Pre–Tissue Plasminogen Activator Blood Pressure Levels and Risk of Symptomatic Intracerebral Hemorrhage

Georgios Tsivgoulis, MD, FESO; James L. Frey, MD; Murray Flaster, MD, PhD; Vijay K. Sharma, MD; Annabelle Y. Lao, MD; Steven L. Hoover, MD; Wei Liu, MD; Elefterios Stamboulis, MD; Anne W. Alexandrov, PhD; Marc D. Malkoff, MD; Andrei V. Alexandrov, MD

Background and Purpose—From small pilot studies, uncontrolled pretreatment systolic blood pressure >185 mm Hg and diastolic blood pressure >110 mm Hg in patients with acute ischemic stroke were introduced in the National Institute of Neurological Diseases and Stroke rt-PA Stroke Study3 as a contraindication for thrombolysis. We sought to determine if pretreatment blood pressure protocol violations in patients with acute ischemic stroke receiving intravenous tissue plasminogen activator are related to the subsequent risk of symptomatic intracerebral hemorrhage (sICH).

Methods—We reviewed medical records of consecutive ischemic stroke admissions treated with intravenous thrombolysis over a 10-year period at our tertiary care hospital. The National Institutes of Health Stroke Scale score on admission was used to determine baseline stroke severity. The closest documented blood pressure values to the time of tissue plasminogen activator bolus (range, 0 to 10 minutes) were considered as pretreatment blood pressure. Pretreatment blood pressure protocol violations were identified as systolic blood pressure >185 or diastolic blood pressure >110 mm Hg prebolus. sICH was defined as brain imaging evidence of intracranial hemorrhage with clinical worsening by the National Institutes of Health Stroke Scale score increase of ≥4 points.

Results—Among 510 patients with ischemic stroke treated with intravenous tissue plasminogen activator (282 men; mean age, 65±15 years), sICH occurred in 31 patients (6.1%). Blood pressure protocol violations were present in 63 patients (12.4%) and they were more frequent in patients with sICH (26% versus 12%; P=0.019). After adjusting for demographic characteristics, onset-to-treatment time, baseline National Institutes of Health Stroke Scale, stroke risk factors and medications, pretreatment blood pressure protocol violations were independently associated with a higher likelihood of sICH (OR, 2.59; 95% CI, 1.07 to 6.25; P=0.034).

Conclusions—These data support current guidelines advising not to use intravenous tissue plasminogen activator when pretreatment blood pressure exceeds the prespecified thresholds by showing that blood pressure protocol violations are independently associated with a higher likelihood of sICH. (Stroke. 2009;40:3631-3634.)

Key Words: blood pressure ■ intracranial hemorrhage ■ outcome ■ stroke ■ thrombolysis ■ tPA

From small pilot studies,1,2 uncontrolled pretreatment systolic blood pressure (SBP) >185 mm Hg and diastolic blood pressure >110 mm Hg in patients with acute ischemic stroke (IS) were introduced in the National Institute of Neurological Diseases and Stroke rt-PA Stroke Study3 as a contraindication for thrombolysis. Current American Heart Association/American Stroke Association guidelines endorse these thresholds and advocate against treating patients with acute IS with intravenous tissue plasminogen activator (tPA) when pretreatment blood pressure (BP) levels are uncontrolled.4 However, little data are available to substantiate the choice of these specific BP values. Because extreme BP elevations are common in the setting of acute IS,5 it is likely that tPA treatment is delayed or even denied in a substantial number of patients with acute IS (especially in cases of extremely elevated BP levels not responding to antihypertensive treatment) because of these stringent BP thresholds. Com-
plicating the issue of BP management further are data to suggest that lowering BP below the recommended cutoff (185/110 mm Hg) may compromise functional outcome.\textsuperscript{6,7} In view of these considerations, we sought to determine whether pretreatment BP protocol violations in patients with acute IS receiving intravenous tPA are related to (1) the subsequent risk of symptomatic intracranial hemorrhage (sICH); and (2) functional outcome at hospital discharge.

Subjects and Methods
A retrospective cohort design was used to analyze single-center stroke registry data prospectively collected from consecutive IS admissions treated with a 0.9-mg/kg dose of intravenous tPA within 3 hours from stroke onset between January 1996 and December 2005.\textsuperscript{4} All patients were prospectively identified and their data were entered in a computerized stroke registry. Details about the stroke registry of our institution have been previously described.\textsuperscript{8} Pretreatment SBP and diastolic blood pressure were measured using automated cuffs. BP protocol violations were identified as SBP $>$185 or diastolic blood pressure $>$110 mm Hg prebolus.\textsuperscript{4} Patients with BP levels exceeding American Heart Association recommendations were treated at the discretion of the attending physician with either labetalol (bolus 10 to 20 mg intravenously over 1 to 2 minutes, repeat same dose every 10 to 20 minutes until desired BP levels are reached, maximum dose 300 mg) or nicardipine (continuous infusion of 5 mg/hr, titration up to the desired effect by 2.5-mg/hr increments at 5- to 15-minute intervals; maximum dose 15 mg/hr).\textsuperscript{4} The onset-to-treatment time was defined as the elapsed time from stroke onset to tPA bolus. Patients excluded from analyses were those with unavailable pretreatment BP levels, those treated outside the 3-hour window or who received combination of intravenous and intra-arterial thrombolytic treatment, and those with other intravenous tPA protocol violations as specified in current American Heart Association/American Stroke Association recommendations.\textsuperscript{4} Functional independence at hospital discharge was defined as a modified Rankin Scale score of 0 to 1. sICH was defined as brain imaging evidence of intracranial hemorrhage and clinical worsening of the National Institutes of Health Stroke Scale score by an increase of $\geq$4 points within 36 hours from tPA bolus.

Statistical Analyses
Statistical comparisons were performed between patients with and without sICH using the $\chi^2$ test, Fisher exact test, unpaired t test, and Mann-Whitney U test as indicated. Multivariable analyses were performed with the use of logistic regression to identify predictor variables of sICH. Associations are presented as ORs with corresponding 95% CIs. The Statistical Package for Social Science (SPSS Inc, Version 11.5 for Windows) was used for statistical analyses.

Results
Among 534 consecutive patients with IS treated with intravenous tPA within 180 minutes of ictus, pretreatment BP values were available in 510 patients (282 men; mean age 65±15 years). Overall, BP protocol violations were found in 63 patients (12.4%), and sICH occurred in 31 patients (6.1%).

The following factors were associated with sICH on univariable analyses ($P<0.2$; Table): age, hypertension, atrial fibrillation, smoking, pretreatment BP protocol violation, baseline National Institutes of Health Stroke Scale score, onset-to-treatment time, and lipid-lowering medication use before stroke onset. Pretreatment BP protocol violations were more frequent in patients with sICH (26% versus 12%; $P=0.019$). More specifically, patients with sICH had higher pretreatment SBP (169±29 mm Hg versus 156±24 mm Hg; $P=0.006$; Figure), whereas pretreatment diastolic blood pressures ($85\pm21$ mm Hg versus $82\pm16$ mm Hg; $P=0.430$) were similar in those with and without sICH.

A total of 43 patients were excluded from the present analyses (n=510) because of additional protocol violations to BP control before tPA bolus. The rate of sICH in this subgroup was 16.2% (6 of 43). There was a linear association between the number of protocol violations (0, 1, $\geq$2) and the rate of sICH (6.1%, 12.4%, and 16.2%, respectively; $P=0.004$ for linear-by-linear association in $\chi^2$ test) in the combined group of patients (n=553). In addition, when the BP threshold of 180/105 mm Hg was used for

<table>
<thead>
<tr>
<th>Variable</th>
<th>sICH-Positive</th>
<th>sICH-Negative</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71±11</td>
<td>66±15</td>
<td>0.064</td>
</tr>
<tr>
<td>Male sex</td>
<td>55%</td>
<td>56%</td>
<td>0.867</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68%</td>
<td>55%</td>
<td>0.163</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19%</td>
<td>13%</td>
<td>0.413</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>23%</td>
<td>11%</td>
<td>0.043</td>
</tr>
<tr>
<td>Smoking</td>
<td>29%</td>
<td>41%</td>
<td>0.196</td>
</tr>
<tr>
<td>Heavy alcohol intake</td>
<td>10%</td>
<td>12%</td>
<td>0.734</td>
</tr>
<tr>
<td>Antiplatelet use before stroke</td>
<td>36%</td>
<td>29%</td>
<td>0.428</td>
</tr>
<tr>
<td>Lipid-lowering medication use</td>
<td>36%</td>
<td>19%</td>
<td>0.031</td>
</tr>
<tr>
<td>Median baseline National Institutes of Health Stroke Scale (IQR)</td>
<td>12 (10)</td>
<td>8 (7)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Median pretreatment serum glucose, mg/dL (IQR)</td>
<td>113 (40)</td>
<td>118 (38)</td>
<td>0.995</td>
</tr>
<tr>
<td>Platelet count, 1000/mm$^3$</td>
<td>273±117</td>
<td>258±83</td>
<td>0.493</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>169±29</td>
<td>156±24</td>
<td>0.006</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85±21</td>
<td>82±16</td>
<td>0.430</td>
</tr>
<tr>
<td>Pretreatment BP protocol violation</td>
<td>26%</td>
<td>12%</td>
<td>0.019</td>
</tr>
<tr>
<td>Antihypertensive medication before tPA bolus</td>
<td>6%</td>
<td>9%</td>
<td>0.322</td>
</tr>
<tr>
<td>Median time from symptom onset to tPA bolus, minutes (IQR)</td>
<td>140 (80)</td>
<td>125 (65)</td>
<td>0.161</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
defining BP protocol violations, the rate of sICH tended to be higher in patients with than without BP protocol violations (10.6% versus 5.2%; \( P = 0.057 \)).

In a multivariable logistic regression model, sICH was more likely in patients with pretreatment BP protocol violations (OR, 2.59; 95% CI, 1.07 to 6.25; \( P = 0.034 \)), higher baseline stroke severity (OR per 1-point increase in National Institutes of Health Stroke Scale: 1.11; 95% CI, 1.05 to 1.18; \( P = 0.001 \), and lipid-lowering medication use before stroke onset (OR, 2.41; 95% CI, 1.09 to 5.33; \( P = 0.030 \)). We also repeated the multivariable regression analyses after substituting pretreatment SBP (as a continuous variable) for pretreatment BP protocol violations in our logistic regression models. Pretreatment SBPs were independently associated with sICH (OR per 10-mm Hg increase in pretreatment SBP: 1.22; 95% CI, 1.06 to 1.41; \( P = 0.008 \)). The sensitivity and specificity of SBP \( \geq 185 \) mm Hg and SBP \( \geq 180 \) mm Hg for predicting sICH were 29%/86% and 23%/89%, respectively.

Patients with uncontrolled pretreatment BP elevations tended toward lower rates of functional independence at hospital discharge (25%) compared with patients with BP protocol deviations (37%; \( P = 0.074 \)). The rates of in-hospital mortality were similar between the 2 groups (8% versus 6%; \( P = 0.510 \)). Patients with BP protocol violations without sICH tended to have lower functional independence rates at hospital discharge compared with patients in which no BP violations and no sICH occurred (29% versus 38%; \( P = 0.177 \)).

**Discussion**

Our study showed that deviations from the recommended pretreatment BP eligibility criteria occurred in approximately one of 8 patients with acute IS who were treated with intravenous thrombolysis sustaining BP levels above the threshold of 185/110 mm Hg before tPA bolus. Patients with BP protocol violations had higher rates of sICH and a trend toward lower functional independence at discharge. The relationship between BP protocol violations and a higher likelihood of sICH after intravenous tPA persisted even after adjustment for potential confounders, including age and stroke severity.

The documented association between pretreatment BP protocol violations and increased odds of 139% for sICH in our cohort provides nonrandomized evidence to support the currently recommended BP eligibility criteria for intravenous tPA in acute IS. Our findings are consistent with a retrospective analysis of the European Cooperative Acute Stroke Study II showing also an independent relationship between pretreatment SBP (evaluated as a continuous variable) and hemorrhagic transformation after tPA therapy.9 Furthermore, mean BP was an independent predictor of all tPA-related intracranial hemorrhage according to the findings of the rt-PA Acute Stroke Survey evaluating prospectively collected data from 1205 patients treated in routine clinical setting with intravenous tPA within 3 hours from stroke onset.10 In addition, our findings are also corroborated by a recent retrospective analysis of the Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register (SITS-ISTR) documenting a strong linear association between SBP (as a categorical variable) and risk of sICH.11 Finally, a multicenter study of transcranial Doppler monitoring of recanalization after intravenous thrombolysis showed that pretreatment SBP \( \geq 185 \) mm Hg was associated with strikingly high rates of persisting occlusion and partial recanalization (86%), whereas an increment of 10-mm Hg increase in pretreatment SBP was independently associated with a 15% lower likelihood of complete recanalization.12 Interestingly, persistent occlusion had a 6-fold higher risk of sICH after adjustment for demographic characteristics, stroke risk factors, and clinical variables in the same data set.13

Certain limitations of the present report need to be acknowledged. First, this is a retrospective analysis of prospectively collected data from a single center. Second, early ischemic changes on brain CT scan, which have been shown to be an independent predictor of sICH,9 were not evaluated and therefore not included in the present analyses. Third, we also did not have detailed information on BP treatment and control during and after tPA infusion. Thus, the lack of post-tPA data does not allow us to analyze the potential association of BP changes during tPA infusion with the risk of sICH. Fourth, BP measurements were not standardized and this may result in a higher variation of BP recordings. Fifth, no follow-up was performed beyond hospital discharge and therefore the potential relationship between BP protocol violation and early functional outcome at 3 months cannot be investigated, whereas it should be noted that modified Rankin Scale score at hospital discharge may be confounded by length of stay.

In conclusion, the present results in addition to the recent SITS-ISTR findings indicate that noncompliance with the National Institute of Neurological Diseases and Stroke rt-PA Stroke Study recommendations for pretreatment BP control is independently associated with an increased likelihood of sICH. These observations support current American Heart Association/American Stroke Association guidelines advising against using intravenous tPA in patients whose BP levels are not controlled at the threshold of 185/110 mm Hg.

**Disclosures**

G.T. is a recipient of a neurosonology fellowship grant from the Neurology Department of Eginition Hospital, University of Athens School of Medicine, Athens, Greece. A.Y.L. received a fellowship grant from the Neurology Department of St Thomas Hospital and Tan Van Kee Foundation, Manila, the Philippines. A.V.A. received grant support and speaking honoraria from Genentech, Inc. V.K.S. received a financial grant for his fellowship from the National Healthcare Group and National University Hospital, Singapore.

**References**


Pre–Tissue Plasminogen Activator Blood Pressure Levels and Risk of Symptomatic Intracerebral Hemorrhage

Georgios Tsivgoulis, James L. Frey, Murray Flaster, Vijay K. Sharma, Annabelle Y. Lao, Steven L. Hoover, Wei Liu, Elefterios Stamboulis, Anne W. Alexandrov, Marc D. Malkoff and Andrei V. Alexandrov

Stroke. 2009;40:3631-3634; originally published online September 17, 2009;
doi: 10.1161/STROKEAHA.109.564096

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/11/3631

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/