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Clotilde Balucani and Steven R. Levine

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Mild Stroke and Rapidly Improving Symptoms

It's Not Always a Happy Ending

Clotilde Balucani, MD; Steven R. Levine, MD

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 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 rtPA treatment. Prior studies^{6–10} 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 program^{11,12} 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 stroke^{15,15a} 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 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 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

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From the Stroke Center and Department of Neurology (C.B., S.R.L.), State University of New York Downstate Medical Center, Brooklyn, and Department of Neurology (C.B.), University of Perugia, Perugia, Italy.

Correspondence to Steven R. Levine, MD, Stroke Center, Department of Neurology, Box 1213, State University of New York Downstate Medical Center, 450 Clarkson Ave, Brooklyn, NY 11203-2098. E-mail steven.levine@downstate.edu

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tool,^{11,12} and for mild stroke and RISS patients, the NIHSS was inconsistently documented¹¹ 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”?

Whereas 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, however.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).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?

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 trial²¹ 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.²¹

What Are the Reasons for Unpredictable Outcomes in Mild Stroke and RISS? The Role of Stroke Mechanism

Whereas stroke subtype analysis might provide some insight into outcomes of mild stroke and RISS, this was not system-

atically addressed in the analysis of Smith et al¹¹ as part of the GWTG data set. Evidence of large-vessel occlusion or stenosis in AIS patients with mild stroke or RISS has been associated with increased odds of poor outcome.^{13,22–24} Early vascular evaluation might identify those patient with mild stroke or RISS at risk for worsening and with a greater need for urgent recanalization.^{13,22–24}

Is There an Established Benefit of IV rtPA in Mild Stroke and RISS?

In general, IV rtPA benefits patients across the spectrum of NIHSS scores.¹ Both a lack of precise application of NINDS rtPA Stroke Trial exclusion/inclusion criteria¹ 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 rtPA in mild stroke and RISS have been conducted. Most patients treated with IV rtPA achieved good outcomes, some recovering without any persisting symptoms. The overall reported risk of symptomatic intracerebral hemorrhage after thrombolysis in patients with mild stroke^{20,25–27} and RISS²⁸ was relatively low, reinforcing prior data that the benefit of IV rtPA may outweigh the risk in these patients. There is also a health economic consideration: according to a recent preliminary study²⁹ 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 rtPA could reduce the number of patients left disabled, saving \$200 million a year in disability costs. These preliminary observations provide a rationale to the “splitters” for conducting a randomized, controlled trial to further clarify the risk-benefit ratio of IV rtPA in mild stroke and RISS patients.

The time to improve outcomes of patients with mild stroke and RISS has come, by using new approaches to definitions, assessments, education, earlier vascular diagnostic investigations, and risk-benefit analyses. There is a great opportunity to work toward increasing the frequency of happy endings in these patients.

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