Review, Historical Context, and Clarifications of the NINDS rt-PA Stroke Trials Exclusion Criteria

Part 1: Rapidly Improving Stroke Symptoms

The Re-examining Acute Eligibility for Thrombolysis (TREAT) Task Force: Steven R. Levine, MD (Co-Chair); Pooja Khatri, MD, MSc (Co-Chair); Joseph P. Broderick, MD; James C. Grotta, MD; Scott E. Kasner, MD, MSCE; Doojin Kim, MD; Brett C. Meyer, MD; Peter Panagos, MD; Jose Romano, MD; Phillip Scott, MD; NINDS rt-PA Stroke Trial Investigators*

Background and Purpose—Since Food and Drug Administration approval of intravenous tissue-type plasminogen activator (tPA) for treatment of acute ischemic stroke in 1996, it has become clear that several criteria used for exclusion from therapy were not based on actual data or operationally defined for use in clinical practice. All eligibility criteria from the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tPA Stroke Study were adopted within the alteplase package insert as contraindications/warnings. Many clinicians have expressed the need for clarification and better definition of these treatment criteria.

Methods—A group of investigators who also practice as stroke physicians convened a collaborative endeavor to work toward developing more clinically meaningful and consensus-driven exclusion criteria for intravenous tPA. The first of these exclusion criteria chosen was rapidly improving stroke symptoms (RISS). We reviewed and clarified the historical context and intention with the original investigators, held e-mail discussions, convened an in-person RISS Summit, and obtained the understanding of experienced stroke physicians broadly.

Results—Historically, the intent of this exclusion criterion within the NINDS recombinant tPA Stroke Trial was to avoid treatment of transient ischemic attacks—who would have recovered completely without treatment. There was unanimous consensus that, in the absence of other contraindications, patients who experience improvement of any degree, but have a persisting neurological deficit that is potentially disabling, should be treated with intravenous tPA. This statement is supported from the methods established for the original NINDS trial, on the basis of detailed discussions and interviews with the former NINDS trialists. It was agreed that improvement should only be monitored for the extent of time needed to prepare and administer the intravenous tPA bolus/infusion. An explicit operational definition of RISS was developed by consensus to guide future decision making in acute stroke. There was unanimous agreement that all neurological deficits present at the time of the treatment decision should be considered in the context of individual risk and benefit, as well as the patient’s baseline functional status.

Conclusions—A structured framework and quantitative approach toward defining RISS emerged through expert opinion and consensus. The term, RISS, should be reserved for those who improve to a mild deficit, specifically one which is perceived to be nondisabling. This is recommended to guide decision making on intravenous tPA eligibility going forward, including the design of future studies. An additional study of patients with rapid improvement to nonmild deficits is not justified because these patients should be treated. (Stroke. 2013;44:2500-2505.)

Key Words: cerebral infarction ▪ clinical trials ▪ patient selection ▪ thrombolysis ▪ TIA ▪ tissue-type plasminogen activator

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When the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue-type plasminogen activator (rtPA) Stroke Trials were designed and the protocols were written, each exclusion criterion was intended to maximize favorable clinical outcomes after intravenous tPA, and avoid treating patients for whom the potential risks might outweigh the potential benefits. In this context, specific clinical, radiological, and laboratory exclusions were uniformly implemented during the early 1990s in the initial pilot (phase Ib) Trial,1,2 and these identical inclusion/exclusion criteria were carried forward into the phase III Trial.3 Given the positive results of the phase III Trial, these exclusion criteria were then written into the tPA labeling as contraindications and warnings, and approved by the Food and Drug Administration in June of 1996.4 Since that time, numerous studies and clinical protocols have been based on the drug’s labeling.

The REexamining Acute Eligibility for Thrombolysis (TREAT) Task Force is comprised of members of the original NINDS rtPA Stroke Trial Steering Committee1 and some other leaders in the field of stroke and emergency medicine. This task force was formed to address specifically the rationale and relevance of individual exclusion criteria by placing each in historical context and, as the main objective, determining whether these criteria require clarifications and more precise definitions given 15 years of subsequent clinical experience since the NINDS Study7 and current clinical practice patterns. In 2012, despite the tremendous improvement in organized stroke systems of care and the acceptance of thrombolysis for acute ischemic stroke (AIS), <6% of all AIS patients receive intravenous tPA.5 We sought to determine whether new data and expert opinion/consensus are needed to optimize individual patient decisions on intravenous rtPA eligibility.

In this project, the first exclusion criterion addressed was rapidly improving stroke symptoms (RISS). Data collected from various sources6–10 (Genentech Inc, unpublished data, 2010 and 2011) have suggested that RISS is one of the most common reasons for excluding otherwise eligible patients from treatment with intravenous rtPA. This subgroup frequently has poor outcomes.11–13 In the NINDS trial, RISS was listed without a precise definition. Its lack of an operational definition, such as the quantitative platelet count, blood pressure, or serum glucose, leaves it being vague and open to widely disparate interpretations. The NINDS trial also lists mild, nondisabling deficit as a separate exclusion, and its relationship to RISS is unclear.

We sought to develop a clinically meaningful definition of RISS that may be used to guide acute stroke decision making specifically related to tPA and possibly future studies. Important questions include: When is major, rapid improvement in neurological deficits sufficient to consider not treating an otherwise rtPA-eligible patient? How should major improvement be defined? Is there reason to think that partial improvement (ie, with remaining significant deficit) will lead to further, continued improvement, and that reperfusion would no longer be useful in this circumstance? Conversely, is there reason to think that partial improvement will lead to further, continued worsening? Is there a threshold of improvement at which we would generally agree that a patient with stroke should/should not be treated without further clinical studies? Is there a threshold of improvement beyond which we cannot agree that a patient with stroke should/should not be treated? Is there an appropriate definition of RISS that goes beyond that of improvement to a mild state? How does the rapidity of improvement factor in (eg, >20 minutes or 3 hours)? How can these findings be used to develop a clinically meaningful definition of RISS to guide the decision about using intravenous tPA?

Methods

Historical Survey

All members (n=22) of the NINDS rtPA Stroke Trial Steering Committee were contacted to provide their individual recollection on the basis of RISS as an exclusion criterion in the trial. A structured questionnaire was developed by 3 members of the TREAT Task Force members (J.B.P., P.K., and S.R.L.) and then contacted via the telephone by a professional medical writer (Richard Hyer, Chicago, IL) to all but 4 individuals. Three of the remaining 4 individuals were personally contacted (S.R.L.) for their recollections (2 responded by telephone and 1 by e-mail), and 1 remained unavailable for comment. Responses were collated and summarized.

In-Person TREAT Summit

Additional clinicians active in the practice of acute stroke treatment and who have a clinical or research interest in RISS were contacted to attend an all-day meeting to further develop and clarify our understanding of RISS and its basis for excluding patients from intravenous tPA and participate in an ongoing TREAT Task Force. Of those invited, the authors named in this manuscript attended on September 7, 2011, in Chicago. Results from the historical interviews were presented and discussed, and proposed definitions of RISS were developed with a goal toward developing consensus-based recommendations and guidelines. Case scenarios were also used to help frame and clarify the discussion. We explored whether any objective criteria for RISS are apparent now that were not explicitly defined at the time of the 1995 NINDS Study.1

Consensus was determined on the basis of prespecified definitions among participating TREAT Task Force members. The following definitions were used to differentiate areas of consensus and contention: consensus, ≥75% agreement; general consensus, >50% but <75% agreement; and contention, ≤50% agreement. These points of consensus were then proposed to additional stroke clinicians for endorsement.

Consensus Development/Results

Historical NINDS Trial Investigators Survey

Twenty-one of 22 (95%) invited individuals involved in the NINDS rtPA Stroke Trial answered the following questions verbatim: What are your personal thoughts on the meaning of RISS? How do you define rapidly improving? Do you remember how you intended that rapidly improving be defined for the NINDS trial? Would you say it was gestalt, defined as an organized whole that is perceived as more than the sum of its parts? Or was it by raw score difference, as on the National Institutes of Health Stroke Scale (NIHSS) scale?2

On the basis of direct interview process, the NINDS Investigators did not realize or intend that these criteria would be subsequently adopted as a basis to not consider using tPA in a patient with any degree of improvement subsequent to the trial in clinical practice. Among the respondents, there was overwhelming agreement that RISS was intended to exclude patients with transient ischemic attacks (TIAs)—who would have completely recovered without treatment—and it was not on the basis of a specific amount of improvement on the NIHSS. Appendix I in the online-only Data Supplement provides key comments from those surveyed.
In-Person Meeting

A major objective of the meeting was to develop areas of consensus and lack of consensus that would serve for future study. The ultimate goal of the meeting was to develop a clinically meaningful definition of RISS to guide the intravenous tPA decision in this condition.

On the basis of data from the NINDS Investigators interviews, the TREAT Task Force agreed that the original intention and practice of RISS used as an exclusion criterion from the NINDS Trial is often not reflected in current clinical practice.

TREAT Task Force members were asked to respond to a series of audience response system9,10 questions to further determine areas of consensus or divergence. Audience response system questions and key discussion points were summarized, whereas concepts with >75% agreement were not discussed further.

There was 100% consensus of the TREAT Task Force that, in the absence of contraindications, patients who experience RISS to a potentially disabling degree (as judged by the clinician or patient/family or both) of remaining neurological deficit should be treated with intravenous tPA. This statement was supported by both the study design of the original NINDS trial and based on our detailed discussions and interviews with the former NINDS trialists about who they intended to include/exclude from the trial. Some participants did note that patient–practitioner perceptions of disabling may be discordant. Patients often perceive their deficits to be less disabling than practitioners perceive them to be, and this determination of what is disabling to patients could be a focus of future investigations. Furthermore, all existing evidence on using nonmild rapid improvement as an exclusion criterion is American Heart Association Level of Evidence C (ie, consensus opinion of experts).9,10 Specifically, there are no data to support the non-treatment of RISS that fails to improve to a minor deficit (ie, nonmild RISS). Furthermore, the inclusion of patients with RISS and continued moderate or severe deficits in the NINDS Trial provides American Heart Association Level of Evidence Grade A (ie, data derived from multiple randomized trials) for treatment. Finally, it was agreed that improvement should only be monitored for the extent of time needed to prepare and administer the intravenous tPA bolus/infusion.

Table 1. Operationalizing RISS: Consensus Areas

<table>
<thead>
<tr>
<th>Case scenario: a 43-year-old woman is brought to the ED within 3 h after acute ischemic stroke.</th>
</tr>
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<tbody>
<tr>
<td>≥75% would typically treat this patient with intravenous thrombolytic therapy in the presence of the following levels of NIHSS score improvement within 10–15 min of arrival in the ED*</td>
</tr>
<tr>
<td>NIHSS score 16 to 12</td>
</tr>
<tr>
<td>NIHSS score 16 to 10</td>
</tr>
<tr>
<td>NIHSS score 16 to 6</td>
</tr>
<tr>
<td>NIHSS score 16 to 2, with residual neurological deficit leading to inability to walk</td>
</tr>
<tr>
<td>≥75% would not typically treat this patient with intravenous thrombolytic therapy in the presence of the following levels of NIHSS score improvement within 10–15 min of arrival in the ED</td>
</tr>
<tr>
<td>NIHSS score 16 to 2, with residual neurological deficit that seems nondisabling</td>
</tr>
</tbody>
</table>

Note: There was general consensus (>50% but <75%) that the following additional clinical data would lead to a change in answer from NO to YES to treating with intravenous rTPA:
- Large penumbral pattern (based on computed tomography or magnetic resonance multimodal imaging)
- The presence of a proximal large artery occlusion, or fluctuation before improvement
- NIHSS score 16–0, with residual isolated truncal ataxia leading to inability to walk

ED indicates emergency department; NIHSS, National Institutes of Health Stroke Scale; RISS, rapidly improving stroke symptoms; and rTPA, recombinant tissue-type plasminogen activator.

Tables 1, 2, and 3 show case presentations and audience response system questions, as well as the responses by task force members at the in-person meeting. Areas of consensus, general consensus, and lack of agreement are displayed. Finally, a consensus preliminary operational definition of mild/minor deficit was also developed to guide future decision making in acute stroke (Table 4).

Discussion

Rapid improvement is one of the most common reasons for exclusion from thrombolytic therapy for AIS.8,10 Task force members had common knowledge of practitioners all over the country who are avoiding treating with tPA because patients are improving a little without treatment (eg, a patient going from an NIHSS score of 15–10).

The pathophysiology of major, rapid clinical improvement can be because of spontaneous recanalization and recruitment of collaterals, and can be associated with residual microvascular occlusions, residual clot burden at the recanalization site, and risk of reocclusion or collapse of collaterals.17–20 Lesser degrees of clinical improvement may be associated with partial recanalization, partial reperfusion, partial compensation by collaterals, and stunned recovering brain.10 These underlying mechanisms may help explain why many patients with stroke with rapid improvement are ultimately disabled.6

It was the unanimous consensus of the task force that, in the absence of contraindications, patients who had nonmild (ie, moderate to severe) stroke, and do not improve to a non-disabling state, should be treated with intravenous tPA. There was agreement that this statement can be supported by the study design and data from the original NINDS Trial, on the basis of patient enrollment by the NINDS trialists, and is, therefore, consistent with an American Heart Association Class I, Level of Evidence A recommendation. Furthermore, post hoc analysis of the NINDS Trial placebo group, which included such patients, supports this recommendation by

Table 2. ARS Question: Relative Contraindications, That Is, Warnings: Are the Following Criteria on Their Own Sufficient to Contraindicate IV Thrombolytic Therapy?

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Response, %</th>
</tr>
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<tbody>
<tr>
<td>Seizure at stroke onset (with ischemic stroke verified on imaging)</td>
<td>0 100</td>
</tr>
<tr>
<td>Major early infarction signs on computed tomography</td>
<td>80 20</td>
</tr>
<tr>
<td>Glucose &lt;50 mg/dL</td>
<td>50 50</td>
</tr>
<tr>
<td>Glucose &gt;400 mg/dL</td>
<td>11 89</td>
</tr>
<tr>
<td>RISS</td>
<td>0 100</td>
</tr>
<tr>
<td>Recent gastrointestinal/genitourinary bleeding (within 21 days)</td>
<td>78 22</td>
</tr>
<tr>
<td>Major surgery within 14 days</td>
<td>89 11</td>
</tr>
<tr>
<td>Arterial puncture at a noncompressible site within 14 days</td>
<td>44 56</td>
</tr>
</tbody>
</table>

ARS indicates audience response system; IV, intravenous; and RISS, rapidly improving stroke symptoms.
showing the natural history without treatment yielded 54% of subjects with worsening, no change, or 1-point improvement from baseline to the 2-hour NIHSS (NINDS rtPA Stroke Trial, unpublished data). Presently, there is no evidence to consider nondisabling, potentially disabling rapid improvement as an exclusion criterion for intravenous tPA eligibility.

Our proposal for a refined and operationalized definition of RISS will be a particularly useful starting point for those who infrequently make intravenous tPA treatment decisions. It should be emphasized that treatment should not be delayed to monitor for improvement; improvement should only be monitored for the extent of time needed to prepare and administer the intravenous tPA bolus/infusion. To make it practical, screening for our new, operationalized definition should include checkboxes to appeal to emergency physicians.

Patients with TIA generally do not get better in a step-wise fashion. Rather, they tend to resolve rapidly and completely.22 An experimental mouse model of TIA shows that the threshold for infarction after middle cerebral artery occlusion was around 12.5 minutes.23 Therefore, a patient who improves from an NIHSS score of 15 to 10 is unlikely to have a TIA and is, therefore, a candidate for intravenous tPA treatment. It is the patient who returns to normal that should not be treated with tPA. After a static deficit for 1 hour, the chance of improving completely (TIA) is <2% per hour thereafter.24 Task force members agreed that RISS requires a formal quantitative definition as proposed herein; otherwise physicians may delay or decline to use thrombolytic therapy.

Translation of the understanding of the NIHSS score from stroke to nonstroke practitioners is a significant barrier that may have limited the uptake of a meaningful and appropriate definition of RISS into practice to date. Nonstroke practitioners often do not use the NIHSS.25 Only with repeated use can this scale be used proficiently. Another limitation of the NIHSS is that it does not fully measure the scope of the problem. For instance, it cannot be used accurately to assess posterior circulation disease. Therefore, we have proposed an operational definition that incorporated both the NIHSS score and the assessment of the potential disability by both the patient and the physician.

There was consensus among the group that an additional study of patients with rapid improvement but persistent nonmild deficits is not needed. The term, RISS, should be reserved for those who improve to a mild deficit, specifically one which is perceived to be nondisabling. It is this latter group of patients and those with mild nondisabling deficits from onset, which comprise a group of patients in whom further clinical study is warranted to see whether tPA improves long-term outcome as compared with standard therapy. Specifically, future studies are needed to address the following question: At what point does the patient in front of you have such a mild deficit (ie, nondisabling) that you do not need to treat with intravenous tPA?

The original NINDS Trial did not study many subjects with very mild deficits whether persistent or because of improvement.26 Future studies might address the efficacy and safety of thrombolytic therapy in patients with an NIHSS score of 0 to 5 and not perceived to be disabling, on the basis of current consensus on which patients should be randomized (Table 3). There may also be a fundamental difference between patients with AIS with RISS who improve from a major to a minor, nondisabling deficit and patients who have a persistent mild, nondisabling deficit since onset. Therefore, it will be important in moving forward and will require recording more than a single baseline NIHSS pretreatment score in patients with RISS. These findings will inform the planned phase 3 randomized clinical trial, Potential for rtPA to Improve Strokes with Mild Symptoms, of intravenous rtPA for mild ischemic stroke within 3 hours of onset, currently under evaluation for sponsorship by Genentech, Inc. Although proponents of treating mild stroke point to the generalizability of tPA from the NINDS data, there is still risk of serious intracranial hemorrhage and the good natural history for the majority of patients with minor stroke to warrant equipoise for selected patients in this trial.28 Recent data from the VISTA (Virtual International Stroke...
Trials Archive) database of the subgroups, where tPA benefit does not clearly emerge are those with baseline NIHSS≥6, recognizing the very small, and likely underpowered sample size. In addition, the ongoing NINDS-funded phase 3 randomized clinical trial Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT; NCT00991029) is testing 90 days of double antiplatelet therapy for patients with high-risk TIA and minor ischemic stroke within 12 hours of onset, and will likely inform future discussions of this population.

The role of imaging in treatment decisions in patients with RISS remains to be determined. Although the group generally agreed that a very minor deficit in the presence of a large penumbral pattern or proximal occlusion might lead to the decision to use intravenous tPA, further evidence is needed to support this approach; data are lacking whether these parameters reflect poorer prognostic markers\(^6,8,11,18,29\) versus treatment modifiers.

Consensus cannot and should not replace evidence-based medicine. However, in this case, we demonstrate that evidence already exists to treat those who improve but remain in a potentially disabling state; these patients were enrolled in the NINDS trials. Therefore, we clarify the appropriate definition of RISS as an intravenous tPA exclusion criterion on the basis of original intention of the NINDS Investigators—to avoid TIAs. It should be noted, however, that we anticipate that our specific definition of disabling state will evolve over time as more prospective data become available. This could include additional outcome analyses of minor stroke syndromes and patient/family/physician interpretations of disability.

There is a clear need for updated recommendations on patient selection for intravenous tPA therapy on the basis of misapplication in clinical practice of the RISS definition for exclusion from the NINDS Trial.

In summary, the intent underlying the concept of RISS within the original NINDS study has clearly been lost. Specifically, the intent of this exclusion criterion was to avoid the unnecessary treatment of TIA. Translation of the understanding of RISS from stroke to nonstroke physicians is a significant barrier to the optimal treatment of patients with AIS. There was unanimous consensus of this group that, in the absence of contraindications, patients who experience rapidly improving stroke symptoms but have residual deficits that are potentially disabling should be treated with intravenous tPA. There was further unanimous consensus that an additional study of patients with improvement but moderate or severe deficits is not needed and inappropriate.

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Disclosures

None of the participants were paid to participate, and Genentech, Inc did not influence the discussion and conclusions of this meeting. Final recommendations were made in closed sessions without any Genentech, Inc representation present. Dr Broderick received study drug from Genentech (supplier of alteplase for National Institute of Neurological Disorders and Stroke (NINDS)–funded CLEARER, IMS III trials), honorarium for participation in stroke advisory board, educational grant to the American Academy of Neurology for 2012 annual meeting program as course director, study drug from Novo Nordisk (supplier of drug for NINDS-funded STOP-IT trial) and Schering Plow (drug for NINDS-funded CLEARER Trial), honoraria from PhotoTherapy for participation on the DSMR. Dr Groth received grant support from National Institutes of Health (NIH) and is on the Steering Committee for DIAS. Dr Kasner received travel reimbursement from Genentech. Dr Khatri received grant support from NIH, Genentech (Potential for rtPA to Improve Strokes with Mild Symptoms Trial PI), and Penumbra (THERAPY Neurology PI). Travel as unpaid consultant from Genentech. Advisory boards consulting fees from Janssen Pharmaceuticals and Lake Biosciences. Speaking honorarium from Medical Dialogues. Expert witness for medical-legal cases. Dr Levine received grant support from NIH and Genentech, has served on Genentech’s Advisory Board (honoraria donated to stroke research), Associate Editor for Medlink, and as an expert in medical-legal cases. Travel reimbursement as unpaid consultant from Genentech. Dr Meyer received grant support from NIH, has served on Genentech’s Advisory Board and Speaker’s Bureau, The Medicines Company Speaker’s Bureau. Dr Panagos received grant support from NIH (SPOTRIAS), served on Genentech’s Speaker’s Bureau, and served as a consultant to the American Heart Association/American Stroke Association. Dr Romano received grant support from Genentech. Dr Scott received grant support from NIH (INSTINCT), The Michigan Department of Community Health, and has served as an expert in medical-legal cases. Dr Kim reports no conflict.

References


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SUPPLEMENTAL MATERIAL

(APPENDICES I AND II)

ONLINE SUPPLEMENT I

Appendix I: Notable Quotes on the meaning of “Rapidly Improving Stroke Symptoms”
From the original Steering Committee of the 1995 NINDS rt-PA Stroke Trial

The following are represented except as noted by asterisk:
William Barsan, MD
Joseph P. Broderick, MD
Thomas Brott, MD
J.D. Easton, MD
Michael R. Frankel, MD
Juergen Froehlich, MD
Kenneth Gaines, MD
James C. Grotta, MD
E. Clarke Haley, MD
Steven H. Horowitz, MD
Rashmi Kothari, MD
Thomas Kwiatkowski, MD
Steven R. Levine, MD
Christopher A. Lewandowski, MD
Richard Libman, MD
Patrick D. Lyden, MD
John R. Marler, MD* (Declined to be interviewed because of his current position with the FDA)
Michael Meyer, MD*
Barbara C. Tilley, PhD
Michael D. Walker, MD
K. Michael Welch, MB, ChB
Justin A. Zivin, MD

Anonymous: It was ALL about TIA without concern of actual risk/benefit about size of stroke.
Do you remember how you intended that “rapidly improving” be defined? “…somebody who you thought by the time you were giving them the drug, they’d be normal--that’s who you would exclude.”
Would you define ‘rapidly improving’ by gestalt? “By gestalt – for sure.”

“What you wanted to avoid was, let’s say the patient who came in, when you first saw them, or when they were first picked up, they were devastated. And by the time you’re ready to deliver the drug, the only thing that they have left is, let’s say, a little bit of a facial droop, but nothing else? I mean, they’ve still got a stroke. They’ve still got something that registers on the NIH stroke scale, but it’s minimal. I wouldn’t want to enter that patient. Even though, at the time they came in, they looked terrible.
“But again, the intent was not to treat somebody who was rapidly improving and who you expected to be normal. And that doesn’t mean somebody who couldn’t speak a word, and now they can speak two words. That’s not what you want to do. That was not the intent of the way the study was set up.”

“Simple answer from me – minor symptoms were isolated facial weakness or isolated sensory symptoms. Rapidly improving symptoms was left to clinical judgment about the likelihood the patient was going to return to normal. We did not use an objective measure of change in NIHSS as one was not specified for this.”
“My recollection… The way we use the criteria was that people had to have fairly dramatic improvement. I felt like, in my clinical judgment, they were headed back to a normal level of function.

“So, if I saw someone who was changing in a positive way, with a deficit that was improving rapidly, and I felt it was likely, based on my clinical knowledge, that this patient was going to go on to become normal, based on the way they looked, getting closer to normal, as I examined them, then I, then they were excluded because of rapid improvement.

“I did not use an NIH Stroke Scale number to decide if they had a certain number of points on the NIH Stroke Scale that was changed, that that represented rapid improvement. It was a clinical judgment.

“Back then this was brand-new stuff and we were doing something that no one had ever done before, and so we were trying to follow the protocol as closely as possible. And if they didn’t meet the criteria for treatment, we didn’t treat them. So I think we were less worried that we were missing an opportunity to help somebody, as much as we were worried that we were going to deviate from the protocol.

“Well I think the intent was to exclude TIAs. It’s hard to define a TIA, in particular in the setting where the patient has a stroke somewhere, has to be picked up urgently and brought to the hospital, the study center. And there’s a time from a few minutes up to a half an hour or so where the patient would have to be brought to the study Center. So within this timeframe the patient could have improved quickly. Rapidly. And I think this exclusion criteria was intended to exclude those patients who have a TIA, because at this time it was felt that the risk of severe side effects giving tPA to patients who may only have a TIA is too high. And in particular when the patient is improving. And if it’s a TIA, within 24 hours the patient should be normal again without treatment.

“And so now going back, as I said, I think two reasons, is the risk of causing intra-cerebral hemorrhage, which can be devastating; and secondly, to avoid any rapidly improving symptoms that would have improved without tPA, so you would have a false positive outcome at 24 hours.

“Yes, I remember us having some discussions around that. I think the idea at the time was that this medication had only been used in a limited number of cases in some pilot studies, and we weren’t completely sure how safe it would be. Therefore, we wanted to avoid using it in patients that had mild symptoms, that we thought might get better. And also in rapidly improving symptoms that might actually represent TIAs, or symptoms that would go ahead and resolve entirely either quickly or within what was then the diagnosis of TIA, recovery within 24 hours.

“So I think the rationale behind “rapidly improving” symptoms was that we did not want to include those patients, because we thought they might get better spontaneously, and we did not want to subject them to a potentially dangerous drug when they might get better anyway.

“Operationally I defined that in my own mind as a meaningful improvement in symptoms; someone whom I thought from experience might go on to be a TIA and have complete resolution. Because TIAs aren’t just like turning off the light switch; they get better gradually. So that’s how I defined it operationally. And I was probably conservative in terms of patients accepted for enrollment for the study. I guess I was primarily concerned about safety issues. I was trying to define a group of patients that I thought from experience would get better spontaneously, and it’s hard to put a number on that. And I don’t think anybody ever even tried to say for example that it would be 4-point improvement in the NIH Stroke Scale. I don’t recall ever hearing a discussion of anything like that. I think maybe everybody operationally defined it in their own way
“Because we were seeing patients within the first hour or two of their stroke, this was largely uncharted territory in terms of the normal clinical behavior of stroke patients. There hadn’t really been a lot of observations of the clinical course of neurological deficits in acute stroke patients. So actually we learned a lot during the study. But it was clear that since we were seeing patients in the first hour or two, that some of these patients would be recovering spontaneously, and be in fact TIAs. At that time, the definition of TIA was still 24 hours, even though we recognized that most TIAs were much shorter than that. So we thought that some patients we were going to be seeing when they came to in the emergency room would have a deficit, but that deficit would resolve quickly, and the patient then of course would not need to be treated because they’d be getting better spontaneously. So it was an effort to identify those patients.

“And the way we did it was, if a patient came in, and they had gone from a severe deficit to a near–normal state, that was what we considered “rapidly improving.”… We didn’t go by NIH Stroke Scale scores.”

“As far as rapidly improving symptoms, I think the primary reason that we included that as a criterion, is that we did not want to be criticized for enrolling patients with TIAs who would most likely get better on their own.

“I know we never defined a precise NIH stroke score level of improvement, because someone who starts with an NIH stroke scale score of, let’s say 15, and goes all the way to 5 is much different than someone who starts with a 5 and goes to a 3. So I think a lot of it was the judgment of the investigator. I’m including myself; it’s not like we had a chart to check and say, okay, this fulfills the criteria for “rapidly improving.” It was I think in our estimation based on our observation of the patient. It appeared that this patient may continue to improve and end up being TI as opposed to stroke.

“My recollection of the writing committee’s thought process was, you don’t want to treat it TIA. So, how do we make sure we don’t treat a TIA? And remember, when we were drafting this, it was before the new definition of TIA came out, when people realized the TIAs were actually very brief.

“So, we were trying to figure this out. And so, the rapidly improving was left vague on purpose. We purposefully didn’t make it to clear, because we all knew what we had in mind. And it never occurred to us, in our wildest imaginations, that our exclusion criteria would become the package insert. Because we were writing a Phase IIB protocol.

“So, we all knew what we meant by rapidly improving, and we didn’t write it down any more clearly, and here’s what we meant:

“If you show a relentless pattern of improvement, we don’t want to treat you. So if every minute that goes by, you’re better and better and better, then that’s what we meant by rapidly improving. Rapidly improving was intended to apply to someone who would have no or very few residual effects after the stroke; one goal as I remember it was to leave out those who might be having a TIA rather than a stroke. In the manual of procedures Page 21 we state:

“Under exclusion criteria a minor stroke is defined as a stroke that is sensory only or ataxia only. Also, if the patient has a motor score of 1 on one limb and 0 for all other limbs this is also a minor stroke. Major improvement is defined by clinical judgment.”

“The NIH Stroke Scale got its footing in history in the tPA trial. So that, nobody was really thinking: How many points shift is going to make a rapid improvement? My recollection is that it went back to the observations of the Phase 1 and Phase 2 investigators who saw a patient come into the ER, who clearly had signs and symptoms of a stroke, and during the process of getting them worked up, and getting them scanned,
and getting the blood work done, those symptoms essentially resolved. And that was the so-called ‘on-the-table response.’

I thought to myself that here is a soft clinical opinion. On the other hand, we hadn’t really fully developed and perfected the NIH Stroke Scale at all, so we had nothing other than opinion. On the other hand we came around to thinking that, when good clinicians, people whom we trust, and who have been well trained in neurology, say

“This patient is getting better,” we have got to believe them. But better by how many points, I don’t think that was particularly in our minds at the time.”

“To my recollection it was not specifically defined; it was left to medical judgment. The whole purpose of the proviso was to avoid treating TIAs, and also minor strokes. A minor deficit you would anticipate after rapid improvement, maybe minor residual. Since TPA would not have a lot of affect on the Stroke Score, it would lower the power of the study if large numbers were recruited. Also it might include some incorrect diagnoses. I think we did discuss that in practice you wouldn’t want to be treating a TIA. And if you had too many of those, that would dilute the power of the study, even though you might expect, with a randomized trial, they would be balanced out.

“The RISS exclusion criterion was meant to exclude patients who might be experiencing a TIA or who improved sufficiently to return to their previous (normal) function, with only minor symptoms and no significant disability, assuming no further deterioration would occur.”
ON LINE SUPPLEMENT II

Appendix II: Stroke clinicians/researchers who have read and endorsed the views expressed in this position paper

Adeoye, Opeolu
Baird, Alison
Barsan, William
Bonomo, Jordan
Chaturvedi, Seemant
Cucchiara, Brett
De Los Ríos La Rosa, Felipe
Derdeyn, Colin
Easton, J. Donald
Frankel, Michael
Froehlich, Juergen
Greenberg, Steven
Hemmen, Thomas
Horowitz, Steve
Jauch, Edward C
Kissela, Brett
Kleindorfer, Dawn
Kothari, Rashmi
Kwiatkowski, Thomas
Lee, Jin-Moo
Lewandowski, Christopher
Libman, Richard B.
Lyden, Patrick
Marshall, Randolph
Martini, Sharyl
Mckinney, James
Merino, Jose
Mullen, Michael T.
Prabhakaran, Shyam
Rosenbaum, Daniel
Rymer, Marilyn
Sansing, Lauren
Stanley, Tuhrim
Tilley, Barbara C.
Walker, Michael
Wechsler, Lawrence R.
Woo, Daniel
Zivin, Justin A.