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-type plasminogen activator (IV rtPA) in improving neurologic outcomes in acute ischemic stroke (AIS) patients,1,2 only about half of those patients who arrive at the hospital in time receive it.3,4 In 2009, 3.4% to 5.2% of AIS patients in the United States received thrombolitics, 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 rtPA treatment. Prior studies6–10 have estimated that 29% to 43% of AIS patients arriving within 3 hours of symptom onset are not treated with IV rtPA because of “mild stroke” or “rapidly improving stroke symptoms” (RISS). In this issue of Stroke, Smith et al11 have reported important results from the American Heart Association Get With The Guidelines (GWTG) nationwide program11,12 involving 1290 participating hospitals, the largest data set to date analyzing outcomes of mild stroke and RISS. During the last 6 years, among 93,517 AIS patients arriving within 2 hours of symptom onset, almost one third (29,200 patients) were excluded from IV rtPA treatment solely because they presented with mild stroke or RISS. This would not be of concern if the outcomes of AIS patients with mild stroke or RISS were 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, 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.

Why Are AIS Patients Who Present With Mild Stroke or RISS so Commonly Excluded From Treatment With IV rtPA?

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, these 2 conditions have frequently been combined as 1 contraindication for IV rtPA. The package insert for the rtPA product label (alteplase [Activase, Genentech, Inc]) states that “the safety and efficacy of treatment 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 used 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 rtPA more difficult. As a historical note, exclusion criteria for the National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Trial1 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” (B.C. Tilley, NINDS rtPA Stroke Trial; Manual of Procedure, January 24, 1991, form 3, p 22). Subsequent to the NINDS rtPA Stroke Trial,1 no formal consensus has been achieved to define mild stroke15,15a and RISS.16 Clinical guidelines17 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 Pretreatment Stroke Severity Assessments?

The GWTG database11,12 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 at the Emergency Department while the NIHSS could have been recorded before, in the midst of, or after clinical improvement. Because “improvement” requires at least 2 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...
and for mild stroke and RISS patients, the NIHSS was inconsistently documented\textsuperscript{11,12} and in fact, was missing in almost 40%. Prospective studies including a serial evaluation of stroke severity with the NIHSS in the early phase before treatment consideration and decision making may help clarify the distinction between mild stroke and RISS and further identify the relation between time and rate of improvement.

Is the NIHSS Really Sufficient to Describe Stroke Deficit and Discriminate Between “Minor” and “Non-Minor”?\textsuperscript{11,12,18}

Whereas the NIHSS predicts outcome, the scale was not constructed with this specific aim.\textsuperscript{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, however.\textsuperscript{19} For example, 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 a 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 (nondisabling stroke).\textsuperscript{20} Perhaps 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 rtPA Improve Rates of Treatment?\textsuperscript{21}

The exclusion criteria of mild stroke and RISS rely on a clinical judgment decision without any specifically defined quantitative aspects, as opposed to many other IV rtPA exclusion criteria that are specific and quantifiable. The clinician may expect and believe that both mild stroke and RISS will result in good neurologic outcomes, whether treated with IV rtPA or not. Perhaps the high rate of perceived risks in treating with IV rtPA contributes to why AIS patients with mild stroke or RISS are excluded from IV rtPA. The recently published PRomoting ACute Thrombolysis in Ischemic Stroke trial\textsuperscript{21} demonstrated the effectiveness of an intensive, multidimensional implementation strategy for increasing the proportion of AIS patients treated with IV rtPA 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 PRomoting ACute Thrombolysis in Ischemic Stroke trial as the “ambiguous contraindications” to IV rtPA) was a less frequent contraindication in the intervention hospitals compared with the nonintervention ones (17% versus 26%), a reduction of 35%, supporting the value of a more critical appraisal of ambiguous exclusion criteria in improving IV rtPA treatment.\textsuperscript{21}

What Are the Reasons for Unpredictable Outcomes in Mild Stroke and RISS? The Role of Stroke Mechanism\textsuperscript{22–24}

Whereas stroke subtype analysis might provide some insight into outcomes of mild stroke and RISS, this was not system-
Outcome in Mild and Rapidly Improving Stroke


Key Words: mild/minor stroke, rapidly improving stroke symptoms, intravenous rtPA, outcomes
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