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 TIA 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 stoke 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.