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Review, Historical Context, and Clarifications of the NINDS rt-PA Stroke Trials Exclusion Criteria: Part 1: Rapidly Improving Stroke Symptoms (RISS):

The "REexamining Acute Eligibility for Thrombolysis" (TREAT) Task Force

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Abstract

Background and Purpose—Since FDA approval of IV t-PA 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 nor operationally defined for use in clinical practice. All eligibility criteria from the NINDS rt-PA 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 IV t-PA. The first of these exclusion criteria chosen was "rapidly improving stroke symptoms" (RISS). We reviewed and clarified the historical context and

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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 rt-PA Stroke Trial was to avoid treatment of transient ischemic attacks (TIAs) – 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 IV t-PA. This statement is supported from the methods established for the original NINDS trial, based on 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 IV t-PA 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 towards 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 regarding IV t-PA eligibility going forward, including the design of future studies. An additional study of patients with rapid improvement to non-mild deficits is not justified as these patients should be treated.

Keywords

thrombolysis; patient selection; cerebrovascular diseases; tissue plasminogen activator; clinical trials; exclusion criteria; TIA

Background

When the NINDS rt-PA Stroke Trials were designed and the protocols were written, each exclusion criterion was intended to maximize favorable clinical outcomes after IV t-PA, 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 IIb) 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 t-PA labeling as contraindications and warnings, and approved by the FDA in June of 1996 (4). Since that time, numerous studies and clinical protocols have been based on the drug’s labeling.

The TREAT Task Force is comprised of members of the original NINDS rt-PA Stroke Trial Steering Committee (3), and some other leaders in the field of stroke and emergency medicine. This task force was formed to specifically address the rationale and relevance of individual exclusion criteria by placing each in historical context and, as the main objective, determining if these criteria require clarifications and more precise definitions given fifteen years of subsequent clinical experience since the NINDS Study (3) 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), less than 6% of all AIS patients receive IV t-PA (5). We sought to determine whether new data and expert opinion/consensus are needed to optimize individual patient decisions regarding IV rt-PA eligibility.

In this project, the first exclusion criterion addressed was “rapidly improving stroke symptoms” (RISS). Data collected from various sources (6-10, Genentech unpublished data) have suggested that RISS is one of the most common reasons for excluding otherwise eligible patients from treatment with IV rt-PA. This subgroup frequently suffers from 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, leads it being vague and open to widely disparate interpretations. The NINDS trial also lists “mild, non-disabling 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 t-PA and possibly future studies. Important questions include: When is major, rapid improvement in neurologic 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 (i.e., 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 stroke patient should/should not be treated without further clinical studies? Is there a threshold of improvement beyond which we cannot agree that a stroke patient 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 (e.g. over 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 IV t-PA?

Methods

Historical Survey

All members (n=22) of the NINDS rt-PA Stroke Trial Steering Committee were contacted to provide their individual recollection of the basis for RISS as an exclusion criterion in the Trial. A structured questionnaire was developed by three members of the TREAT Task Force Members (JBP, PK, SRL) and then administered via the telephone by a professional medical writer (Richard Hyer, Chicago, IL) to all but four individuals. Three of the remaining 4 individuals were personally contacted (SRL) for their recollections (two responded by telephone and one by email), and one 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 IV t-PA, and participate in an ongoing TREAT Task Force. Of those invited, the authors 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 towards 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 (3).

Consensus was determined based on pre-specified 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 rt-PA 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 NIHSS scale?"

Based on 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 t-PA in a patient with any degree of improvement subsequent to the trial in clinical practice. Amongst the respondents, there was overwhelming agreement that RISS was intended to exclude patients with TIAs - who would have completely recovered without treatment – and it was not based on a specific amount of improvement on the NIHSS. On line Supplement 1 (Appendix 1) 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 IV t-PA 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 system (ARS)(14,15) questions to further determine areas of consensus or divergence. ARS questions, as well as key discussion points, were summarized while 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 IV t-PA. 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 regarding using non-mild rapid improvement as an exclusion criterion is American Heart Association (AHA) Level of Evidence C (i.e., consensus opinion of experts) (16). Specifically, there are no data to support the non-treatment of RISS that fails to improve to a minor deficit (ie non-mild RISS). Further, the inclusion of patients with RISS and continued moderate or severe deficits in the NINDS Trial provides AHA Level of Evidence Grade A (i.e., data derives 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 IV t-PA bolus/infusion.

Tables 1, 2, and 3 show case presentations and ARS questions, and 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).

Endorsement

On line supplement 2 (Appendix 2) lists the individuals from whom we have received endorsement. The term, RISS, should be reserved for those who improve to a mild deficit, specifically one which is perceived to be nondisabling.

Discussion

Rapid improvement is one of the most common reasons for exclusion from thrombolytic therapy for acute ischemic stroke (6,10). Task Force members had common knowledge of practitioners all over the country who are avoiding treating with t-PA because patients are improving a little without treatment - for example, a patient going from an NIHSS score of 15 to 10.

The pathophysiology of major, rapid clinical improvement can be due to spontaneous recanalization and/or 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/or stunned recovering brain (10). These underlying mechanisms may help explain why many stroke patients with rapid improvement are ultimately disabled (6).

It was the unanimous consensus of the Task Force that, in the absence of contraindications, patients who suffer from non-mild (i.e., moderate-to-severe) stroke, and do not improve to a non-disabling state, should be treated with IV t-PA. There was agreement that this statement can be supported by the study design and data from the original NINDS Trial, based on patient enrollment by the NINDS trialists, and is therefore is consistent with an American Heart Association (AHA) 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 showing the natural history without treatment yielded 54% of subjects with either worsening, no change, or 1 point improvement from baseline to the 2 hr NIHSS (21, NINDS rt-PA Stroke Trial unpublished data). Presently, there is no evidence to consider “non-mild, potentially disabling” rapid improvement as an exclusion criterion for IV t-PA eligibility. Our proposal for a refined and operationalized definition of RISS will be a particularly useful starting point for those who infrequently make IV t-PA 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 IV t-PA bolus/infusion. To make it practical, screening for our new, “operationalized” definition should include checkboxes in order to appeal to emergency physicians.

TIA patients 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 MCA occlusion was around 12.5 minutes (23). Therefore, a patient who improves from an NIHSS score of 15 to 10 is unlikely to be suffering from a TIA and is therefore a candidate for IV t-PA treatment. It is the patient who returns to normal that should not be treated with t-PA. After a static deficit for one hour, the chance of improving completely (TIA) is less than 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 non-stroke practitioners is a significant barrier that may have limited the uptake of a meaningful and appropriate definition of RISS into practice to date. Non-stroke 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 physician.

There was consensus among the group that an additional study of patients with rapid improvement but persistent non-mild 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, as well as those with mild nondisabling deficits from onset, which comprise a group of patients in whom further clinical study is warranted to see if t-PA improves long-term outcome as compared to 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 (i.e. non disabling) that you do not need to treat with IV t-PA?”

The original NINDS Trial did not study many subjects with very mild deficits whether persistent or due to improvement (26). Future studies might address the efficacy and safety of thrombolytic therapy in patients with an NIHSS score of 0 (27) to 5 and not perceived to be disabling, based on current consensus regarding which patients should be randomized (Table 3). There may also be a fundamental difference between AIS patients with RISS who improve from a major to a minor, non-disabling deficit and patients who have a persistent mild, nondisabling deficit since onset. Therefore, it will be important moving forward and will require recording more than a single baseline NIHSS pre-treatment score in patients with RISS. These findings will inform the planned phase 3 randomized clinical trial, Potential for rt-PA to Improve Strokes with Mild Symptoms (PRISMS), of IV rtPA for mild ischemic stroke within 3 hours of onset, currently under evaluation for sponsorship by Genentech, Inc. While proponents of treating mild stroke point to the generalizability of t-PA from the NINDS data, there is still risk of serious intracranial hemorrhage and the good natural history for the majority of minor stroke patients to warrant equipoise for selected patients in this trial (28). Recent data from the VISTA database of the subgroups where t-PA benefit does not clearly emerge are those with baseline NIHSS < 6, recognizing the very small, and likely underpowered sample size. Additionally, 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. While 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 IV t-PA, 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 IV t-PA exclusion criterion based on the 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 IV t-PA therapy based on the 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 non-stroke physicians is a significant barrier to the optimal treatment of patients with acute ischemic stroke. 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 IV t-PA. There was further unanimous consensus that an additional study of patients with improvement but moderate or severe deficits is not needed and inappropriate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Operationalizing RISS: Consensus Areas

Case Scenario: A 43-year-old female is brought to the ED within 3 hours following acute ischemic stroke.

- **≥75%** would typically treat this patient with IV thrombolytic therapy in the presence of the following levels of NIHSS score improvement within 10-15 minutes of arrival in the ED*:
  - ○ NIHSS score 16 to 12
  - ○ NIHSS score 16 to 6
  - ○ NIHSS score 16 to 2, with residual neurological deficit leading to inability to walk

≥75% would **not** typically treat this patient with IV thrombolytic therapy in the presence of the following levels of NIHSS score improvement within 10-15 minutes of arrival in the ED:

- ○ NIHSS score 16 to 2, with residual neurological deficit that appears nondisabling

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 IV rtPA:

- ○ Large penumbral pattern (based on computed tomography or magnetic resonance multimodal imaging)
- ○ Presence of a proximal large artery occlusion, or fluctuation prior to improvement.
- ○ NIHSS score 16 to 0, with residual isolated truncal ataxia leading to inability to walk

Table 2

ARS Question: Relative Contraindications, i.e. Warnings: Are the following criteria on their own sufficient to contraindicate IV thrombolytic therapy?

Criterion	Response (%)	
	Yes	No
Seizure at stroke onset (with ischemic stroke verified on imaging)	0	100
Major early infarction signs on computed tomography	80	20
Glucose <50 mg/dL	50	50
Glucose >400 mg/dL	11	89
RISS	**0**	**100**
Recent gastrointestinal/genitourinary bleeding (within 21 days)	78	22
Major surgery within 14 days	89	11
Arterial puncture at a noncompressible site within 14 days	44	56

RISS: rapidly improving stroke symptoms

Table 3

ARS Question: Clinical Trial Considerations: Would you be willing to randomize RISS patients to placebo in a clinical trial based on the following criteria?

Criterion	Response (%)	
	Yes	No
Improvement by ≥10 NIHSS points regardless of score at time of pretreatment decision	0	100
Improvement to pretreatment NIHSS ≤5	30	70
Improvement to pretreatment NIHSS ≤3	30	70
Improvement to pretreatment NIHSS 0	40	60
Improvement to a deficit that you perceive to be non-disabling	80	20

NIHSS, National Institutes of Health Stroke Scale

Note: Task Force Members who were willing to randomize RISS patients to placebo based on improvement to pretreatment NIHSS ≤, ≤3, or 0 stated that deficits would have to be nondisabling in order not to treat.

While there was consensus among the group on willingness to randomize RISS patients to placebo if they showed improvement to a deficit that was perceived to be non-disabling, members again pointed out the potential for patient-practitioner discordance with regard to perceptions of non-disabling and the need to consider both perspectives.

Table 4

Task Force Consensus: Definition and Clinical Context of Rapidly Improved Stroke Symptoms (RISS) as an Exclusion Criterion for IV t-PA

- Improvement to a mild stroke such that any remaining deficits appear non-disabling
- The following typically should be considered disabling deficits:
  - Complete hemianopsia (≥ 2 on the NIHSS Question #3), or
  - Severe aphasia (≥ 2 on NIHSS Question #9), or
  - Visual or sensory extinction (≥ 1 on NIHSS Question #11), or
  - Any weakness limiting sustained effort against gravity (≥ 2 on NIHSS Questions #6 or #7),
  - Any deficits that lead to a total NIHSS >5, or
  - Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required.

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.