95% CI: 0.54 to 1.23), 8.1 mm Hg; death at the end of follow-up (odds-ratio: 0.96; 95% CI: 0.31 to 1.65), 14.4 mm Hg; and combined death or dependency at the end of follow-up (odds ratio: 0.95; 95% CI: 0.11 to 1.72), 14.6 mm Hg. Although large falls or increases in BP are associated with a worse outcome, modest reductions may reduce death and combine death or dependency, although the CIs are wide and compatible with an overall benefit or hazard. (Hypertension. 2009;54:775-781.)

Key Words: acute stroke ■ blood pressure ■ metaregression ■ randomized, controlled trial

Both acute ischemic stroke and primary intracerebral hemorrhage are associated with high blood pressure (BP) in ≥75% of patients.1,2 BP falls spontaneously in most patients over the first week, although a third of patients remain with an elevated BP.3-5 The mechanisms underlying hypertension in stroke are complex, but preexisting hypertension (present in 50% to 60% of patients), hospitalization stress, activation of the neuroendocrine pathways, and the Cushing reflex each contribute.5

Several studies have identified a “U-shaped” relationship such that both low and high BPs are associated independently with increased early death and later death or dependency.6-8 A high BP is also associated with increased early recurrence.6-9 In ischemic stroke, high BP also appears to adversely affect outcome by increasing the risk of cerebral edema but not hemorrhagic transformation.6 Hematoma expansion is related to high BP in patients with primary intracerebral hemorrhage, although this relationship may be confounded by stroke severity and time to presentation.10

Although debated >22 years ago, it still remains unclear whether high BP should or should not be treated acutely after stroke.11,12 Recent guidelines recommend that acute lowering of BP should be delayed for several days or even weeks unless other life-threatening conditions are present (eg, hypertensive encephalopathy, aortic dissection, cardiac ischemia, pulmonary edema, or acute renal failure).13-16 Unfortunately, these guidelines are inconsistent and are based on theoretical arguments and individual case reports and not on the results of systematic overviews or large intervention trials of BP manipulation in acute stroke.

Low BP is not common in acute stroke but it, like high BP, is associated with a poor outcome.6 Possible reasons for low BP include hypovolemia, sepsis, impaired cardiac output secondary to cardiac failure, arrhythmias or cardiac ischemia, and aortic dissection.17 Guidelines recommend that causes of hypotension in the setting of acute stroke should be sought with the view to correcting reversible causes, such as hypovolemia and cardiac arrhythmias.15

This systematic review assessed the relationship between drug-induced BP changes after stroke and subsequent clinical outcomes and used data from existing randomized, controlled trials and the technique of metaregression. Implicit in the review is the hypothesis that BP changes, whether positive or negative, may drive outcome after stroke.
Methods

Types of Studies
Included studies were composed of published and unpublished randomized, controlled trials in acute ischemic stroke or acute primary intracerebral hemorrhage of drugs that had the potential for altering BP. Therapy had to be initiated within 1 week of stroke onset. Uncontrolled studies, confounded trials (where interventions were compared with each other rather than control/placebo), studies of patients with subarachnoid hemorrhage, and studies where BP or clinical outcome data were unobtainable were excluded.

Type of Participants
Adults (age ≥18 years) of either sex with acute ischemic or hemorrhagic stroke who were eligible for randomization to either active treatment or placebo/open control were included.

Study Search
The Cochrane Library (issue 2, 2008), Medline (1966 to January 2009), EMBASE (1980 to January 2009), and Science Citation Index (ISI Web of Science, 1981 to January 2009) were searched. No language restrictions were applied. The search strategy for Medline, EMBASE, and Science Citation Index are detailed in the online Data Supplement (please see http://hyper.ahajournals.org). Trials were also identified from reference lists of relevant trial publications and existing review articles, including earlier reviews from the Blood Pressure in Acute Stroke Collaboration.18,19

Data Collection
Early (within 1 month) and end-of-trial mortality, end-of-trial death or dependency, and baseline and on-treatment systolic BPs in active and control groups were collected. Disability and dependency were defined as a Barthel Index 0 to 55 or Rankin score 3 to 5. Information on the methods of randomization, concealment of allocation, blinding, analysis (intention-to-treat or efficacy analysis), stroke type (ischemic or hemorrhage), drug dose, route of administration (oral, transdermal, or intravenous) and timing, and measurement of BP and primary outcome were all collected. The methodologic quality of trials was also assessed. In instances where BP or outcome data were unavailable in the trial publications, authors and principle investigators were also contacted to obtain relevant data. Otherwise, BP data were obtained by enlarging published graphs and measuring data using a “screen grab” program (Mac Grab).

Data Analysis
Odds ratios (ORs) and 95% CIs were calculated with random-effects models for clinical outcomes using RevMan version 5 for Macintosh. Random-effects models were used because biological heterogeneity was expected among the trials, taking into account different trial protocols, including different vasoactive drugs and classes, time to and length of treatment, functional outcome measures, and type of stroke (ischemic or hemorrhagic). Heterogeneity was calculated using the Q-squared test and the I² statistic. This approach is recommended by the Cochrane collaboration and is the one that we use routinely in meta-analysis.20 Odds ratios <1 indicate a beneficial effect, whereas those >1 indicate a detrimental effect of the intervention. On-treatment systolic BP (SBP) differences were calculated as the difference between the treatment groups; negative values indicate that BP was higher in the control group. A scatter plot between each clinical outcome and on-treatment BP differences was drawn using Stata 10 for Mac (Stata Corp); metaregression lines were then plotted with 95% CIs to assess the relationship between BP and clinical outcome. Sensitivity analyses were performed in subgroups of studies by time to recruitment: ≤24 hours or >24 hours; baseline SBP: <160 mm Hg or ≥180 mm Hg; and length of treatment: ≤14 days or ≤28 days. Egger test and Beggs funnel plot were performed to assess any publication bias in included trials.21,22

Results
Thirty-seven trials involving 9008 patients were included (4705 active and 4303 control patients; Figure 1). The patients receiving placebo or control treatment in 8 trials acted as controls for >1 group of actively treated patients explaining the difference in patient numbers in the groups; control subjects in these studies were divided equally between each active treatment group to avoid artificially inflating patient numbers and narrowing CIs artificially (Table S1 in the online Data Supplement). A total of 86 studies were excluded (Table S2). Patients were recruited into trials within 6 to 120 hours from stroke onset; most were enrolled within 24 to 168 hours (Table S1). The treatment duration varied from 24 hours to 9 months (Table S1).

Thirteen drug classes were studied: angiotensin-converting enzyme inhibitors (lisinopril); angiotensin receptor antagonists (candesartan); β-receptor antagonists (atenolol, labetalol, and propranolol); calcium channel blockers (flunarizine, isradipine, nicardipine, and nimodipine); basic fibroblast growth factor (fiblast) hemoglobin analogues; magnesium sulfate; naftidrofuryl; NO donors (glyceryl trinitrate); piracetam; prostacyclin; phenylephrine; and mixed/“usual” antihypertensive therapy (Table S1). Of these, β-receptor antagonists, calcium channel blockers (PO), NO donors, and prostacyclin significantly reduced SBP, and basic fibroblast growth factor (fiblast) hemoglobin analogue and phenylephrine increased it (Figure S3). Some drugs were given in 2 phases, initially intravenously and then orally (calcium channel blocker, naftidrofuryl, and piracetam).

When assessing different drug classes, β-receptor antagonist and basic fibroblast growth factor (fiblast) hemoglobin analogue showed a tendency for adverse outcomes, whereas candesartan showed a favorable trend toward mortality at the end of follow-up (Figures 2, S1, and S2). Other drug classes showed no significant effect on clinical outcomes, whether assessed as death or as combined death or dependency.

U- and J-shaped relationships were observed between on-treatment BP difference and early death (<1 month), mortality at the end of 90-day follow-up, and combined death or dependency at the end of follow-up (Figures 3 through 5). The lowest odds of early death (ie, best treatment effect; OR: 0.87; 95% CI: 0.54 to 1.23) occurred at on-treatment BP
Figure 2. Death or dependency by class of vaso-active drug.
difference of 8.1 mm Hg (Figure 3). Similarly, the lowest odds for death at the end of follow-up (OR: 0.96; 95% CI: 0.31 to 1.65) was present at a BP difference of 14.4 mm Hg (Figure 4). The lowest odds for combined death and dependency at the end of follow-up (OR: 0.95; 95% CI: 0.11 to 1.72) occurred at a BP difference of 14.6 mm Hg (Figure 5). Increases or large falls in BP in the active group were associated with poor outcomes, whether assessed as death or combined death or dependency (Figures 3 through 5); in the case of vasopressor effects, the increases in death and combined death or dependency were significant. When early mortality was analyzed by time to recruitment (Table), <24-hour (12 data sets) and <48-hour (24 data sets) ORs were 0.69 (95% CI: 0.14 to 1.24) and 0.94 (95% CI: 0.50 to 1.39). There were insufficient data sets to analyze shorter times of <6 hours (4 data sets) and <12 hours (9 data sets).

When data were analyzed by baseline SBP (<160 mm Hg and <180 mm Hg), there was no statistical association between early death and baseline SBP (Table). Analysis of data by treatment duration showed treatment <14 days associated significantly with early mortality (Table). There was no evidence of publication bias using the Egger test (P for bias=0.13), and there was no asymmetry on visual inspection of the Begg funnel plot (plot not shown).
Discussion

Individual trials involving the alteration of BP have varied in their findings on the effect of treatment on outcome. Treatment with antihypertensive agents, eg, angiotensin receptor antagonists and angiotensin-converting enzyme inhibitors, in small studies has been associated with reduced recurrent vascular events (angiotensin receptor antagonists) or death (angiotensin-converting enzyme inhibitors), although these findings need confirmation in larger trials.23,24 Conversely, a trial of DCLHb was associated with an increase in BP and a worse outcome25; similarly, some trials where BP was lowered have also found a worse outcome, as seen with calcium channel blockers and β-receptor antagonists.26,27 However, most trials were neutral reflecting, in part, that many were too small to reliably detect effects on outcome. As a result, integration of the existing data using meta-analysis and meta-regression techniques is necessary to provide a sufficient sample size for further analysis.

The present study covered 13 drug classes and included 37 trials involving 9008 patients with acute stroke. For each of early death, end-of-trial death, and end-of-trial death or dependency, a U- or J-shaped curve was present for the relationship between outcome and SBP. Both large reductions and any increase in BP were associated with a worse outcome. The nadir of these curves, where active BP lowering might improve outcome, had reductions in SBP ranging between 8.1 mm Hg (early death) and 14.4 mm Hg (end-of-trial death), with combined death and dependency at 14.6 mm Hg. However, in no case was outcome significantly improved (the 95% CIs for ORs all included 1), and these

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N indicates No. of data sets.
*Data have no U- or J-shaped curve.
†Data are significant results.
modest reductions in BP might either be beneficial (≥40% reduction in poor outcome) or hazardous (≥30% increase in poor outcome). With respect to vasopressor effects, significant elevations in SBP were associated with significant increases in death and combined death or dependency. These data support the rationale for several ongoing large, randomized, controlled trials of lowering BP in stroke, including the Efficacy of Nitric Oxide in Stroke Trial, Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial 2, and Scandinavian Candesartan Acute Stroke Trial.28–30

These findings are subject to several caveats. First, the BP data relate to a comparison of on-treatment measurements and are not adjusted for baseline values. Several trials had mismatching of baseline BP such that a comparison of on-treatment BP in these appears to suggest that vasodepressing drugs actually increased BP, as is evident in the graphs for some trials of the ß-receptor antagonists, calcium channel blockers, and nitrates.27,31–34 Unfortunately, baseline BP was not available for some trials, so it was not possible to correct on-treatment values for those at baseline. Second, the on-treatment BP differences are not adjusted for other baseline prognostic factors, such as age, stroke severity, and type of stroke. Baseline imbalances in these would have profound effects on outcome and, therefore, change the BP-outcome relationship.27,31,34–36 Third, individual patient data were not available; the presence of this would have addressed the first 2 issues. Fourth, although we performed a comprehensive search for trials where BP changes may have occurred, it is conceivable that some studies will have been missed, especially trials where there was no intention to change BP. Last, 86 identified trials had to be excluded because they did not publish data for on-treatment BP and/or outcome (Table S2).

Although SBP was not adjusted for baseline BP, sensitivity analysis showed no significant association between baseline SBP and outcome (Table). Similarly, variations in treatment duration were assessed, and the results suggest that short-term treatment (<2 weeks) might reduce early mortality; this supports the rationale for shorter treatment durations in several ongoing large, randomized, controlled trials of lowering BP in acute stroke. Additional BP lowering treatment might be more efficiently started very soon after the stroke (eg, within 6 to 12 hours of onset). Unfortunately there were insufficient data to analyze treatment effects in the hyperacute phase (<6 hours).

Perspectives
Although large falls or increases in BP were associated with a worse outcome, modest reductions might be associated with improved outcome, although the CIs were wide and compatible with benefit or hazard. Ongoing large trials, such as Efficacy of Nitric Oxide in Stroke Trial, Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial 2, and Scandinavian Candesartan Acute Stroke Trial, will be able to address this issue.28–30

Disclosures
We were involved with 3 completed trials that were included in this analysis.31,37,38 P.B. is the Stroke Association Professor of Stroke Medicine.

References


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ONLINE SUPPLEMENT

MANUSCRIPT TITLE
RELATIONSHIP BETWEEN THERAPEUTIC CHANGES IN BLOOD PRESSURE AND OUTCOMES IN ACUTE STROKE: A META-REGRESSION

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SHORT TITLE
BLOOD PRESSURE IN ACUTE STROKE

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SEARCH STRATEGY

MEDLINE search strategy

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EMBASE search strategy

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Science Citation Index search strategy

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112. diaspiron cross linked haemoglobin or DCLHb.TI.
113. 100 AND/OR 3, 4, 9, 16
114. cerebral blood flow.TI/TW
115. autoregulation.TI.
116. stroke outcome.TI.
117. 101-112 AND/OR 1-4
118. 101-112 AND/OR 12-16
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<th>Trial</th>
<th>Size A/C</th>
<th>Male %</th>
<th>Age</th>
<th>Stroke type</th>
<th>Enrolment time (hrs)</th>
<th>Intervention (route)</th>
<th>Rx Duration (days)</th>
<th>Primary outcome</th>
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<td>ACCESS 1</td>
<td>173/166</td>
<td>51</td>
<td>68</td>
<td>IS</td>
<td>24-46</td>
<td>Candesartan 4mg on day 1 dose increase 8-16mg if &gt;BP160/100/placebo (po)</td>
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<td>Case fatality and disability at 3 months</td>
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<tr>
<td>Ahmed 1 2</td>
<td>101/100</td>
<td>46</td>
<td>72</td>
<td>IS</td>
<td>24</td>
<td>Nimodipine 1mg/placebo (iv followed by po)</td>
<td>iv: 5 po: 16</td>
<td>Transformed Orgogozo score and transformed BI score at day 21</td>
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<td>Ahmed 2 2</td>
<td>94/100</td>
<td>46</td>
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<td>IS</td>
<td>24</td>
<td>Nimodipine 2mg/placebo (iv followed by po)</td>
<td>iv: 5 po: 16</td>
<td>Transformed Orgogozo score and transformed BI score at day 21</td>
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<td>ASCLEPIOS 3</td>
<td>120/114</td>
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<td>72</td>
<td>Isradipine/placebo (iv followed by po)</td>
<td>iv: 3 po: 28</td>
<td>Transformed Orgogozo score, BI Neurological assessments day1, day8, month1 and 6.</td>
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<td>Bareratenolol 4</td>
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<td>72</td>
<td>Clinical stroke</td>
<td>48</td>
<td>Atenolol 50mg/control (po)</td>
<td>28</td>
<td>Neurological assessments day1, day8, month1 and 6.</td>
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<td>Propanolol 80mg/ control (po)</td>
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<td>Neurological assessments day1, day8, month1 and 6.</td>
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<td>Age (mean, SD)</td>
<td>Stroke Location</td>
<td>Time to Treatment (days)</td>
<td>Treatment</td>
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<td>Propranolol 80mg/placebo (po)</td>
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<td>Death/dependency at 2 weeks post stroke Death/dependency at 2 weeks post stroke NIHSS score at day14, BI &amp; mRS at day14 and 90. Combined BI + mRS at day 90 Combined BI + mRS at day 90 Modified Mathew scale day 1,3,5,7,14,21 and 6 months. BI day 1, and 21. Mortality at 4 weeks Neurological and psychiatric assessment using own scales NIHSS day 3,</td>
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<td>Odds Ratio</td>
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<td>Common odds ratio for death or disability at 90 days</td>
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<td>16 weeks</td>
<td>Neurological assessment using MRC, BI</td>
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</table>

A: active; BI: Barthel Index; BP: blood pressure; C: control/placebo; HR: heart rate; IS: ischaemic stroke; mRS: modified Rankin Scale; PICH: primary intracerebral haemorrhage; po: per oral; td: transdermal; * unpublished observations
Table S2: Excluded trials

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<tr>
<td>(Perindopril)</td>
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<td>Nazir 2005</td>
<td>ACEI (perindopril)</td>
<td>Unable to obtain BP data from the author</td>
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<td>ACEI (perindopril), ARB (candisartan)</td>
<td>Head to head comparisons (perindopril, candisartan or conventional therapy)</td>
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<td>ARB (losartan)</td>
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<td>Gladstone 2006</td>
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<td>Dexamphetamine</td>
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* Unpublished observations
### SUPPLEMENTAL FIGURES

#### Figure S1

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**Note:**
- Study or Subj Name: Different studies or subjects involved in the experiment.
- Treatment and Control: Different groups or conditions being compared.
- Gadda Ratio: Ratio of gene expression in different conditions.
- Gadda Ratio K1 and K2: Different ratios or factors affecting gene expression.

#### Myocardial Infarction (MI)

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**Note:**
- Study or Subj Name: Different studies or subjects involved in the experiment.
- Treatment and Control: Different groups or conditions being compared.
- Gadda Ratio: Ratio of gene expression in different conditions.
- Gadda Ratio K1 and K2: Different ratios or factors affecting gene expression.

#### AFLF

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**Note:**
- Study or Subj Name: Different studies or subjects involved in the experiment.
- Treatment and Control: Different groups or conditions being compared.
- Gadda Ratio: Ratio of gene expression in different conditions.
- Gadda Ratio K1 and K2: Different ratios or factors affecting gene expression.

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#### Reference

- Figure S1: Description of the supplemental figures showing experimental results and statistical analysis.
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**Figure S3**
SUPPLEMENTAL FIGURE LEGENDS

Figure S1. Death within one month

Figure S2. Death at end of follow up

Figure S3. On treatment systolic blood pressure