Postthrombolysis Blood Pressure Elevation Is Associated With Hemorrhagic Transformation

Kenneth Butcher, MD, PhD; Søren Christensen, PhD; Mark Parsons, PhD, FRACP; Deidre A. De Silva; Martin Ebinger; Christopher Levi; Thomas Jeerakathil, MD, MSc; Bruce C.V. Campbell, MBBS; P. Alan Barber, PhD, FRACP; Christopher Bladin; John Fink; Brian Tress, FRACR; Geoffrey A. Donnan, MD, FRACP; Stephen M. Davis, MD, FRACP; for the EPITHET Investigators

Background and Purpose—Reliable predictors of hemorrhagic transformation (HT) after stroke thrombolysis have not been identified. We analyzed hemorrhage in a randomized trial of tissue plasminogen activator (t-PA) vs placebo in ischemic stroke patients. We hypothesized that acute diffusion-weighted imaging (DWI) lesion volumes would be larger and blood pressures would be higher in patients with HT.

Methods—HT was assessed 2 to 5 days after treatment in 97 patients. Hemorrhage was assessed by using susceptibility-weighted imaging sequences and was classified as petechial hemorrhagic infarction (HI) or parenchymal hematoma (PH).

Results—PH was more frequent in t-PA– (11/49) than in placebo- (4/48) treated patients (P=0.049). Patients with PH had larger DWI lesion volumes (63.1±56.1 mL) than did those without HT (27.6±39.0 mL, P=0.033). There were no differences in baseline systolic blood pressure (SBP) between patients with and without hemorrhage. Weighted average SBP 24 hours after treatment was higher in patients with PH (159.4±18.8 mL, P<0.011) relative to those without HT (143.1±20.0 mL). Multinomial logistic regression indicated that PH was predicted by DWI lesion volume (odds ratio=1.16 per 10 mL; 95% CI, 1.03 to 1.30), atrial fibrillation (odds ratio=9.33; 95% CI, 2.30 to 37.94), and 24-hour weighted average SBP (odds ratio=1.59 per 10 mm Hg; 95% CI, 1.14 to 2.23).

Conclusions—Pretreatment DWI lesion volume and postthrombolysis BP are both predictive of HT. Consideration should be given to excluding patients with very large baseline DWI volumes from t-PA therapy and to more stringent BP control after stroke thrombolysis. (Stroke. 2010;41:72-77.)

Key Words: diffusion-weighted imaging ▪ perfusion-weighted imaging ▪ thrombolysis ▪ intracerebral hemorrhage ▪ blood pressure

Hemorrhagic transformation (HT) is the most feared and most common complication of thrombolysis for acute ischemic stroke. Based on neuroimaging, transformation can be classified as hemorrhagic infarction (HI), which is limited to petechial bleeding, or parenchymal hemorrhage (PH).1–4 HT can also be classified as symptomatic or asymptomatic on the basis of contemporaneous clinical deterioration.5 The definition of symptomatic transformation can be somewhat subjective, however, as the clinical state of acute stroke patients often fluctuates, irrespective of the presence of hemorrhage.6 Even when classified as “asymptomatic,” PH has been shown to be associated with poor outcome, whereas HI generally has not been shown to be clinically significant.6–8 Furthermore, the precise timing of HT relative to neurologic changes is virtually never known. Therefore, many studies have used objective radiologic definitions of HT, based solely on posttreatment imaging.2,4,6,7,9,10

The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was a randomized, controlled trial of tissue plasminogen activator (t-PA) or placebo in ischemic stroke patients treated 3 to 6 hours after onset and who were imaged serially with diffusion- (DWI) and perfusion- (PWI) weighted imaging.11 In this study, we aimed to determine the predictors of HT, defined by standardized radiologic criteria, irrespec-
tive of symptoms. We hypothesized that acute DWI lesion volumes would be larger and blood pressures (BPs) would be higher in patients with HT.

Subjects and Methods

Protocol

The EPITHET protocol has been described in detail previously. Acute ischemic stroke patients with no contraindications to thrombolysis were randomized to treatment with intravenous t-PA or placebo 3 to 6 hours after symptom onset. Patients were excluded when systolic BP (SBP) was >185 mm Hg, despite acute treatment, or when they had early ischemic changes on computed tomography (CT) involving >1/3 of the middle cerebral artery territory. Patients had serial magnetic resonance imaging (MRI) studies before treatment and again at days 3 and 90 after treatment. Patients were randomized irrespective of the MRI findings. All patients were kept on a cardiac monitor and continuous noninvasive BP monitor for 24 hours after randomization. Heart rate and BP were recorded every 15 minutes for the initial 2 hours, every 30 minutes for 4 hours, hourly for 4 hours, every 2 hours for 8 hours, and then every 4 hours thereafter. The study protocol and informed consent procedures were approved by local research ethics committees.

Imaging Protocol and Analysis

MRI scans were obtained with 1.5-T echoplanar imaging–equipped scanners (GE Signa/Siemens Vision/Symphony/Philips Intera). PWI and DWI postprocessing and region of interest analysis were performed centrally. Tmax maps were calculated with the use of singular value decomposition, and a threshold of ≥2 seconds was used to provide an objective PWI volume (Tmax ≥2 secondsvol). DWI lesion volume (DWIvol) was measured by planimetric techniques. Mismatch volume was calculated as Tmax ≥2 secondsvol - DWIvol and the mismatch ratio as Tmax ≥2 secondsvol/DWIvol. A malignant PWI-DWI profile was defined as a Tmax ≥8 secondsvol and/or a DWIvol >100 mL. Target mismatch was defined as a PWI-DWI ratio of >1.2 with an absolute mismatch >10 mL in the absence of a malignant profile.

HT Assessment

HT was assessed by posttreatment MRI studies, including susceptibility-weighted (T2*) images, DWI, and T2-weighted images. The T2* images were obtained as part of the PWI sequence. The precontrast T2* images were used to define hemorrhagic changes. When MRI data were unavailable, CT scans were obtained 24 hours after treatment were used to assess for hemorrhage.

HT was classified by consensus among 3 raters using the European Cooperative Acute Stroke Study (ECASS) algorithm. HI was defined as small petechiae along the margins of the infarct (HI1) or confluent petechiae within the infarcted area but no space-occupying effect (HI2; Figure 1). PH was defined as blood clot in ≤30% of the infarcted area with some slight space-occupying effect (PH1) or blood clot in >30% of the infarct area with substantial space-occupying effect (PH2). PH (PH1 and PH2) and HI (HI1 and HI2) events were grouped together in this analysis. Symptomatic HT was defined as a PH2 associated with a decline in the National Institutes of Health Stroke Scale (NIHSS) score of ≥4 points within 36 hours of treatment, as defined in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).

Statistical Analysis

Statistical analysis was performed with SPSS (SPSS Inc, Chicago, IL). Differences in MRI lesion volumes and BP were tested with 1-way ANOVA and post hoc Tukey’s tests. The frequency of HT in t-PA and placebo treatment groups and atrial fibrillation by hemorrhage type was tested by Fisher’s exact test. Weighted average BP was calculated as the area under the curve describing pressures over 24 hours. Univariate multinomial logistic regression was used to determine the effect of independent variables on the trichotomous outcome of “no hemorrhage” (reference group), “HI,” and “PH.” Variables with a significant (P<0.05) univariate relation were included in a multivariate multinomial regression model.

Results

Baseline Characteristics

There were 97 patients (53 men; mean±SD age, 71.2±14.0 years) in this study, of whom 49 were randomized to t-PA and 48 to placebo. Three of the original 100 EPITHET patients were excluded. In 2 t-PA–treated patients, the follow-up scans were lost at the study center, although radiologist’s reports indicated no hemorrhagic changes. Another t-PA–treated patient developed a remote hemorrhage at the site of a cerebral microbleed contralateral to the infarct, subsequent to anticoagulation on day 2, and was also excluded.

Patients were imaged with MRI at a median of 4.3 hours (interquartile range [IQR], 3.5 to 4.8) after symptom onset. Follow-up imaging was performed at a median of 3 (IQR, 2 to 4) days. Follow-up MRI data were available for 91 patients, and a CT scan was used to assess for hemorrhage in the remaining 6. The median acute NIHSS score was 11 (IQR, 8 to 18).

Frequency of HT

Approximately 50% of patients in both the t-PA and placebo treatment groups developed HT (Figure 2). PH occurred more frequently in t-PA– (12/49) versus placebo- (20/48) treated patients (P=0.049). There was a trend toward lower rates of HI in t-PA– (12/49) versus placebo- (20/48) treated patients (P=0.056).

MRI Lesion Volumes and HT

Larger pretreatment DWI lesion volumes were associated with more severe hemorrhagic changes (Figure 3). Patients with PH had greater DWI lesion volumes (63.1±56.1 mL) than did those without HT (27.6±39.0 mL, P=0.033). Patients with HI had intermediate pretreatment DWI lesion volumes (46.5±54.6 mL, P=0.186). Univariate multinomial logistic regression indicated that PH was predicted by acute
DWI lesion volume (odds ratio [OR] = 1.16 per 10 mL; 95% CI, 1.03 to 1.30). Regression indicated no relation between DWI lesion volume and the presence of HI (OR = 1.10 per 10 mL; 95% CI, 0.99 to 1.23). Apparent diffusion coefficient values were not predictive of HT (Table 1).

PWI-DWI mismatch ratios in patients with PH (5.3 ± 4.7) were not significantly lower than those in patients without HT (16.9 ± 5.2, P = 0.191; Figure 3). There was a nonsignificant trend toward an increased incidence of PH and HI in the 33 patients with a malignant PWI-DWI profile (d² = 5.13, P = 0.075; Table 2). The frequency of HT in patients with and without target mismatch patterns was similar (d² = 1.03, P = 0.597).

BP and HT
There were no differences in baseline BP in patients with or without HT (Table 1). However, the temporal profile of BP in the posttreatment period was different in patients who developed PH (Figure 4). In the 24 hours after treatment, patients with PH had significantly higher weighted average SBP (159.4 ± 18.8 vs 143.1 ± 20.0 mm Hg, P = 0.011), diastolic BP (85.2 ± 16.4 vs 76.0 ± 12.2 mm Hg, P = 0.036), and mean arterial pressure (109.9 ± 16.1 vs 98.3 ± 13.7 mm Hg, P = 0.008), compared with those without HT. Weighted average pressures were not elevated in patients with HI (Table 1).

Multinomial logistic regression indicated that PH was predicted by the 24-hour weighted average SBP (OR = 1.59 per 10 mm Hg; 95% CI, 1.14 to 2.23). Thus, for every 10-mm Hg elevation in BP in the posttreatment period, the odds of PH increased by 59%. PH was also predicted by the 24-hour weighted average diastolic BP (OR = 1.75 per 10 mm Hg; 95% CI, 1.10 to 2.76) and mean arterial pressure (OR = 1.93 per 10 mm Hg; 95% CI, 1.21 to 2.06). In contrast, HI was not predicted by 24-hour weighted BPs (Table 1).

There were no differences in 24-hour weighted SBPs between patients with and without reperfusion (145 ± 17 vs 142 ± 27 mm Hg, P = 0.60) or recanalization (132 ± 37 vs 141 ± 17 mm Hg, P = 0.25). Weighted average SBP was also similar in patients with and without subacute DWI lesion growth (144 ± 24 vs 145 ± 13 mm Hg, P = 0.92). Weighted diastolic and mean arterial pressures over 24 hours were also unrelated to reperfusion, recanalization, lesion growth, or neurologic outcome. Thus, BP during the initial 24 hours after treatment was higher only in patients with PH.

Other Predictors of HT
Atrial fibrillation was more frequent in patients with PH (79%) than in those with HI (44%) or no hemorrhage (30%; P = 0.003, d² for trend). Univariate multinomial logistic regression indicated that atrial fibrillation predicted PH (OR = 9.33; 95% CI, 2.30 to 37.94) but not HI (OR = 1.82; 95% CI, 0.72 to 4.57). Logistic regression indicated that t-PA treatment, age, glucose value, platelet count, time to treat-
stent, NIHSS score, PWI-DWI mismatch volume, malignant mismatch profile, and reperfusion did not predict hemorrhage of any type (Table 1). The hypoperfused tissue volume demonstrated on PWI was weakly predictive of HI (OR = 1.04 to 2.04) and atrial fibrillation (OR = 1.88 per 10 mm Hg; 95% CI, 1.19 to 2.97) and atrial fibrillation (OR = 10.13; 95% CI, 1.77 to 57.91). DWI lesion volume did not predict HT in this smaller subset of patients (OR = 1.16 per 10 mL; 95% CI, 0.99 to 1.36). In placebo-treated patients, only atrial fibrillation was predictive of PH (OR = 7.29; 95% CI, 0.64 to 82.62).

**Symptomatic HT**

Four t-PA–treated patients had symptomatic HT, as defined by SITS-MOST criteria. There were no differences in mean DWI lesion volume between patients with and without symptomatic hemorrhage (39.6 ± 49.7 vs 33.6 ± 13.9 mL, P = 0.814). Baseline SBP was also similar in these 2 groups (147.2 ± 18.0 vs 154.8 ± 10.7 mm Hg). In contrast, 24-hour weighted average SBP was significantly higher in symptomatic (175.3 ± 22.0 mm Hg) than in asymptomatic (143.8 ± 23.9 mm Hg, P = 0.011) hemorrhage patients.

**Discussion**

For the first time, we have shown that BP after t-PA treatment is predictive of PH. This finding is consistent with 2 opposing hypotheses. The more intriguing from a therapeutic point of view is the possibility that more aggressive BP control, based on lower treatment thresholds, may decrease the frequency of thrombolysis-related hemorrhage. Conversely, BP elevation after t-PA treatment may herald the onset of acute hemorrhagic complications. Both hypotheses have important implications for clinical practice and should be tested in dedicated studies. This study also confirms the previously reported finding

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**Table 1. Predictors of HT**

<table>
<thead>
<tr>
<th></th>
<th>No HT</th>
<th>HI</th>
<th>OR</th>
<th>95% CI</th>
<th>PH</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.9±140.3</td>
<td>71.3±13.1</td>
<td>1.002</td>
<td>0.97–1.04</td>
<td>74.4±9.1</td>
<td>1.023</td>
<td>0.97–1.08</td>
</tr>
<tr>
<td>Time to treatment, min</td>
<td>296.5±42.1</td>
<td>297.9±48.3</td>
<td>1.001</td>
<td>0.99–1.01</td>
<td>283.2±54.2</td>
<td>0.994</td>
<td>0.98–1.006</td>
</tr>
<tr>
<td>NIHSS score, IQR (range)</td>
<td>11 (4–23)</td>
<td>15 (5–25)</td>
<td>1.07</td>
<td>0.98–1.17</td>
<td>16 (7–26)</td>
<td>1.10</td>
<td>0.99–1.23</td>
</tr>
<tr>
<td>Acute glucose value, mmol/L</td>
<td>7.4±2.5</td>
<td>8.2±4.0</td>
<td>1.09</td>
<td>0.94–1.25</td>
<td>8.6±4.2</td>
<td>1.11</td>
<td>0.94–1.31</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30%</td>
<td>43.8%</td>
<td>1.82</td>
<td>0.72–4.57</td>
<td>78.6%</td>
<td>9.33</td>
<td>2.93–37.94</td>
</tr>
<tr>
<td>DWI volume, mL</td>
<td>27.6±39.0</td>
<td>46.5±54.6</td>
<td>1.10</td>
<td>0.99–1.23</td>
<td>63.1±56.1</td>
<td>1.16</td>
<td>1.03–1.30</td>
</tr>
<tr>
<td>Apparent diffusion coefficient (core), relative values</td>
<td>0.74±0.08</td>
<td>0.72±0.07</td>
<td>0.03</td>
<td>0.0–17.55</td>
<td>0.72±0.05</td>
<td>0.04</td>
<td>0.0–169.5</td>
</tr>
<tr>
<td>PWI volume, mL</td>
<td>149.4±116.9</td>
<td>220.1±122.1</td>
<td>1.05</td>
<td>1.01–1.10</td>
<td>165.6±85.4</td>
<td>1.06</td>
<td>1.0–1.07</td>
</tr>
<tr>
<td>Mismatch volume, mL</td>
<td>121.8±110.7</td>
<td>173.6±119.5</td>
<td>1.04</td>
<td>1.0–1.09</td>
<td>111.5±81.5</td>
<td>0.99</td>
<td>0.93–1.05</td>
</tr>
<tr>
<td>Mismatch ratio</td>
<td>16.8±25.5</td>
<td>14.2±23.2</td>
<td>0.99</td>
<td>0.98–1.02</td>
<td>5.3±4.6</td>
<td>0.93</td>
<td>0.86–1.02</td>
</tr>
<tr>
<td>Reperfusion, %</td>
<td>40.6±48.9</td>
<td>44.6±46.4</td>
<td>1.002</td>
<td>0.99–1.01</td>
<td>46.1±36.9</td>
<td>1.003</td>
<td>0.99–1.02</td>
</tr>
<tr>
<td>Baseline SBP, mm Hg</td>
<td>147.3±19.0</td>
<td>146.3±16.4</td>
<td>0.89</td>
<td>0.70–1.13</td>
<td>150.9±16.5</td>
<td>1.09</td>
<td>0.79–1.51</td>
</tr>
<tr>
<td>Baseline diastolic BP, mm Hg</td>
<td>78.1±13.6</td>
<td>79.4±13.4</td>
<td>1.08</td>
<td>0.77–1.51</td>
<td>75.6±13.0</td>
<td>0.87</td>
<td>0.56–1.35</td>
</tr>
<tr>
<td>Baseline mean arterial pressure, mm Hg</td>
<td>101.8±12.3</td>
<td>101.3±12.0</td>
<td>0.97</td>
<td>0.67–1.4</td>
<td>101.1±12.1</td>
<td>0.96</td>
<td>0.59–1.54</td>
</tr>
<tr>
<td>24-hour weighted average SBP, mm Hg</td>
<td>143.1±20.0</td>
<td>146.4±16.5</td>
<td>1.10</td>
<td>0.86–1.40</td>
<td>159.4±18.8</td>
<td>1.59</td>
<td>1.14–2.23</td>
</tr>
<tr>
<td>24-hour weighted average diastolic BP, mm Hg</td>
<td>76.0±12.2</td>
<td>78.7±10.2</td>
<td>1.21</td>
<td>0.83–1.8</td>
<td>85.2±16.4</td>
<td>1.75</td>
<td>1.10–2.76</td>
</tr>
<tr>
<td>24-hour weighted average mean arterial pressure, mm Hg</td>
<td>98.3±13.7</td>
<td>101.2±9.4</td>
<td>1.21</td>
<td>0.84–1.74</td>
<td>109.9±16.1</td>
<td>1.93</td>
<td>1.21–3.06</td>
</tr>
</tbody>
</table>

*No HT* is the reference group. Reperfusion (%) = (day 3–5 PWIvol/acute PWIvol)×100. DWI, PWI, and mismatch volume ORs are given per 10-mL increase. All BP ORs are per 10-mm Hg increase.

**Table 2. Frequency of HT in Patients With Malignant and Target Mismatch PWI-DWI Profiles**

<table>
<thead>
<tr>
<th>Malignant Profile, % (λ² = 5.13, P = 0.075)*</th>
<th>Target Mismatch, % (λ² = 1.03, P = 0.597)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmalignant, % (λ² = 5.13, P = 0.050)†</td>
<td>Nonmalignant, % (λ² = 1.03, P = 0.597)†</td>
</tr>
<tr>
<td>No HT</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>HI</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>PH</td>
<td>7 (21.2)</td>
</tr>
</tbody>
</table>

*Relative to patients with a nonmalignant mismatch pattern.† Relative to patients with a nontarget mismatch pattern.
that atrial fibrillation increases the risk of PH and substantially strengthens the previously inconsistent finding that larger baseline DWI lesions predict PH. These findings may assist clinicians in stratifying HT risk before treatment.15–17

BP and Hemorrhage

Clinical studies of HT in thrombolysis to date have assessed BP before thrombolytic therapy alone. In the Australian Streptokinase Trial, higher baseline BP was exponentially associated with the risk of symptomatic HT in both the treatment and control groups.18 Subsequent randomized, controlled trials of t-PA in acute stroke failed to demonstrate a relation between BP and bleeding risk. However, the selection criteria for those trials resulted in the exclusion of markedly hypertensive patients, usually defined as those with a baseline SBP >185 mm Hg or a diastolic BP >110 mm Hg.7 A more recent analysis of data from the SITS-MOST registry (N=6483) indicated that elevations in baseline SBP significantly increased the odds of symptomatic HT, but the temporal course of arterial pressures after thrombolysis was not assessed.19 A secondary analysis of the NINDS trials provides some evidence for the importance of BP in the 24 hours after symptom onset, with a trend toward increased symptomatic hemorrhage in patients administered antihypertensives for hypertension, regardless of whether they received t-PA or placebo.20

Differences in posttreatment BP do appear to be related specifically to hemorrhage and are not explained by DWI lesion growth, recanalization, or reperfusion. The logistic-regression model used in this study permits statistical prediction based on posttreatment BP, but it does not allow determination of causality. The primary limiting factor is the lack of precise temporal information regarding the onset of HT. The elevation in BP in PH patients was most evident ~6 hours after treatment (Figure 4), which is consistent with hypertension secondary to an elevation in intracranial pressure subsequent to hemorrhage. Nonetheless, the hypothesis that hypertension results in HT via increased arteriolar hydrostatic pressure is also biologically plausible and could be considered consistent with our results. A randomized trial of alternative BP management strategies after thrombolysis that includes more frequent imaging assessments for HT is required to adequately test these hypotheses. Given concerns related to cerebral perfusion compromise after antihypertensive therapy, such studies should also include measures of cerebral blood flow.

MRI Lesion Volumes and Hemorrhage

Previous studies of the association between DWI lesion volume and thrombolysis-related hemorrhage have been inconsistent. A number of retrospective and prospective studies have indicated that large DWI lesions and/or PWI deficits predispose to symptomatic HT.13,15,16 Another study suggested that hemorrhage could not be predicted by DWI lesion volume.8 Our own univariate analysis of MRI lesions supports the a priori hypothesis that acute DWI volume is predictive of HT. A precise lesion size associated with hemorrhage cannot be predicted from our results. Nonetheless, we advise caution in treating patients with DWI lesions larger than the mean volume in the PH group (56 mL). Unlike in previous studies, a relation between HT and the degree of bioenergetic compromise measured by apparent diffusion coefficient values was not seen.21,22 An association between the risk of HT and a malignant PWI-DWI profile was not found either, which is inconsistent with a previous MRI study.11 It is important to note, however, that patients with the malignant profile had consistently poor outcomes in EPITHET, and we do not believe they are optimal thrombolysis candidates.11 The lack of consistency between studies likely reflects the fact that the development of HT is multifactorial and difficult to predict. Similarly, the lack of a relation between clinical factors such as hyperglycemia, age, and stroke severity with hemorrhagic complications in EPITHET likely reflects the sample size. The additional

![Figure 4. Temporal course of SBP in patients without HT, HI, and PH. A, All patients (t-PA and placebo). B, t-PA–treated patients only. C, Twenty-four-hour weighted SBP in t-PA– and placebo-treated patients. Posttreatment pressures were significantly higher in PH patients treated with t-PA.](http://stroke.ahajournals.org/)

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risk of HT conferred by these clinical factors is relatively small and therefore likely only becomes evident in larger studies. This study has a number of limitations. Susceptibility-weighted imaging was used to assess for HT in all patients, except those with large hematomas who were intolerant of a subacute MRI scan. Thus, our data are not directly comparable to other hemorrhage-in-thrombolysis studies, which have primarily been based on CT. This is most relevant to HI, rather than PH. In addition, the relatively small number of patients studied necessitated the grouping of all HI and PH patients. Although it would have been preferable to assess individual ECASS groups, this combination is supported by previous studies, indicating that HI and PH are very different in terms of patient prognosis.8,10 Previous investigations have consistently reported that PH is associated with poor outcome.6–8 Most studies have demonstrated that outcomes after HI are similar to those of patients without HT.8,10 It has been suggested that PH and HI result from distinct pathophysiological processes and therefore should be assessed separately.8

Conclusions
Arterial pressure during the initial 24 hours after treatment is associated with t-PA–related hemorrhagic complications. This finding does need to be confirmed in larger patient datasets, such as the SITS-MOST registry.9 Ultimately, the hypothesis that lower BP treatment thresholds will decrease hemorrhage rates should be tested in a randomized trial. Finally, patients with large baseline DWI lesion volumes should be considered higher-risk thrombolysis candidates.

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Disclosures
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