The Relationship Between Baseline Blood Pressure and Computed Tomography Findings in Acute Stroke: Data From the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST)
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The Relationship Between Baseline Blood Pressure and Computed Tomography Findings in Acute Stroke

Data From the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST)

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Background and Purpose—High blood pressure (BP) is present in ≈80% of patients with acute ischemic stroke and is independently associated with poor outcome. There are few data examining the relationship between admission BP and acute CT findings.

Methods—TAIST was a randomized controlled trial assessing 10 days of treatment with tinzaparin versus aspirin in 1489 patients with acute ischemic stroke (≤48 hr) with admission BP of ≥220/120 mm Hg. CT brain scans were performed before randomization and after 10 days. The relationships between baseline BP and adjudicated CT findings were assessed. Odds ratios per 10 mm Hg change in BP were calculated.

Results—Higher systolic BP (SBP) was associated with abnormal CT scans because of independent associations with chronic changes of leukoariosis (OR, 1.12; 95% CI, 1.05–1.17) and old infarction (OR, 1.12; 95% CI, 1.06–1.17) at baseline, and signs of visible infarction at day 10 (OR, 1.06; 95% CI, 1.00–1.13). A lower SBP was associated with signs of acute infarction (OR, 0.94; 95% CI, 0.89–0.99). Hemorrhagic transformation, dense middle cerebral artery sign, mass effect, and cerebral edema at day 10 were not independently associated with baseline BP.

Conclusion—Although high baseline BP is independently associated with a poor outcome after stroke, this was not shown to be through an association with increased hemorrhagic transformation, cerebral edema, or mass effect; trial design may be suboptimal to detect this. Higher SBP is associated with visible infarction on day 10 scans. The influence of changing BP in acute stroke on CT findings is still to be ascertained. (Stroke. 2009;40:41-46.)

Key Words: acute stroke ■ CT ■ hypertension ■ ischaemia ■ outcome

High blood pressure (BP) (systolic BP [SBP] >140 mm Hg) is present in ≈80% of patients with acute ischemic stroke. Multiple studies have shown that high BP is associated independently with poor outcome, including both early death and late death/dependency. Mechanisms for this relationship in ischemic stroke include an increased risk of early recurrence and severe cerebral edema. Studies of experimental stroke have shown a relationship between hypertension and hemorrhagic transformation, although this was not found in the International Stroke Trial (IST), a trial of 19435 patients with ischemic stroke. To date, there are few published studies exploring the relationship between baseline BP and acute and subacute CT findings in acute stroke; CT findings such as arterial occlusion (hyperdense artery) and mass effect might be associated with early hypertension.

This study assesses the relationship between blood pressure and CT findings using data from the Tinzaparin in Acute Ischemic Stroke Trial (TAIST). Previous analysis of the data from this trial has shown high BP to be associated with poor outcome.9

Methods

Subjects

TAIST compared the safety and efficacy of tinzaparin (low-molecular-weight heparin) given at high dose (175 anti-Xa IU/kg per day) or medium dose (100 anti-Xa IU/kg per day), and aspirin (300 mg od) in patients with acute ischemic stroke. Subjects were included within 48 hours of stroke onset with 47% recruited within 24 hours. Exclusion criteria included significant hypertension (SBP >220 mm Hg or diastolic BP [DBP] >120 mm Hg). All data were collected prospectively as part of the trial protocol.
Blood Pressure
SBP, DBP, and heart rate were measured in all patients on 1 to 6 occasions in the 6 hours leading up to randomization. Mean time to randomization was 26.1 hours; therefore, measurements of BP were approximately 24 hours after stroke onset. In the present analysis, the baseline SBP, DBP, and heart rate were calculated from the average of the first 3 measurements. Further hemodynamic measurements were calculated as follows: pulse pressure = SBP - DBP; mean arterial pressure = DBP + 1/3 pulse pressure; pulse pressure index = pulse pressure/mean arterial pressure; and rate pressure product = SBP x heart rate.

CT Scans
All subjects had a baseline CT scan before randomization. Mean time from symptom onset to baseline CT was 15.8 hours. A second CT scan was performed after 10 days of treatment. Each CT scan was independently adjudicated centrally by 2 radiologists blinded to treatment and clinical findings. If there was disagreement, then the scans were reviewed by a third radiologist with the majority decision standing.

CT Scan Definitions
A scan was defined as abnormal if it showed any abnormality outside normal anatomic variation. On baseline scans, early signs of hypodensity were defined as acute infarction; early signs of infarction were other signs of acute infarction, including loss of gray/white matter differentiation (contrast reduction) and sulcal effacement. Dense middle cerebral artery refers to scan evidence of thrombus in the middle cerebral artery, and hemorrhiedema was edema resulting in ventricular effacement on the side of the stroke. Leukoaraiosis was defined by the presence of perivenricular white matter lucency, and old infarction was defined by the presence of established hypodense lesions.

On the day 10 scan, evidence of subacute hypodensity in keeping with ischemic stroke defined infarction evident (>1 focus defined as multiple infarction). Definitions for bleeding parameters in TAIST were used in MAST E11 and FISS-bis12 and are as follows: hemorrhagic transformation is definite as petechial bleeding within the infarct; intracranial hematoma represents significant confluent bleeding within the infarct; additional hematoma is bleeding unrelated to the infarct; and interventricular bleeds are adjudicated as blood in ventricles. The definitions used in this analysis have been described previously.13,14

Statistical Methods
The relationship between hemodynamic measures and clinical classifications was assessed using Student t test. The relationship between hemodynamic measures and CT findings were assessed using unadjusted (t test) and adjusted (logistic regression) models; adjustment included age, sex, baseline severity (Scandinavian Stroke Scale), time to treatment, and treatment allocation (day 10 scan only). Odds ratios refer to a change in hemodynamic measure by 10 mm Hg. Significance was taken at P<0.05, and SD or 95% CI are given. All analyses were performed using SPSS (version 11.0 for Mac OS; SPSS Inc).

Results
Subjects
Of 1489 randomized patients, emerging exclusion criteria prevented treatment in 15 patients and baseline BP was not recorded in 5 patients; 177 patients had no baseline CT adjudicated and 168 had no day 10 scan adjudicated. Twenty-one patients in both the baseline and day 10 scans had unsatisfactory scan quality; therefore, the information from these scans is reported variably. As such, the denominator for the different imaging variables varies. Baseline characteristics of randomized patients in TAIST have been published previously.10 Mean baseline BP in all randomized TAIST patients was 156.4 mm Hg (SD, 22.8). Baseline SBP was significantly related to OCSP clinical subtype:15 LACS patients had significantly higher SBP than non-LACS patients (mean SBP 160.1 mm Hg vs 155.0 mm Hg; P<0.0001); TACS patients had significantly lower baseline SBP than non-TACS patients (mean SBP 154.5 mm Hg vs 157.5 mm Hg; P=0.01). Baseline SBP was also significantly related to TOAST subtype16 (P=0.0001; with mean SBPs for lacunar 160.1 mm Hg, large artery=153.8, and cardioembolic=154.5 mm Hg).

Baseline Scan
Baseline scan findings were compared with SBP, DBP, mean arterial pressure, rate pressure product, and pulse pressure. All of the hemodynamic variables were associated with scan findings with the exception of DBP. The results for SBP with odds ratios for the data with and without adjustment for confounding factors are shown in Table 1. Figure 1 shows baseline CT findings and mean SBP with standard deviations. Before adjustment, all of the baseline CT findings were associated with SBP. Patients with a higher baseline SBP were more likely to have had an abnormal scan, with this being related to an increase in leukoaraiosis and the presence of old infarction. These associations remained statistically significant after adjustment. The rest of the baseline CT findings, including evidence of acute infarction, early signs of infarction such as loss of gray white matter differentiation, mass effect, and hemorrhiedema, were more common in patients with lower BP. With the exception of evidence of acute infarction, all of these factors ceased to be statistically significant after adjustment.

Day 10 Scan
Day 10 scan findings were compared with baseline SBP, DBP, mean arterial pressure, rate pressure product, and pulse pressure. Once again DBP was not associated with scan findings. Of the remaining hemodynamic measurements, the relationship with SBP remained the most consistent. The results for SBP with odds ratios for the data with and without adjustment for confounding factors are shown in Table 2. Figure 2 shows day 10 CT findings and mean baseline SBP with standard deviations. Patients with higher baseline BP were significantly more likely to have an infarct (all infarcts and nonhemorrhagic infarcts) seen on the day 10 scan; this remained significant after adjustment.

In the trial 435 patients (29%) had evidence of hemorrhagic transformation of their infarct, 11 (0.7%) of which were symptomatic.10 Hemorrhagic transformation (petechial bleeding within the infarct) was not associated with baseline BP after adjustment, nor was the amount of petechial bleeding. Larger bleeds forming intracranial hematomas, hematoma not related to the infarct, and interventricular bleeds were less common and were not significantly related to BP.

Patients with symptomatic bleeds had nonsignificantly higher baseline SBP than those without (165.3 mm Hg, SD 14.6 vs 156.4 mm Hg, SD 22.8) after adjustment for confounding factors P=0.246. Seventy patients (4.7%) died before day 10. Twenty of these had adjudicated clinical scans
performed between day 1 and 10. Of these patients, 14 of 20 (70%) had mass effect evident on CT (P = 0.0001). The group who died before day 10 did not have a higher baseline SBP than those who did not die (157.8 mm Hg vs 156.4 mm Hg; P = 0.598).

Discussion
This exploratory analysis of a large, randomized, controlled trial in acute stroke sought to examine whether the association between high BP and poor outcome in stroke is related to mechanisms visible on CT scan. This study shows that BP levels at entry into the trial (~24 hours after stroke onset) are associated with CT findings. Early infarction, as visible on the baseline CT, appears to be independently related to lower BP. In contrast, other apparent associations between baseline CT findings and BP (dense middle cerebral artery, hemiedema, mass effect) disappear after adjustment.

The association between lower BP and evidence of acute infarction may be related to clinical subtype; therefore, stroke severity. Data from this study concur with that from IST, which revealed that patients with a total anterior circulation strokes (TACS, Oxford Community Stroke Project classification) had lower blood pressures; TACS are more likely to be visible on early CT scans. This is in accordance with

<table>
<thead>
<tr>
<th>CT Findings at Baseline</th>
<th>N of Patients Finding Present/Absent/Missing</th>
<th>SBP OR (95% CI) Unadjusted</th>
<th>SBP OR (95% CI) Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal scan</td>
<td>736/560/190</td>
<td>1.13 (1.07–1.18)</td>
<td>1.09 (1.03–1.15)</td>
</tr>
<tr>
<td>Acute infarction</td>
<td>395/898/193</td>
<td>0.90 (0.87–0.96)</td>
<td>0.94 (0.89–0.99)</td>
</tr>
<tr>
<td>Early signs of infarction</td>
<td>157/1137/192</td>
<td>0.90 (0.83–0.97)</td>
<td>0.94 (0.87–1.02)</td>
</tr>
<tr>
<td>Contrast reduction</td>
<td>151/1115/220</td>
<td>0.91 (0.84–0.98)</td>
<td>0.95 (0.88–1.03)</td>
</tr>
<tr>
<td>Lentiform nucleus involvement</td>
<td>96/1172/218</td>
<td>0.91 (0.78–0.94)</td>
<td>0.90 (0.81–0.99)</td>
</tr>
<tr>
<td>Insular zone involvement</td>
<td>95/1172/219</td>
<td>0.84 (0.77–0.93)</td>
<td>0.90 (0.82–1.00)</td>
</tr>
<tr>
<td>Dense MCA</td>
<td>64/1191/1255</td>
<td>0.82 (0.73–0.91)</td>
<td>0.87 (0.78–1.00)</td>
</tr>
<tr>
<td>Hemiedema</td>
<td>148/1127/211</td>
<td>0.87 (0.82–1.00)</td>
<td>0.93 (0.87–1.00)</td>
</tr>
<tr>
<td>Mass effect</td>
<td>75/1219/192</td>
<td>0.87 (0.78–1.00)</td>
<td>0.92 (0.83–1.00)</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>597/696/193</td>
<td>1.15 (1.09–1.21)</td>
<td>1.12 (1.05–1.17)</td>
</tr>
<tr>
<td>Old infarctions</td>
<td>483/811/192</td>
<td>1.14 (1.07–1.20)</td>
<td>1.12 (1.06–1.17)</td>
</tr>
</tbody>
</table>

ORs are for each 10-mm Hg change in BP. MCA indicates middle cerebral artery. Controlled for age, sex, baseline Scandinavian stroke scale, and time to treatment. P < 0.05 are shown in bold.

Figure 1. Stock chart showing baseline SBP (mean, SD) in baseline scan by type of abnormality. The BP scale shows the top end of the BP scale and does not cross the x-axis at 0. SD bars; *significant before adjustment; **significant after adjustment; MCA, middle cerebral artery.
the observation that patients with early signs of acute infarction had a lower BP in this analysis. Low BP is also associated with poor outcome after stroke after adjustment for stroke severity.1 This may be because of concurrent medical problems (cardiac failure, sepsis), or it may be hypothesized that low perfusion pressure in the ischemic penumbra causes it to develop into frank infarction.

Additionally, a key confounding variable is time between ictus and scan because BP declines progressively from stroke onset over the first hours and days.18 CT findings in acute ischemic stroke take time to develop after clinical presentation so it may be that the lower BP seen with some CT features are explained by longer ictus to scan times; statistical adjustment may not completely control for this.

Analysis of the TAIST data provide some insights into the association between BP and poor outcome. Although the link between high BP and poor outcome after stroke is well-established, the explanation for this relationship remains unclear. Suggested mechanisms include increased recurrence,1,9 fatal cerebral edema,1 and increased hemorrhagic transformation.4–6

Table 2. Relationship Between Hemodynamic Factors and Day 10 CT Findings

<table>
<thead>
<tr>
<th>CT Findings at Day 10</th>
<th>N of Patients Finding Present/Absent/Missing</th>
<th>SBP OR (95% CI) Unadjusted</th>
<th>SBP OR (95% CI) Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal scan</td>
<td>367/930/189</td>
<td>0.98 (0.93–1.04)</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Infarction evident</td>
<td>912/383/191</td>
<td>1.02 (0.96–1.07)</td>
<td><strong>1.06 (1.00–1.13)</strong></td>
</tr>
<tr>
<td>Nonhemorrhagic infarct</td>
<td>483/815/188</td>
<td><strong>1.08 (1.03–1.14)</strong></td>
<td><strong>1.08 (1.03–1.14)</strong></td>
</tr>
<tr>
<td>Hemorrhagic infarct</td>
<td>435/862/189</td>
<td>0.93 (0.87–0.98)</td>
<td>0.96 (0.91–1.02)</td>
</tr>
<tr>
<td>Petechial bleeding &gt;50%</td>
<td>143/286/6</td>
<td>1.04 (0.95–1.14)</td>
<td>1.04 (0.94–1.15)</td>
</tr>
<tr>
<td>Intracerebral hemorrhoma</td>
<td>14/1284/188</td>
<td>0.99 (0.79–1.24)</td>
<td>0.98 (0.77–1.23)</td>
</tr>
<tr>
<td>Additional hemorrhoma</td>
<td>1/1278/207</td>
<td>0.96 (0.40–2.30)</td>
<td>1.06 (0.46–2.45)</td>
</tr>
<tr>
<td>Blood in ventricles</td>
<td>4/1275/207</td>
<td>0.92 (0.60–1.42)</td>
<td>0.90 (0.59–1.38)</td>
</tr>
<tr>
<td>Total superficial bleed</td>
<td>48/449/NA</td>
<td>1.03 (0.90–1.17)</td>
<td>1.07 (0.94–1.20)</td>
</tr>
<tr>
<td>Partial superficial bleed</td>
<td>343/120/NA</td>
<td>0.95 (0.90–1.00)</td>
<td>0.97 (0.91–1.02)</td>
</tr>
<tr>
<td>Deep bleed</td>
<td>237/212/NA</td>
<td><strong>0.93 (0.88–0.99)</strong></td>
<td>0.96 (0.90–1.03)</td>
</tr>
<tr>
<td>Multiple infarcts</td>
<td>14/1264/208</td>
<td>0.89 (0.71–1.13)</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Mass effect</td>
<td>215/1063/208</td>
<td>0.94 (0.88–1.00)</td>
<td>0.98 (0.91–1.06)</td>
</tr>
<tr>
<td>Midline shift</td>
<td>23/1254/209</td>
<td>0.90 (0.76–1.10)</td>
<td>1.01 (0.83–1.20)</td>
</tr>
</tbody>
</table>

ORs are for each 10-mm Hg change in BP. Controlled for age, sex, baseline Scandinavian stroke scale, time to treatment, and treatment group. *P<0.05 are shown in bold.

Figure 2. Bar chart showing baseline SBP (mean, SD) in day 10 scan by type of abnormality. The BP scale shows the top end of the BP scale and does not cross the x-axis at 0. SD bars; *significant before adjustment; **significant after adjustment.
Analysis of the TAIST data based on day 0 and 10 CT scans does not reveal a significant association between hypertension and cerebral edema, which was present on 11% of baseline scans. In contrast, data from IST reported a possible relationship between BP and fatal (presumed) cerebral edema; in IST, the outcome of fatal cerebral edema was derived and not dependent on clinical or imaging data. A case-control analysis of patients with ischemic stroke revealed a relationship between fatal cerebral edema and 12-hour systolic hypertension, although this does not prove causality. The cerebral edema may have caused an increase in BP through a Cushing response or, alternatively, been a consequence of raised BP caused by vasocostriction and breakdown of the blood–brain barrier.

One explanation for the current findings is the timing of the CT scans. Baseline scans were performed on average 15 hours after stroke onset at a time that may be too early to detail many cases of cerebral edema. Similarly, scans at day 10 may also miss the peak incidence of cerebral edema, and 70 patients with severe stroke died before day 10. This is supported by data from 20 of these 70 patients who had an adjudicated clinical scan before death; in this group, early death was strongly associated with the presence of mass effect, although the number was too small to confirm an association with SBP. Another explanation is that exclusion of patients with hemorrhagic transformation on baseline scan from enrollment in the trial. This will have excluded the most severe strokes and, therefore, those most prone to cerebral edema.

Analysis of the TAIST data also fails to confirm experimental studies that show a link between baseline hypertension and hemorrhagic transformation of the infarction. Although patients with hemorrhage on baseline scan were excluded from TAIST, one-third of patients had evidence of hemorrhagic transformation (defined as petechial bleeding within the infarct) at day 10. There was no evidence of an association between baseline BP and subsequent hemorrhagic transformation or amount of petechial bleeding. There were no significant associations between more clinically relevant bleeds (hematoma formation, interventricular bleeds or symptomatic bleeds) and BP, although less of these events occurred, reducing statistical power. Analysis of IST also failed to show a link between BP and hemorrhagic transformation.

However, this analysis cannot provide information on the relationship between BP at onset and hemorrhagic transformation in the hyperacute phase of ischemic stroke, because patients with early evidence of hemorrhagic transformation were excluded from this trial. Further information from hyperacute studies are needed to examine effects of BP in the first few hours after onset. A recent retrospective analysis of 386 placebo-treated patients in the ECASS II thrombolysis trial did not show an association between baseline BP (taken within 6 hours) and hemorrhagic transformation.

The presence of leukoariosis and old infarctions are significantly associated with high BP at baseline. These imaging changes are chronic and will have antedated the index event. TAIST confirms earlier studies showing a link between high BP, leukoariosis, and recurrent infarction.

At day 10, the only CT finding that was associated with high BP after adjustment was the presence of a visible infarction. Statistical adjustment included baseline severity, so the presence of this visible CT lesion is not primarily related to the severity of the presenting stroke. This may be because most strokes were lacunar (42% in the TAIST trial using a modified version of the TOAST classification) and, whereas these strokes are less likely to be visible acutely, they are associated with leukoariosis and past history of hypertension, which is associated with high baseline BP. It may also be that patients with long-standing hypertension, who are more likely to have a higher BP in the days after stroke onset, have more severe atherosclerosis, and, therefore, more severe infarcts.

Although the findings on the relationship between baseline BP and early CT findings are novel, there are several limitations to this study. Importantly, the data come from a randomized controlled trial with specific inclusion–exclusion criteria so that selection bias will be present inherently. In particular, patients with a very high BP (BP >220/120 mm Hg) were excluded from the trial; therefore, there are no data on severely hypertensive patients who may have significant CT findings. However, IST showed patients with SBP over 170 mm Hg to have worse outcomes, and previous analysis TAIST trial data shows hypertension to be related to poor outcome. Additionally, patients with hemorrhagic transformation on baseline scan were excluded, which will have led to an underrepresentation of patients with very severe stroke. Finally, CT scans at day 10 may have missed some infarcts caused by “fogging.” However, 912 of 1484 patients had evidence of infarct at day 10, so this problem appears to be minimal. Nevertheless, the data come from a large, high-fidelity, double-blinded, double-dummy trial, and the nature of the trial with blinded adjudication of CT scans and blinding to treatment arrangement makes analysis of BP and CT findings robust. This article does not address outcome in patients with elevated BP in the TAIST trial, because this has already been assessed and published. This analysis was designed to assess possible mechanisms from CT findings rather than outcome.

Overall, this analysis provides insight into the association between baseline BP and CT findings in acute and subacute stroke. Although we have not shown cerebral edema or hemorrhagic transformation to be related to BP, patients with elevated SBP are more likely to have visible infarctions by day 10, an intermediate explanation for a poor functional outcome. This is an exploratory analysis, and as such there can be no firm recommendations for the treating physician regarding hypertension in acute ischemic stroke. There are currently large-scale ongoing trials in this area (SCAST and ENOS) which should provide robust data on which to base clinical practice, as well as the opportunity to prospectively analyze CT data in relation to BP, including the influence of changing BP in acute stroke.

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Disclosures
None.

References