Effect of Blood Pressure During the Acute Period of Ischemic Stroke on Stroke Outcome

A Tertiary Analysis of the GAIN International Trial

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Background and Purpose—The effects of blood pressure (BP) and its fluctuations during the acute phase on the clinical course of ischemic stroke are incompletely understood. We tested the hypotheses that baseline mean arterial BP [MAP=(2×diastolic BP+systolic BP)/3], weighted average MAP, and an increase or decrease of >30% from baseline MAP are independently associated with stroke outcome.

Methods—We studied the 1455 patients with ischemic stroke in the Glycine Antagonist (Gavestinel) in Neuroprotection (GAIN) International Trial. BP management was at the discretion of investigators and was measured at 0, 0.5, 4, 12, 12.25, 60, and 60.25 hours. Outcome was assessed by mortality, Barthel Index (dead or 0 to 55 versus 60 to 90 versus ≥95), National Institutes of Health Stroke Scale (NIHSS) score (dead or ≥2), and Rankin Scale (dead or ≥2). Cox proportional-hazards and stepwise logistic regression modeling corrected for demography, medical history, stroke severity, and clinical subtype.

Results—Elevated weighted average MAP was associated with poor outcome assessed by mortality at 3 months (hazard ratio, 1.16; 1.06 to 1.27 per 10 mm Hg), NIHSS score (odds ratio [OR] 1.14; 95% confidence interval [CI], 1.01 to 1.28), and Barthel Index at 1 month (OR, 1.12; 95% CI, 1.03 to 1.23). A 30% increase from baseline MAP was associated with poor outcome assessed by NIHSS score and Barthel Index at 1 and 3 months and by Rankin score at 1 month (OR, 2.01; 95% CI, 1.16 to 3.49 to OR, 3.03; 95% CI, 1.30 to 7.02).

Conclusions—Baseline MAP was not associated with poor ischemic stroke outcome. However, variables describing the course of BP over the first 2.5 days have a marked and independent relationship with 1- and 3-month outcome. (Stroke. 2003;34:2420-2425.)

Key Words: blood pressure ■ outcome ■ stroke, ischemic

Casual blood pressure (BP) levels are commonly elevated during the first 24 hours after the onset of stroke symptoms (>80% of acute stroke patients will have a systolic BP [SBP] >160 mm Hg and diastolic BP [DBP] >90 mm Hg during the initial poststroke phase) and fall spontaneously in the subsequent 10 to 14 days.1 Because cerebral autoregulation is impaired after an acute stroke, cerebral blood flow is believed to be very sensitive to changes in systemic BP. Therefore, elevation of BP after acute stroke may be of benefit in terms of increasing cerebral blood flow in the ischemic areas of brain. Conversely, elevated BP can increase the risk of cerebral edema and hemorrhagic transformation of the infarct.

Although there is evidence that raised BP levels in the acute phase of stroke are associated with a poor prognosis,2-4 other work suggests that BP has little prognostic value5,6 or even that constantly high BP may indicate good prognosis.7 There is a possibility of a J-shaped relationship between BP and stroke outcome, with poorer outcome in the groups with extreme BP.8,9

The clinical impact of BP-lowering drugs in the acute phase of stroke is also poorly understood. Calcium channel blockers (CCBs), β-blockers (BBS), and probably the angiotensin-converting enzyme (ACE) inhibitors, prostacyclin and nitric oxide each effectively reduce BP during the acute phase of stroke according to a Cochrane Database Systematic Review.10 None of the drug groups significantly alters acute stroke outcome apart from BBs and streptokinase, which increase early case fatality. The review concluded that there is insufficient evidence to evaluate reliably the effect of altering BP on acute stroke outcome.

This study was conducted to gain further knowledge about the complex relationships between BP, its management in...
acute stroke care, and stroke outcomes using data from the Glycine Antagonist (Gavestinel) in Neuroprotection (GAIN) International Trial.\textsuperscript{11} We investigated (1) the relationship between the course of mean arterial BP [MAP\(=\frac{(2\times DBP+SBP)}{3}\)]\textsuperscript{12} over the first 60.25 hours and stroke outcome and (2) the relationship between use of various antihypertensive agents and stroke outcome.

We hypothesized (1) that elevated baseline MAP, elevated weighted average MAP, and a substantial increase or decrease from baseline MAP are independently associated with stroke poor outcome and (2) that use of groups of drugs that affect BP during the first 7 days of the study is associated with stroke outcome.

### Subjects and Methods

The sample used for the analysis comprises the intention-to-treat group with ischemic stroke in the GAIN International Trial. GAIN International was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial conducted to test the effectiveness of gavestinel for acute stroke treatment. The trial was approved by the regulatory and ethics committees of each participating institution. Written or witnessed verbal informed consent was obtained from all patients. The trial included previously independent patients \(>18\) years of age who presented within 6 hours of acute stroke symptoms. Subjects had to have limb weakness (with at least a drift within 10 seconds for the arm or 5 seconds for the leg; if mild, arm and leg both had to be affected). Inclusion criteria tolerated a wide range of BP but excluded malignant hypertension (DBP \(>130\) mm Hg). Other exclusion criteria were previously reported.\textsuperscript{11}

Standard stroke care was accompanied by gavestinel or placebo administration. Gavestinel did not show any superiority over placebo on stroke outcome and did not significantly alter BP.\textsuperscript{11} Therefore, both treatment groups were combined for our analysis. Management of BP was at the discretion of physicians. According to the trial protocol, BP measurements were taken at baseline, 30 minutes, and 4, 12, 12.25, 60, and 60.25 hours after the start of the loading infusion of the randomized treatment.

As measures of BP, we looked at baseline MAP, weighted average MAP, and substantial increase or decrease (by \(>30\%\)) from baseline MAP. The weighted average MAP is an area under the curve describing MAP over the course of the measurement divided by duration of the measurement period (up to 60.25 hours). Medications prescribed to the patients at any time from the start of the study drug infusion to day 7 (or hospital discharge if earlier) were recorded. We identified drugs that potentially affect BP. CCBs, BBs, ACE inhibitors, diuretics, diprydamole, and nitrates were classified as drugs that decrease BP.

The primary outcomes were those of the GAIN International statistical analysis plan: mortality, Barthel Activities of Daily Living Index\textsuperscript{13} at 7 days (or at hospital discharge if earlier), 1 and 3 months (trichotomized as dead or \(0\) to 55 versus \(60\) to 90 versus \(\geq 95\)), National Institutes of Health Stroke Scale (NIHSS)\textsuperscript{14} at 7 days and 1 and 3 months (dichotomized as dead or \(\geq 2\) versus 0 to 1), and modified Rankin Scale\textsuperscript{15,16} at 1 and 3 months (dichotomized as dead or \(\geq 2\) versus 0 to 1). Secondary outcome measures were NIHSS score change from baseline at 7 days, 1 month, and 3 months (dichotomized at the median; dead was excluded from analysis) and hemorrhagic transformation of the stroke and progression of the stroke by day 7 recorded as events common to stroke patients.

### Statistical Analysis

Descriptive statistics of the entire sample and groups divided by quartiles of weighted average MAP are presented. Forward stepwise multivariate ordinal logistic modeling was used to identify baseline factors (baseline NIHSS score, age, sex, treatment group, time to treatment, stroke risk factors, and stroke subtype by Oxfordshire Community Stroke Project [OCSP]\textsuperscript{17} classification) that independently predict weighted average MAP category.

Forward stepwise multivariate logistic regression and multivariate Cox proportional-hazards modeling was used to identify the association between each MAP variable and outcome separately, after correction for baseline factors forced into the models without selection. Kaplan-Meier curves of groups stratified by weighted average MAP quartiles are presented, with differences tested by the log-rank test.

Forward stepwise multivariate logistic regression and Cox proportional-hazards modeling were also used to identify associations between each drug use and outcome separately after controlling for patient baseline factors and MAP variables. Baseline factors and MAP variables were forced into the model without selection. Results were not adjusted for multiple comparisons. All models were constructed at the 5\% significance level.

### Results

We included 1455 patients in the analysis. Baseline characteristics of the sample and groups subdivided by quartiles of weighted average MAP are presented in Table 1. MAP declined gradually (Figure 1). However, the behavior of BP in individual patients was more variable. A 30\% decrease and a 30\% increase from baseline MAP occurred in 11\% and 6\% of patients, respectively.

Multivariate ordinal logistic regression identified baseline variables that were associated with weighted average MAP level (Table 1). History of hypertension (odds ratio [OR], 2.44; 95\% confidence interval [CI], 2.01 to 2.96), increased alcohol consumption (OR, 1.67; 95\% CI, 1.21 to 2.29), age (OR, 1.18; 95\% CI, 1.09 to 1.28 per decade), and baseline NIHSS score (OR, 1.02; 95\% CI, 1.01 to 1.04 per point) predicted higher weighted average MAP. Previous myocardial infarction (OR, 0.65; 95\% CI, 0.50 to 0.86) and partial anterior circulation infarction by OCSP classification (OR, 0.80; 95\% CI, 0.66 to 0.98) predicted lower MAP.

Overall, 1842 prescriptions of drugs that affect BP were used in the study sample during the recording period of 7 days or discharge from hospital (if earlier). We found that 29\% of patients received at least 1 diuretic; 21\%, at least 1 CCB; 20\%, at least 1 BB; 19\%, at least 1 ACE inhibitor; 14\%, diprydamole; and 7\%, at least 1 nitrate. Only 0.5\% of patients received at least 1 drug that increases BP.

### Primary Outcomes

Baseline MAP and a 30\% decrease from baseline MAP were not associated with primary outcomes after correction for baseline factors (baseline NIHSS score, age, sex, treatment group, time to treatment, stroke risk factors, and stroke subtype by OCSP). Elevated weighted average MAP was associated with poor outcome assessed by mortality at 3 months, Barthel Index, and NIHSS score at 1 month (Table 2). A 30\% increase from baseline MAP was associated with poor Barthel Index at 1 and 3 months, poor NIHSS score at 1 and 3 months, and poor outcome by Rankin Scale score at 1 month. Univariate Kaplan-Meier curves of groups stratified by weighted average MAP quartiles (Figure 2) showed that patients with MAP \(<95\) mm Hg fared better than all others (log-rank test, \(P<0.0004\)).

Treatment with at least 1 diuretic was associated with mortality (hazard ratio [HR], 1.72; 95\% CI, 1.33 to 2.17) and with poor Barthel Index at 3 months (OR, 1.43; 95\% CI, 1.10 to 1.87) after correction for baseline factors and BP variables.
Treatment with dipyridamole was associated with survival (HR, 0.46; 95% CI, 0.28 to 0.75) and good Barthel Index at 3 months (OR, 0.69; 95% CI, 0.50 to 0.97). Treatment with at least 1 drug that increases BP was associated with mortality (OR, 3.05; 95% CI, 1.04 to 8.99).

**Secondary Outcomes**

The medians of NIHSS score reduction from baseline at 7 days, 1 month, and 3 months were 2, 5, and 6 points, respectively, among survivors. NIHSS score changes were dichotomized as less than the median (poor outcome) and greater than or equal to the median (good outcome). BP variables did not show any association with changes in NIHSS score after correction for baseline factors. Only treatment with dipyridamole was associated with good outcome by change in NIHSS score at 7 days (OR, 0.57; 95% CI, 0.40 to 0.80) and 1 month (OR, 0.71; 95% CI, 0.51 to 1.00).

Progression of stroke (eg, cerebral edema or coma) was recorded in 296 patients (20%). Elevated baseline MAP (OR, 1.11; 95% CI, 1.03 to 1.21 per additional 10 mm Hg), elevated weighted average MAP (OR, 1.15; 95% CI, 1.03 to 1.27 per additional 10 mm Hg), and a 30% MAP decrease from baseline (OR, 1.84; 95% CI, 1.27 to 2.77) were associated with progression of stroke after correction for baseline factors. Treatment with at least 1 diuretic (OR, 1.85; 95% CI, 1.39 to 2.48) was associated with progression of stroke, and treatment with dipyridamole was associated with no progression of stroke (OR, 0.42; 95% CI, 0.25 to 0.70) after correction for baseline factors and BP variables.

Hemorrhagic transformation of stroke was recorded in 71 patients (5%) and was not associated with BP variables after correction for baseline factors. Treatment with at least 1 BB (OR, 2.04; 95% CI, 1.17 to 3.55) and CCB (OR, 2.15; 95% CI, 1.12 to 3.63) was associated with hemorrhagic transformation of stroke after correction for baseline factors and BP variables.

**Discussion**

The original exclusion and inclusion criteria need to be taken into account when the results of this study are gener-
alized to hospital-based common practice. Our sample includes previously independent patients >18 years of age within 6 hours of stroke onset. It excludes very mild and very severe patients (patients were required to have limb weakness and symptoms that were neither rapidly improving nor thought likely to resolve completely within 24 hours and could not be obtunded or were otherwise unconscious). Patients with other severe diseases were also excluded (severe congestive heart failure, malignant hypertension, and known history of significant renal or hepatic impairment).

In addition to history of hypertension, we have identified age, baseline NIHSS score, and increased alcohol consumption as predictors of higher weighted average MAP. Partial anterior circulation infarction and previous myocardial infarction were associated with lower average MAP. Casual BP measurements carry limited prognostic significance compared with beat-to-beat measurements. This underscores the limitation of studies that have addressed the value of single measurements of BP after stroke in predicting outcome. Our analysis, however, could rely on repeated BP measurements at fixed intervals and was able to consider the effects of both a longer course of BP (weighted average MAP) and BP fluctuations (a 30% increase and decrease from baseline MAP). In this study, all analyses were corrected for atrial fibrillation, which may contribute to BP instability. Other strengths of this study are the high quality of the data and the detailed recording of demographic and clinical information, which allows correction for stroke prognostic factors.

Our findings do not support the hypothesis of a J-shaped relationship between poor outcome and BP because the difference between the linear models (presented) and generalized additive models (which allows any shape of relationship) of baseline MAP and weighted average MAP on stroke outcome was not significant (analysis of variance, \( P > 0.05 \)). However, it cannot be excluded that patients with low BP were treated before the baseline measurement of BP or that they were simply excluded from the trial and therefore we fail to show a negative effect of low values of initial BP on stroke outcome, although this is an unlikely scenario. Similarly the actual relationship between high BP and poor outcome may also have been somewhat underestimated in this study because our sample excluded patients with extremely high BP (DBP >130 mm Hg).

### Table 2. Statistically Significant Associations Between Primary Outcomes and BP Variables

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>30% Increase From Baseline MAP</th>
<th>Weighted Average MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>( P )</td>
</tr>
<tr>
<td>Mortality, HR</td>
<td>3 mo</td>
<td>&gt;0.05</td>
<td>1.16 (1.06–1.27)</td>
</tr>
<tr>
<td>Barthel Index (dead or 0–55 vs 60–90 vs ≥95)</td>
<td>7 d</td>
<td>&gt;0.05</td>
<td>1.12 (1.03–1.23)</td>
</tr>
<tr>
<td></td>
<td>1 mo</td>
<td>2.01 (1.16–3.49)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>3 mo</td>
<td>2.39 (1.42–4.03)</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>NIHSS score (dead or ≥2)</td>
<td>7 d</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>1 mo</td>
<td>2.74 (1.11–6.73)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>3 mo</td>
<td>2.87 (1.33–6.20)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rankin Scale score (dead or ≥2)</td>
<td>1 mo</td>
<td>3.03 (1.30–7.02)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>3 mo</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

*Per additional 10 mm Hg.

Figure 2. Kaplan-Meier curves of groups stratified by weighted average MAP quartiles. ---, Lower quartile; - - - -, lower quartile to median; - - , median to upper quartile; - , upper upper quartile.
Our observational study cannot prove causality regarding the associations of marked (>30%) changes with primary and secondary outcome variables because it is not clear whether BP alterations led to poor outcome or if they occurred secondary to some other predictor of poor outcome. In addition, progression of stroke or hemorrhagic transformation could have preceded some of the measurements of BP because these events were recorded at day 7 without their time of onset specified. Therefore, the events themselves may have affected the course of BP. At any rate, this study suggests that sharp fluctuations in BP (both increasing and decreasing) should be avoided in clinical practice and may constitute the focus of future drug trials assessing the impact of BP modulation. Our study also clearly indicates that patients with lower BP over the first 2.5 days have better outcome.

Drugs that decrease BP may not have been prescribed to patients with the prime aim of reducing BP but rather to treat other conditions. Our findings may also be biased toward overuse of drugs that decrease BP because we did not count intravenous fluid infusions as a result of methodological constraints of measuring their impact. Again, the associations presented in this study are important for illustrating BP treatment in acute stroke care in the context of a randomized clinical trial and aspects that should be addressed by future studies.

Diuretic prescription did not necessarily cause poor stroke outcome but rather may have been the consequence of a poor health status leading to more aggressive treatment. Therefore, we have corrected for all known and available events common to stroke that occurred during the first 7 days. Nevertheless, diuretics remained significant predictors of mortality (HR, 1.33; 95% CI, 1.03 to 1.73). Therefore, the question of adverse effect of diuretics on stroke outcome (possibly because of dehydration) remains unanswered, and further investigation of the matter is needed.

The association between mortality and drugs that increase BP can likely be explained by treatment of hypotension that occurs before death. The association between hemorrhagic transformation and BB and CCB, although strong, should also not be overinterpreted because of the relatively small number of events (n=71).

The beneficial effect of dipyridamole treatment is worth mentioning. This effect was not necessarily related to a reduction in BP but could also be the consequence of the antiplatelet activity of this drug. Although dipyridamole and aspirin are considered a first-line therapy for secondary prevention of stroke, the use of dipyridamole was low (14%). The association can be explained in part by the facts that dipyridamole was prescribed to patients with milder stroke and that we may have failed to correct for all prognostic factors. Because dipyridamole is usually prescribed together with aspirin (8% of patients were prescribed both), the beneficial effect of dipyridamole may be due to the correlation with aspirin. If corrected for aspirin, all presented ORs and HRs were still significant with the trend of their increase by 0.03 to 0.01. Therefore, these data suggest that dipyridamole has an independent beneficial effect on stroke outcome, and its use in this indication should be further explored.

Ongoing clinical trials such as Efficacy of Nitric Oxide in Stroke (ENOS) and Intravenous Magnesium Efficacy in Acute Stroke (IMAGES) may provide additional observational and experimental data on the role of BP in acute stroke care. However, to resolve the controversy of BP management in acute stroke care, there is a need for a randomized clinical trial that will investigate the different patterns of BP management and demonstrate a cause-effect relationship between BP and stroke outcome. Analysis from observational studies such as ours will clearly be helpful when such trials are planned.

In conclusion, data from well-conducted clinical trials provide a valuable source of information for investigating the natural history of stroke and its association with BP. There is no evidence to conclude that a single casual MAP measurement at baseline is associated with ischemic stroke outcome. However, variables that describe the course of BP over the first 60 hours (higher weighted average MAP and a 30% increase from baseline MAP) have a marked and independent relationship with poor outcomes from ischemic stroke at 1 and 3 months.

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References


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