Plasma VAP-1/SSAO Activity Predicts Intracranial Hemorrhages and Adverse Neurological Outcome After Tissue Plasminogen Activator Treatment in Stroke

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Background and Purpose—Vascular adhesion protein-1 (VAP-1) is a cell surface and circulating enzyme involved in recruitment of lymphocytes and neutrophils through its semicarbazide-sensitive amine oxidase (SSAO) activity. We aimed to study plasma VAP-1/SSAO activity in relation to the risk for intracranial bleeding complications in patients with stroke treated with tissue plasminogen activator (tPA), the greatest safety concern with this treatment.

Methods—In 141 patients with ischemic stroke, we measured VAP-1/SSAO activity in plasma taken before tPA administration. Hemorrhagic events were classified according to brain CT criteria and functional outcomes evaluated using the National Institutes of Health Stroke Scale. We also assessed the potential therapeutic effect of blocking VAP-1/SSAO activity in a rat embolic stroke model treated with tPA.

Results—We saw significantly higher levels of plasma VAP-1/SSAO activity in patients who subsequently experienced hemorrhagic transformation. Elevated plasma VAP-1/SSAO activity also predicted worse neurological outcome in these patients. In the rat model, we confirmed that use of the inhibitor semicarbazide prevented adverse effects caused by delayed tPA administration, leading to a smaller infarct volume.

Conclusions—Our data demonstrate that baseline VAP-1/SSAO activity predicts parenchymal hemorrhage after tPA, suggesting the safety of thrombolytic agents could be improved by considering VAP-1/SSAO activity. Furthermore, anti-VAP-1/SSAO drugs given with tPA may prevent neurological worsening in patients with ischemic stroke. (Stroke. 2010;41:1528-1535.)

Key Words: animal model ■ hemorrhagic transformation ■ semicarbazide ■ stroke ■ thrombolysis ■ VAP-1/SSAO

Beyond prevention strategies, the only available treatment during the acute phase of ischemic stroke is the use of thrombolytic drugs to restore brain perfusion. A beneficial effect of intravenous tissue plasminogen activator (tPA) administered no later than 3 to 4.5 hours after symptom onset has been demonstrated.1,2 However, <5% of patients with stroke are treated with tPA. This is partly because tPA-treated patients with stroke have a 10-fold higher risk of intracranial hemorrhage than untreated patients. To improve the safety and widen the use of thrombolytic agents, the underlying mechanisms of intracranial hemorrhage complications must be identified. Indeed, some biomarkers have been described to predict thrombolysis-related injuries and intracranial hemorrhage. These include matrix metalloproteinase-9 and cellular fibronectin, both of which are implicated in alteration of the blood–brain barrier.

Vascular adhesion protein-1 (VAP-1) is a circulating and membrane-bound ectoenzyme involved in lymphocyte and neutrophil recruitment through its semicarbazide-sensitive amine oxidase (SSAO) activity. Abnormally high plasma VAP-1/SSAO activity has been found in patients with certain vascular and/or inflammatory conditions.7,8

We describe our findings on associations between plasma VAP-1/SSAO activity and hemorrhagic transformation (HT) and neurological outcome in patients with ischemic stroke treated with tPA. Finally, we evaluated the therapeutic effects of VAP-1/SSAO inhibition in ischemic rats subjected to clot embolism using semicarbazide as an inhibitor.
Methods

Study Population
We performed a prospective study of patients with acute ischemic stroke who had been admitted to our hospital’s emergency room within 3 hours after symptom onset. A total of 141 consecutive patients with a nonlacunar stroke involving the vascular territory of the middle cerebral artery or the basilar artery were evaluated. All patients underwent urgent carotid ultrasound and transcranial Doppler examinations. Patients received tPA in a standard 0.9-
mg/kg dose (10% bolus, 90% continuous infusion for 1 hour). We excluded patients with a known inflammatory or malignant disease; 140 patients were included for analysis. A subgroup of patients that either had (n = 6) or had not (n = 7) had a HT was randomly selected, and serial samples were obtained to ascertain temporal changes in VAP-1/SSAO activity. A group of age- and sex-matched healthy subjects (n = 30) was evaluated to establish their range for plasma VAP-1/SSAO activity.

Clinical Protocol
A detailed history of vascular risk factors was obtained from each patient. To identify possible mechanisms of cerebral infarction, we performed a set of diagnostic tests and classified the cohort according to previously defined etiologic subgroups. Our cohort included 64 cardioembolic strokes, 36 atherothrombotic strokes, and 41 patients with an undetermined etiology. Clinical examination was performed on admission and at 12, 24, and 48 hour after symptom onset. Stroke severity was assessed based on the National Institutes of Health Stroke Scale. We defined neurological improvement as a decrease in National Institutes of Health Stroke Scale score by ≥4 points and defined neurological deterioration as either death or an increase in this by ≥4 points at 48 hours. Our study was approved by the Ethics Committee of Vall d’Hebron Hospital (Barcelona, Spain), and all patients or their relatives gave written informed consent.

Computed Tomography
All patients underwent CT within the first 3 hours of stroke onset; this was repeated after 24 to 48 hours (or earlier in the case of rapid neurological deterioration) to evaluate the presence of HT. The CT scans were reviewed by a neuroradiologist with extensive experience in acute stroke. The presence and HT type were determined based on the following criteria: inappropriate occlusion of the middle cerebral artery or the basilar artery were evaluated. Animals were anesthetized under spontaneous respiration with 2% isoflurane (Abbot Laboratories, Kent, UK) in oxygen during surgery and body temperature was maintained at 37°C. Arterial blood from a donor rat was mixed with rat thrombin (0.004 U/µL; Sigma-Aldrich Inc, Barcelona, Spain) to form single fibrin-rich clots (length: 4 cm; diameter: 0.3 mm). Continuous laser–Doppler flowmetry (Moor Instruments, Devon, UK) was used to monitor regional cerebral blood flow and only animals that exhibited a >75% reduction in regional cerebral blood flow during middle cerebral artery occlusion were included in the study. tPA (9 mg/kg; Actilyse, Boehringer Ingelheim, Germany) was administered intravenously (2.5 µL/min) at 2, 3, or 4 hours after embolization. Cotreatment (10 minutes before tPA administration) with VAP-1/SSAO inhibitor semicarbazide (100 mg/kg, intraperitoneally; Sigma-Aldrich) or saline (control group) was given blindly at 3 and 4 hours after occlusion (delayed periods). Animals were randomly assigned to either the saline or the semicarbazide group (n = 10 per group). Of the 171 original animals, 58 were excluded based on the following criteria: inappropriate occlusion of the middle cerebral artery after embolization (n = 30); spontaneous reperfusion before tPA administration (n = 13); or death within 5 to 10 minutes after occlusion (n = 15). Sham animals were also treated with tPA to determine if this treatment could alter plasma VAP-1/SSAO activity levels.

Measuring Infarct Volume
Animals were deeply anesthetized and then transcardially perfused with ice-cold saline at 24 hours after clot embolism. The brains were removed, sliced into 2-mm-thick sections, and stained with 2% 2,3,5-triphenyltetrazolium chloride (Sigma-Aldrich) for 30 minutes at 37°C. The infarct volume was calculated by integration of the lesion areas considering the average of anterior and posterior views. Edema correction of infarct volume was calculated as: volume correction = (infarct volume × contralateral volume) / ipsilateral volume.

Assessment of Neurological Deficit and Systemic Bleeding
Rats were assayed with a 9-point neurological deficit scale before tPA administration and 24 hours after occlusion as previously described. The occurrence of systemic bleeding was blindly examined in operated rats after tPA administration. Animals were analyzed for the presence of hemorrhage in the neck and/or in the head surgical wound (scored as 1), the absence of hemorrhage (scored as 0), or death.

VAP-1/SSAO Activity Assay
Peripheral blood was collected in sodium citrate tubes and plasma was immediately separated by centrifugation at 3000 rpm for 15 minutes and stored at −80°C. For human brain homogenates, frozen brain tissue samples were weighed out and then mixed in cold lysis buffer (50 mmol/L Tris-HCl, pH 7.6, 150 mmol/L NaCl, 5 mmol/L CaCl2, 0.05% Brij-35, 0.02% NaN3, and 1% Triton X-100) containing protease inhibitors (1 mmol/L phenylmethylsulfonyl fluoride and 7 µg/mL aprotinin). Rat blood was also collected in sodium citrate tubes. VAP-1/SSAO activity was determined radiochemically in 50 µL of human or rat plasma, or 200 µg of brain homogenates, at 37°C as previously described using [14C]-benzylamine (3 µCi/mmol; Am-
Table. Baseline Characteristics of Patients According to the Presence or Absence of HT or PH*

<table>
<thead>
<tr>
<th></th>
<th>No HT (n=92)</th>
<th>HT (n=48)</th>
<th>P</th>
<th>No PH (n=124)</th>
<th>PH (n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>38 (48.3%)</td>
<td>26 (54.2%)</td>
<td>0.147</td>
<td>54 (43.5%)</td>
<td>10 (62.5%)</td>
<td>0.152</td>
</tr>
<tr>
<td>Age, years</td>
<td>70.2±12.5</td>
<td>71.9±10.5</td>
<td>0.420</td>
<td>70.2±12.0</td>
<td>75.7±8.8</td>
<td>0.076</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (50.0%)</td>
<td>30 (65.2%)</td>
<td>0.159</td>
<td>65 (53.3%)</td>
<td>10 (62.5%)</td>
<td>0.484</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>34 (37.4%)</td>
<td>10 (20.8%)</td>
<td>0.042†</td>
<td>41 (33.3%)</td>
<td>3 (18.8%)</td>
<td>0.219</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (20.9%)</td>
<td>8 (16.7%)</td>
<td>0.547</td>
<td>26 (21.1%)</td>
<td>1 (6.3%)</td>
<td>0.114</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>12 (13.2%)</td>
<td>8 (17.0%)</td>
<td>0.548</td>
<td>17 (13.9%)</td>
<td>3 (18.8%)</td>
<td>0.618</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>16 (11–18)</td>
<td>18 (14–20.75)</td>
<td>0.021†</td>
<td>16.5 (11–19)</td>
<td>18 (12.75–21)</td>
<td>0.117</td>
</tr>
<tr>
<td>Proximal occlusion</td>
<td>57 (62.6%)</td>
<td>35 (72.9%)</td>
<td>0.219</td>
<td>81 (65.9%)</td>
<td>11 (68.8%)</td>
<td>0.817</td>
</tr>
<tr>
<td>CT early signs</td>
<td>16 (24.6%)</td>
<td>8 (32.0%)</td>
<td>0.483</td>
<td>23 (27.4%)</td>
<td>1 (6.3%)</td>
<td>0.548</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>153.5±27.4</td>
<td>155.8±27.9</td>
<td>0.658</td>
<td>153.5±27.3</td>
<td>161.1±28.9</td>
<td>0.310</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>83.2±16.7</td>
<td>85.6±17.4</td>
<td>0.447</td>
<td>84.2±17.3</td>
<td>83.1±14.6</td>
<td>0.800</td>
</tr>
<tr>
<td>Platelets</td>
<td>119.6±37.1</td>
<td>139.4±48.2</td>
<td>0.011†</td>
<td>124.9±41.3</td>
<td>141.0±48.9</td>
<td>0.181</td>
</tr>
<tr>
<td>Leukocytes×10⁵/L</td>
<td>10 805.5±13 683.2</td>
<td>9295.2±2202.7</td>
<td>0.480</td>
<td>10 445.3±11 947.3</td>
<td>9250.0±2452.2</td>
<td>0.692</td>
</tr>
<tr>
<td>aPTT</td>
<td>0.92±0.10</td>
<td>0.92±0.07</td>
<td>0.769</td>
<td>0.92±0.09</td>
<td>0.94±0.81</td>
<td>0.440</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.30±0.72</td>
<td>3.51±0.79</td>
<td>0.168</td>
<td>3.36±0.69</td>
<td>3.51±1.10</td>
<td>0.478</td>
</tr>
<tr>
<td>VAP-1/SSAOa &gt;2.70</td>
<td>29 (31.5%)</td>
<td>33 (68.8%)</td>
<td>&lt;0.001†</td>
<td>48 (38.7%)</td>
<td>14 (87.5%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>VAP-1/SSAOa &gt;3.07</td>
<td>18 (19.6%)</td>
<td>20 (41.7%)</td>
<td>0.006†</td>
<td>27 (21.8%)</td>
<td>11 (68.8%)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

*Values are mean or no. (%).
†Factors with a P value <0.05.
NIHSS indicates National Institutes of Health Stroke Scale, SBP, systolic blood pressure; DBP, diastolic blood pressure; aPTT, activated partial thromboplastin time.

Myeloperoxidase Determination
Serum samples were obtained from patients at baseline (before tPA administration) and serially at 1 and 2 hours after tPA administration and at 12 and 24 hours after stroke onset. Plasma myeloperoxidase concentrations were measured by an enzyme-linked immunosorbent assay (Oxis International Inc) following the manufacturer’s instructions. The within-run and between-run coefficients of variation of our laboratory were 5.1% and 6.5%, respectively.

Statistical Analysis
Statistical analyses were obtained using SPSS software, Version 14.0. Statistical significances were used by Fisher exact test or the Student t test and analysis of variance. Plasma VAP-1/SSAO activity was normally distributed (Kolmogorov-Smirnov). Temporal profile activity was assessed by Friedman and Wilcoxon signed ranks test. Receiver operator characteristic curves were used to calculate the specificity and sensitivity of VAP-1/SSAO activity values for predicting HT or PH. A logistic regression analysis was performed to identify independent predictors of HT/PH subtypes. Percentages of infarct volumes in the embolic rat model were not normally distributed. Kruskal-Wallis or Mann-Whitney tests were performed to assess intergroup differences. Fisher exact test was used to analyze animal mortality or bleeding. Statistical significance is expressed as *P<0.05, **P<0.01, or ***P<0.001.

Results

Demographic Factors, Baseline Stroke Variables, and Their Influence on VAP-1/SSAO Activity
Our study population comprised 141 patients with an acute ischemic stroke. The majority of strokes involved the middle cerebral artery territory (n=132). The median National Institutes of Health Stroke Scale score of the series on admission was 17 (range, 3 to 29). The patients with stroke showed a mean baseline VAP-1/SSAO activity of 2.66±0.08 pmol/min·mg, similar to control patients (2.40±0.14 pmol/min·mg; P=0.17; Supplemental Figure I; available at http://stroke.ahajournals.org). Demographic characteristics of stroke patients are shown in Supplemental Table I, available at http://stroke.ahajournals.org.

Elevated Plasma VAP-1/SSAO Activity Predicts Intracranial Hemorrhage and Adverse Neurological Outcome in tPA-Treated Patients
In total, 48 patients (34.3%) had HT: 21 with HI-1 (15%); 11 with HI-2 (7.9%); 10 with PH-1 (7.1%); and 3 with HI-2 (2.1%); and 3 with PH-R (2.1%). The Table summarizes the main baseline characteristics of the patients with or without HT. A significantly higher level of baseline VAP-1/SSAO activity level was found among patients who later had an HT (P=0.002; Figure 1A). The highest baseline VAP-1/SSAO activity was found in patients with an ulterior PH (PH: 3.41±1.07; HI: 2.79±0.75; and non-HT: 2.48±0.92; P=0.001; Figure 1B). A graded response was obtained between baseline VAP-1/SSAO activity and the bleeding degree on CT (P<0.001). Patients who had a PH-R showed greater activity than those without any HT (P=0.01; Figure 1C).

Receiver operator characteristic curves identified the optimal cut points for VAP-1/SSAO activity association with either HT or PH.
min · mg cut points are shown in Supplemental Table II, available at http://stroke.ahajournals.org. A VAP-1/SSAO activity >2.7 pmol/min · mg was the main baseline predictor of HT (OR, 5.84; 2.16 to 15.80; P=0.001). Hyperglycemia was independently associated with HT as well (OR, 1.03; 1.01 to 1.05; P=0.008). Baseline VAP-1/SSAO activity remained the only independent predictor of PH using both the 2.7 VAP-1/SSAO cutoff (OR, 11.18; 2.19 to 56.93; P=0.004) and the 3.07 VAP-1/SSAO cutoff (OR, 8.94; 2.29 to 34.93; P=0.002).

Interestingly, baseline VAP-1/SSAO activity was correlated to myeloperoxidase levels determined only after 2 hours (P=0.004) of tPA administration and 12 hours (P=0.006) of stroke onset.

The temporal profile of VAP-/SSAO activity, according to the presence or absence of HT, showed that patients who had an HT presented an increase of plasma VAP-1/SSAO activity within the first day after symptom onset (Figure 2). Neurological outcome assessment, within 48 hours after admission, revealed a higher baseline VAP-1/SSAO activity (3.12±0.86 pmol/min · mg) in patients with neurological worsening (15 [10.8%]), whereas a lower baseline activity (2.48±0.72 pmol/min · mg; P=0.012) was found for patients who improved (86 [61.9%]; Figure 3).

VAP-1/SSAO Protein and Activity Levels in Stroke Patients’ Brains

Immunostaining of stroke patients’ brains for VAP-1/SSAO revealed its presence in the blood vessels and capillaries of the infarcted (Figure 4A) and contralateral areas (Figure 4B). The protein was clearly expressed in vessels showing white blood cell extravasation and infiltration (Figure 4C) in the infarcted areas associated to HT. VAP-1/SSAO activity was greater in the infarcted (7.63±0.79 pmol/min · mg) than in the corresponding contralateral area (4.56±0.83 pmol/min · mg; P=0.053) or in healthy control brain (4.05±0.33 pmol/min · mg; P=0.035; Figure 4D).
VAP-1/SSAO Inhibition Prevents Deleterious Effects of Delayed tPA Treatment in Ischemic Rats

VAP-1/SSAO activity of ischemic rats treated peaked at 2 hours post-tPA administration (12.45 ± 0.58 pmol/min·μL; \( P = 0.008 \)) compared with baseline (9.07 ± 0.40 pmol/min·μL). The animals cotreated with the SSAO inhibitor, semicarbazide, presented lower levels 2 hours post-tPA treatment (7.23 ± 0.26 pmol/min·μL; \( P < 0.001 \)) than the saline group (12.45 ± 0.58 pmol/min·μL) (Supplemental Figure II, available at http://stroke.ahajournals.org). The activity of sham control animals treated with tPA (30 minutes, 2 hours, and 24 hours postadministration) was not different from baseline activity. Plasma VAP-1/SSAO activity from ischemic rats treated with tPA did not differ from that of untreated rats either (data not shown).

Ischemic rats treated with tPA 2 hours after the occlusion exhibited a smaller infarct volume (7.67% [4.7% to 12.7%]) than did the untreated rats (23.53% [0% to 50.8%]). However, delayed tPA infusion corresponded to a larger infarct volume; at 3 hours, the volume was 8.86% (7.79% to 41.70%), and at 4 hours, 41.12% (27.38% to 59.28%; Figure 5B). Animals cotreated with delayed tPA and semicarbazide showed a reduction in the infarct volume (8.73% [0% to 25.51%]) involving both the cortical and striatum areas compared with delayed-tPA plus saline group (35.46% [8.43% to 45.83%]; \( P = 0.036; \)

Discussion

This study shows for the first time that circulating plasma VAP-1/SSAO activity measured before the administration of thrombolytic therapy in patients with acute stroke predicts intracerebral hemorrhage and neurological outcome in patients with stroke. Our group has previously described that in the HTs that occur after human ischemic stroke, infiltration of the ischemic brain tissue by peripheral blood neutrophils is related to basal lamina degradation, which compromises blood–brain barrier integrity.\(^{17}\) Neutrophils use matrix metalloproteinases for their migration and, as we have recently demonstrated, tPA promotes neutrophil degranulation and matrix metalloproteinase-9 release in vitro.\(^{18}\) Thus, our group, among others, has hypothesized that blocking leukocyte transmigration might prevent tPA-induced neutrophil degranulation at the injury site. We believe that a potentially valuable strategy to study prevention mechanisms for fatal hemorrhagic complications would be to target the molecules involved in the infiltration of ischemic tissues by neutrophils. VAP-1 is one of the endothelial cell adhesion molecules that mediate leukocyte migration; it participates in rolling, firm adhesion, and transmigration of leukocytes through inflamed vasculature.\(^{19}\) The physiological role of circulating VAP-1/
SSAO, which is cleaved from the cell surface to the bloodstream, remains unknown. The oxidative deamination of primary amines by VAP-1/SSAO could induce a rise in its metabolic products such as aldehydes and hydrogen peroxide, which are involved in generating advanced glycation end products and oxidative stress.

We found that baseline VAP-1/SSAO activity is associated with HT appearance. This finding underscores the potential of using pretreatment plasma VAP-1/SSAO activity levels as a new biomarker for predicting the occurrence of PH in tPA-treated patients with stroke. Furthermore, we have observed a positive correlation between baseline VAP-1/SSAO activity and myeloperoxidase levels, a peroxidase most abundantly present in neutrophil granulocytes, after 2 hours of tPA administration to 12 hours of symptoms onset. This result suggests a possible role of circulating VAP-1/SSAO in the activation of white blood cells and recruitment of neutrophils a few hours after the occlusion. In fact, VAP-1 has been reported to play an essential role in the polymorphonuclear cell extravasation during inflammation. Indeed, polymorphonuclear cells are clearly present around VAP-1/SSAO-positive vessels in the infarcted areas of human stroke brain.

Nevertheless, whether VAP-1/SSAO activity might be combined with other biomarkers to predict the appearance of HT is an interesting working hypothesis that might increase the predictive value of this individual marker and that needs to be addressed. Matrix metalloproteinase-9, cellular fibronectin, or oxidative stress-related markers that have already been linked to brain bleeding complications are interesting candidates.

We did not find differences in plasma VAP-1/SSAO activity between tPA-treated patients with stroke and a healthy control group; however, we did observe that in those patients who later developed a HT, this activity peaked during the first 24 hours after stroke onset. Likewise, Garpenstrand et al did not find differences in SSAO activity between patients with stroke and control subjects either. However, a recent study reported higher soluble VAP-1 levels in ischemic strokes. It also showed that the frequency of VAP-1-positive vessels was diminished in the peri-infarcted region of stroke patients’ brains. However, our measurements of the enzymatic activity in human brain homogenates revealed that VAP-1/SSAO-specific activity is higher in infarcted areas than in the corresponding contralateral or healthy brains. Thus, quantification of VAP-1/SSAO protein level and/or catalytic activity might provide specific information that should be considered.

Using a stroke model of clot embolism in rats, we observed that delayed tPA treatment induced adverse effects, as previously shown. We focused on delayed treatment because this was the most suitable condition for evaluating the effect of VAP-1/SSAO inhibition. We have confirmed that delayed tPA therapy coadministered with the VAP-1/SSAO inhibitor semicarbazide considerably reduces the infarct volume and afforded lower mortality and systemic bleeding. Although this is the first study showing the benefits of VAP-1/SSAO inhibition in tPA-treated animals subjected to an embolic
ischemic episode, a previous study showed that rats treated only with an SSAO inhibitor significantly improved after a transient forebrain ischemia. We observed a peak plasma VAP-1/SSAO activity in rats after 2 hours post-tPA treatment, suggesting that the circulating form of this enzyme could be implicated in the inflammatory response to cerebral ischemic–reperfusion damage. In our experimental model, owing to the low rate of HT, we were unable to evaluate this parameter. Interestingly, the use of spontaneously hypertensive rats has been described to afford a greater incidence of intracranial hemorrhage in embolic stroke models; therefore, we will consider it for future experiments.

Summary

Our results demonstrate that plasma VAP-1/SSAO activity is a strong predictor of PH after tPA treatment of patients with stroke. Thus, we suggest that its quantification may help physicians to estimate the risks of thrombolysis on a patient and consequently improve the safety profile of this treatment. Moreover, because VAP-1/SSAO activity is also related to neurological outcome, the coadministration of tPA with a VAP-1/SSAO inhibitor to patients with stroke beyond 3 hours might provide further therapeutic benefit.

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Disclosures

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