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Mild Stroke and Rapidly Improving Symptoms: It's Not Always A Happy Ending

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Despite the substantial benefit of intravenous recombinant tissue plasminogen activator (IV rt-PA) in improving neurological outcomes in acute ischemic stroke (AIS) patients[1,2] only about half of those patients who arrive in time receive it[3,4]. In 2009, 3.4% to 5.2% of AIS patients in the United States received thrombolytics, approximately double the rate of treatment in 2005[5]. Rapid recognition and transport and quick treatment in the Emergency Department are clear goals for further improving treatment rates[5].

There have been more controversial barriers to the use of IV rt-PA treatment. Prior studies[6–10] have estimated that 29–43% of AIS patients arriving within 3 hours of symptom onset are not treated with IV rt-PA because of "mild stroke" or "rapidly improving stroke symptoms (RISS)". Smith et al.[11] report important results from the American Heart Association Get With The Guidelines (GWTG) nationwide program[11,12], involving 1,290 participating hospitals – the largest data set to date analyzing outcome of mild stroke and RISS. Over the last 6 years, among 93,517 AIS patients arriving within 2 hours of symptoms onset, almost one third (29,200 patients) were excluded from IV rt-PA solely because of presenting with mild stroke or RISS. This would not be of concern if outcome of AIS patients with mild stroke or RISS was invariably benign. However, data have suggested that this is frequently not true[9,13]. Their outcome is indeed unpredictable, as confirmed by Smith et al.[11] In the GWTG population, approximately 28% went to inpatient rehabilitation or skilled-nursing facilities and 1% died; Almost 30% were not fully functionally independent at hospital discharge. These outcomes were worse than those of patients diagnosed with Transient Ischemic Attacks[11]. These are key data to argue for a more effective approach to these AIS patients.

There are critical questions that need to be addressed.

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Why are AIS patients presenting with mild stroke or RISS so commonly excluded from treatment with IV rt-PA?

There is a need for clearer definitions/exclusion criteria. For those who like to split within categorical classifications, one thought immediately arises: can we lump mild stroke and RISS together? Even though they may potentially overlap, the degree of similarity depends on the magnitude of improvement in RISS and may carry distinctive clinical implications from someone with a stable mild deficit. However, they have frequently been combined as one contraindication for IV rt-PA. The package insert for the rt-PA product label [alteplase (Activase, Genentech)] states that "the safety and efficacy of treament with Activase in patients with minor neurological deficit or with rapidly improving symptoms..has not been evaluated. Therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended"[14].

Methodologically, the GWTG data collection form employed a single check box for "mild or rapidly improving" stroke[11,12]. This lack of clear distinction between mild stroke and RISS makes the process of dissecting out the specific barriers limiting the use of IV rt-PA, more difficult. As a historical note, exclusion criteria for The NINDS rt-PA Stroke Trial[1] originally called for separately excluding only patients with either very specific minor stroke syndromes or with "*major* [authors' italics] symptoms that are rapidly improving by the time of randomization". [Tilley B.C., The NINDS rt-PA Stroke Trial; *Manual of Procedure*, January 24,1991, Form 3, p.22]. Subsequent to The NINDS rt-PA Stroke Trial[1], no formal consensus has been achieved to define mild stroke[15] and RISS[16]. Clinical guidelines[17] have partially clarified this issue. Specifically, RISS has been operationalized as "the neurological deficit should not be clearing spontaneously" and for mild stroke: "the neurological signs should not be minor and isolated"[17].

Is there a need for serial pre-treatment stroke severity assessments?

The GWTG database[11,12], includes only a single assessment of stroke severity by the National Institutes of Health Stroke Scale (NIHSS), preventing a systematic evaluation of change over time. Improvement in symptoms may occur before or after arrival to the Emergency Department while the NIHSS could have been recorded prior to, in the midst of, or following clinical improvement. As "improvement" requires at least two different time point evaluations, it was not possible to estimate the frequency of mild stroke and RISS separately in this study. The GWTG program is a voluntary self-reporting tool[11,12] and for mild stroke and RISS patients the NIHSS was inconsistently documented[11], missing in almost 40%. Prospective studies including a serial evaluation of stroke severity with NIHSS in the early phase before treatment consideration and decision may help clarify the distinction between mild stroke and RISS and further identify the relationship between time and rate of improvement.

Is NIHSS really sufficient to describe stroke deficit and discriminate between "minor" and "non minor"?

While the NIHSS predicts outcome, the scale was not constructed with this specific aim[18]. It was designed as a tool to quantify the neurologic deficits commonly seen in acute stroke. Not all stroke signs are captured on the NIHSS[19]. The NIHSS does not directly test gait, balance, cognition, and hand strength. It is a frequent observation that patients with low NIHSS scores are functionally worse than expected. Furthermore, an NIHSS score of 3 could represent the deficit of a person with moderately severe language impairment (disabling stroke), but it could also represent mild facial weakness or asymmetry, mild dysarthria, and a mild drift of an upper extremity (non disabling stroke)[20]. Perhaps, a further

refinement of the NIHSS may help decision making about treatment in AIS patients presenting with mild stroke or RISS.

Could training physicians for a more critical assessment of “ambiguous contraindications” to IV rt-PA improve rates of treatment?

The exclusion criteria of mild stroke and RISS rely on clinical judgment decision without any specifically defined quantitative aspects, as opposed to many other IV rt-PA exclusion criteria that are specific and quantifiable. The clinician may expect and believe that both mild stroke and RISS will result in good neurological outcomes, whether or not treated with IV rt-PA. Perhaps, the high rate of perceived risks in treating with IV rt-PA, contributes to why AIS patients with mild stroke or RISS are excluded from IV rt-PA. The recently published The PRomoting ACute Thrombolysis in Ischemic stroke (PRACTISE) trial[21] demonstrated the effectiveness of an intensive multi-dimensional implementation strategy for increasing the proportion of AIS patients treated with IV rt-PA in real-life settings. Better application of contraindications for thrombolysis represents an apparently pivotal factor in the improvement of the treatment rate. Specifically, “mild or rapidly improving symptoms” (considered in the PRACTISE trial as the “ambiguous contraindications” to IV rt-PA) was a less frequent contraindication in the interventions hospitals compared to the non-intervention ones [17% versus 26%], a reduction of 35%, supporting the value of a more critical appraisal of ambiguous exclusion criteria in improving IV rt-PA treatment[21].

What are the reasons for unpredictable outcome in mild stroke and RISS? The role of stroke mechanism.

While stroke subtype analysis might provide some insight into outcome of mild stroke and RISS, this was not systematically addressed in the analysis of Smith et al[11] as part of the GWTG dataset. The evidence of large-vessel occlusions or stenosis in AIS patients with mild stroke or RISS has been associated with an increased odds of poor outcome[13,22–24]. Early vascular evaluation might identify the patient with mild stroke or RISS at risk for worsening and with greater need for urgent recanalization[13,22–24].

Is there an established benefit of IV rt-PA in mild stroke and RISS?

In general, IV rt-PA benefits patients across the spectrum of NIHSS scores[1]. Both a lack of precise application of The NINDS rt-PA Stroke Trial exclusion/inclusion criteria[1] in the community for the past 15 years and a splitting of baseline stroke severities have brought us the perceived need for additional studies in specific subgroups of patients. In the last decade some exploratory studies[20,25–28] to assess the safety and efficacy of IV rt-PA in mild stroke and RISS have been conducted. Most patients treated with IV rt-PA achieved good outcome, some recovering without any persisting symptoms. The overall reported risk of symptomatic ICH after thrombolysis in patients with mild stroke[20, 25–27] and RISS[28] was relatively low, reinforcing prior data that the benefit of IV rt-PA may outweigh the risk in these patients. There is also a health economic consideration: according to a recent preliminary study[29] that analyzed hospital records from 437 patients with mild ischemic stroke at 16 sites in the Greater Cincinnati/Northern Kentucky region in 2005, treating mild strokes with IV rt-PA could reduce the number of patients left disabled saving $200 million a year in disability costs. These preliminary observations provide a rational to the “splitters” for conducting a randomized controlled trial in order to further clarify the risk/benefit ratio of IV rt-PA in mild stroke and RISS patients.

The time to improve outcome of patients with mild stroke and RISS has come using new approaches to definitions, assessments, education, earlier vascular diagnostic investigations,

and risk-benefit analyses. There is a great opportunity to work towards increasing the frequency of happy endings in these patients.

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