Current Practice Versus Willingness to Enroll in Clinical Trials
Paradox Among Vascular Neurologists About Treatment for Acute Ischemic Stroke

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Background and Purpose—Clinical trials are assessing the efficacy of fibrinolysis in extended time windows for acute ischemic stroke.

Methods—An Internet-based survey was sent to 400 US vascular neurologists affiliated with a university to assess whether there are consensus opinions on how they treat patients beyond 3 hours from symptom onset and which patients they are willing to enroll into clinical trials of fibrinolysis for acute ischemic stroke.

Results—We received 161 responses; 81% were male. Ninety-three percent of respondents treat patients with intravenous tissue plasminogen activator beyond 3 hours. More than 80% were treated beyond 3 hours with intra-arterial therapy (IAT). When asked if IAT improves stroke outcome, 50% selected the choice of “yes for middle cerebral artery and basilar occlusions” and only 2% selected the choice that “IAT does not improve outcome.” Over half believe that imaging could be used to approximate the penumbra but with improvements to better identify salvageable tissue. Eighty-seven percent were willing to enroll patients into a placebo-controlled intravenous thrombolysis beyond 3 hours. For IAT trials, >80% would randomize beyond 3 hours with or without prior intravenous treatment.

Conclusions—Vascular neurologists have been treating acute ischemic stroke beyond 3 hours with intravenous tissue plasminogen activator even before the American Heart Association guidelines supported extending the therapeutic window. There is a paradox among the respondents willing to enroll patients into trials involving IAT given that a majority is offering IAT as part of their practice. These results suggest that clinical practice may impair enrollment into trials testing reperfusion therapies for acute ischemic stroke. (Stroke. 2010;41:00-00.)

Key Words: acute ischemic stroke ▲ clinical trial design ▲ intra-arterial therapy ▲ neuroimaging ▲ vascular neurologist

Stroke is the third leading cause of death1 and the principal cause of neurological disability in the United States.2 Fourteen years after the US Food and Drug Administration (FDA) approved intravenous tissue plasminogen activator (IV tPA) for the treatment of acute ischemic stroke (AIS),3 there are still no other approved therapies for stroke treatment. Multiple treatment modalities are currently being evaluated in clinical trials to expand the window for reperfusion therapy. Several clinical trials are testing several approaches such as intra-arterial therapy (IAT) that are already in clinical practice but not proven to improve outcome.4,5 There are divergent opinions on the effectiveness of IAT and therefore a lack of equipoise, rendering randomized trials difficult to complete.6 In addition, multimodal imaging with CT or MRI is being used by some clinicians to select patients for thrombolytic therapy in extended time windows without any definitive data that have validated their use to approximate salvageable brain tissue.7 Several trials have used multimodal imaging or are currently using such imaging in future studies.8-14 We conducted a survey to capture the most current practices among vascular neurology specialists about reperfusion therapy for AIS, the use of thrombolytics in extended time windows, IAT, and the implementation of multimodal imaging. We sought to determine if there are any consensus practices or opinions about reperfusion therapy for AIS beyond the standard of care and to understand if there is equipoise about experimental reperfusion treatments currently in clinical trials.

Methods
An Internet-based survey was sent from October 2008 until July 2009 to 400 US vascular neurologists affiliated with a university to assess whether there are consensus opinions on how they treat patients beyond 3 hours from symptom onset, what imaging modality they use for patient selection, and what patients they are willing to enroll into clinical trials of fibrinolysis for acute ischemic stroke.
### Table. The Survey

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| What is your gender? | ● Male  
● Female |
| Years since you finished clinical training. | ● 0–5 years  
● 6–10 years  
● 11–15 years  
● 16–20 years  
● 21–25 years  
● 26–30 years  
● Older than 30 years |
| Do you currently treat ischemic strokes beyond the 3-hour window? | ● Yes  
● No |
| The ECASS III study showed that IV tPA was beneficial when given between 3 and 4.5 hours after symptom onset. In response to these results, will you wait for FDA approval before changing your decision-making about giving tPA beyond 3 hours? | ● Yes  
● Not sure  
● No |
| If you currently treat patients with anterior circulation stroke beyond 3 hours, what therapies do you use? Check all that apply. | ● IV tPA  
● IA thrombolysis  
● Clot retrieval devices  
● IV then IA treatment (thrombolysis or clot retrieval)  
● Do not treat beyond 3 hours |
| How many patients with anterior circulation ischemic strokes do you estimate that your center treats beyond 3 hours with IA thrombolysis or a device per year? | ● 0  
● 1–10  
● 11–20  
● 21–30  
● 31–50  
● >50  
● Not sure  
● No |
| Do you believe that imaging (DW/PWI mismatch on MRI or mismatch between blood flow/time to peak and blood volume on CT perfusion) can be used to identify the penumbra that is still salvageable? Check all that apply. | ● Yes  
● Yes, but current approaches using CT or MRI need refinement to provide a better approximation of the penumbra  
● Not sure  
● No |
| If you use imaging to approximate the penumbra (so-called penumbral area or mismatch imaging) in patients with anterior circulation stroke, do you primarily use diffusion/perfusion MRI, perfusion CT, or both before treatment with IV tPA or IA treatment? | ● Diffusion/perfusion MRI  
● CT perfusion  
● Both modalities  
● None of the above  
● Do not use imaging to approximate the penumbra  
● Other |
| If penumbral identification by imaging was required in a clinical trial using IV or IA treatment (thrombolysis or clot retrieval) for patients with anterior circulation stroke, which modality would you consider most appropriate? | ● Diffusion/perfusion MRI  
● CT perfusion  
● Both modalities are required  
● Either one  
● No penumbral identification is necessary  
● Other |
| For patients with basilar artery occlusion, do you routinely use? | ● IA thrombolysis  
● Clot retrieval device  
● Both  
● None  
● Other |
to enroll into clinical trials of fibrinolysis for AIS (Table). Reminders were sent 3 times, in January, April, and July 2009. The survey was designed and completed on a professional web site. The survey was disseminated from the web site to the e-mail addresses of the sample population. For those institutions where a “spam protection program” filtered out the e-mail invitation, surveys were e-mailed directly to individual people. A systematic effort was made to identify all academic stroke physicians at university hospitals on faculty at medical schools across the United States. Names and e-mails were collected from web sites of university hospitals, directors of academic stroke programs, colleagues in the stroke field, and neurologists in charge of specific geographic consortia of stroke physicians. The web sites of all medical schools in the United States were searched for a stroke program and/or stroke physicians on faculty. A total of 412 stroke neurologists were identified of which 400 people had e-mail addresses that could be found. All answers were kept confidential. The Table displays all survey questions in the form in which they were presented to respondents.

### Statistical Analysis

We report the results as the percentage of every possible answer for a specific question. The denominator for a specific question is the total number of respondents who answered that question. For questions that specified “check all that apply,” there was >1 answer for each respondent.

### Results

#### Demographics

We received a total of 161 responses (40%); 81% were male. Less than 2% of the respondents were endovascular neurologists. One third of the respondents completed their training within the past 10 years, 36% in the past 11 to 20 years, 17% within 21 to 30 years, and 13% >30 years ago.

#### Clinical Practice

The European Cooperative Acute Stroke Study (ECASS) III study was published 1 month before starting the survey. Over 90% of vascular neurologists indicated that they treat patients with AIS beyond the 3-hour window. Over half of the respondents (55%) are not waiting for FDA approval to extend the IV tPA window from 3 to 4.5 hours. The majority...
of the neurologists in this survey (60%) belong to academic centers that perform between 1 and 20 IAT procedures per year, whereas 4% perform IAT in >50 patients per year. Six percent do not work at centers that offer endovascular procedures for AIS. For basilar artery occlusion, 76% of the respondents use both mechanical and lytic agents. Among potential treatments that respondents would offer beyond 3 hours for anterior circulation strokes, 45% use IV tPA, 84% use intra-arterial thrombolysis, 82% use the clot retrieval device, and 43% use IV followed by IAT (both thrombolysis or clot retrieval device; Figure 1). One third of the respondents are more likely to offer IAT in extended time windows beyond 3 hours since the results of ECASS III were published. When asked if IAT improves functional outcome, 8% of respondents chose “yes, for middle cerebral artery (MCA) occlusion,” 9% chose “yes, for basilar occlusion,” 52% chose “yes, for both MCA and basilar occlusions,” and only 2% selected the choice that “IAT does not provide benefit” (Figure 2). Regarding imaging as a selection criterion for patients strokes beyond 3 hours from onset, nearly one fourth of respondents believe that current imaging (diffusion-weighted imaging/perfusion-weighted imaging on MRI or mismatch between blood flow/time to peak and blood volume on CT perfusion) can be used to identify the penumbra, and over half believe that imaging could be used to approximate the penumbra but with improvements to better identify salvageable tissue. Only 3% would not use mismatch CT or MR. For those who rely on imaging, 39% use CT perfusion, 22% use MR perfusion, and 34% use both modalities.

**Clinical Trial Design**

In a hypothetical placebo-controlled IV thrombolysis trial, respondents would randomize patients in the following windows: 3 to 4.5 hours (26%), 4.5 to 6 hours (34%), and 6 to 9 hours (15%; Figure 3). Only 12% would not randomize patients to such a study. In a hypothetical placebo-controlled IAT trial (clot retrieval and/or lytic), respondents were willing to randomize in the following windows: within 3 hours (5%), 3 to 6 hours (25%), 3 to 9 hours (37%), 4.5 to 6 hours (30%), 4.5 to 9 hours (38%), and 9 hours (16%). Only 5% would not enroll patients into such a study. In a hypothetical placebo-controlled IAT trial (clot retrieval or lytic) for patients who already received IV tPA, respondents were willing to randomize in the following windows: within 3 hours (29%), 3 to 6 hours (39%), 3 to 9 hours (49%), 4.5 to 6 hours (25%), 4.5 to 9 hours (26%), and 9 hours (9%; Figure 4). Only 3% would not enroll patients into such a study. There was no significant difference in willingness to randomize patients to clinical trials whether the vascular neurologists trained <10 or >10 years ago.

**Discussion**

The results of this survey reflect current practices of vascular neurologists regarding reperfusion therapies at academic medical centers. The only FDA-approved, proven therapy for acute ischemic stroke is IV tPA within 3 hours of symptom onset. The ECASS III study supports the efficacy of IV tPA out to 4.5 hours after symptom onset but the FDA has not yet approved the label change. Despite the lack of FDA approval, the majority of vascular neurologists who completed our survey are treating patients with IV tPA in the 3- to 4.5-hour window. This finding indicates that neurologists likely believe the results of the ECASS III study and feel it unneces-
Our survey was also conducted to assess opinions on clinical trial design, testing reperfusion therapies for AIS. Based on these results, more than one third would randomize patients to a placebo-controlled study testing IV tPA in the 4.5- to 6-hour window, but only one fourth would randomize to a trial with a 3- to 4.5-hour window. These results are consistent with current practice, but it is surprising that more respondents did not choose a window beyond 4.5 hours. One possibility may be that many respondents do not believe IV tPA is effective beyond 4.5 hours and do not think a randomized trial beyond this time point is worth conducting. Despite a large percentage of respondents already believing that IAT improves outcome, they are still willing to randomize patients to placebo-controlled studies involving IAT, but there is wide variation about which time windows to use. Interestingly, the majority of the respondents are willing to randomize to a placebo-controlled study of IAT in which patients are already treated with IV tPA.

This study is limited by the low response rate, which introduces selection bias. However, our response rate is higher than the accepted 35% response rate of online surveys\(^2\) and is in league with recent surveys on stroke clinical practice.\(^2\) The results of the survey may help to explain the low frequency of enrollment into endovascular trials such as MR Rescue and Interventional Management of Stroke (IMS) III. A majority of respondents are offering this therapy as part of their clinical practice. Vascular neurologists may be less likely to enroll patients into such studies if they already believe IAT may benefit their patients. Conversely, more aggressive practices could also be viewed as an opportunity to launch a larger and perhaps more global, controlled trial of reperfusion beyond conventional windows. However, the response rate limits generalizing the results of this survey to the wider community of vascular neurologists.

### Disclosures

S.I.S. attended as a Consultant an Advisory Board Meeting for Genentech. There are no other conflicts to report.

### References


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