

# Severe ischemic stroke

## Too severe for thrombolysis?

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Twenty years after the introduction of IV thrombolysis with recombinant tissue plasminogen activator (rtPA), only a small proportion of stroke patients are treated with rtPA.<sup>1</sup> The strict inclusion and exclusion criteria in the stroke guidelines, based on criteria used in the rtPA trials, partially explains the low number of treated patients. Fear of intracranial hemorrhage after rtPA also drives the strict selection of patients, despite evidence of the safety and potential effectiveness of rtPA treatment in an off-label setting.<sup>2,3</sup> According to the European Medicines Agency, very severe stroke, defined as an NIH Stroke Scale (NIHSS) score of more than 25 points, represents a contraindication for rtPA.<sup>4</sup> The American Heart Association Stroke Council recommends an upper NIHSS score limit of 25 for patients presenting between 3 and 4.5 hours of stroke onset.<sup>5</sup> Japanese guidelines discourage the use of rtPA when the NIHSS score is above 23 points.<sup>6</sup>

In this issue of *Neurology*®, Mazyra et al.<sup>7</sup> compared the safety of rtPA treatment in 868 “off-label” treated patients with a very severe stroke (NIHSS score >25) with 19,995 patients having a severe stroke (NIHSS score 17–25), in the Safe Implementation of Treatments in Stroke (SITS) registry. The SITS registry is a reliable, predominantly European, prospective Web-based registry, with currently more than 58,000 rtPA-treated patients. As expected, patients with very severe strokes had a worse functional outcome compared to patients with severe stroke. No difference was found in the incidence of (symptomatic) intracerebral hemorrhage (ICH). Patients with very severe stroke had more frequent posterior circulation stroke (most likely basilar artery occlusion) than those with severe stroke. Because posterior strokes had a lower ICH risk than anterior circulation strokes but higher NIHSS scores, the comparable ICH rate between severe and very severe stroke could be confounded by the higher incidence of posterior strokes in the very severe stroke group. Although the stroke territory was known in less than a quarter of the included patients, the authors did additional analyses with adjustment for stroke territory and found the same results as in the whole group. Only 29 patients with very severe

stroke and 308 patients with severe stroke were treated with endovascular thrombectomy. These low numbers likely reflect the historical nature of the data, collected between 2002 and 2013. Patients with very severe stroke likely have a proximal intracranial arterial occlusion and many of these patients would now be considered for endovascular thrombectomy following administration of IV rtPA, recently proven highly effective and safe in this subgroup of patients.<sup>8</sup>

Should the (European) restriction of rtPA in patients with NIHSS score above 25 be abandoned? When considering rtPA treatment in an individual patient, treatment effect should be balanced against treatment risk. We can learn from this study that the hemorrhage risk in very severe stroke is not higher than the risk in severe stroke patients. This study did not report the relative benefit of rtPA in this subgroup. Reanalysis of the National Institute of Neurological Disorders and Stroke trial showed no differential effect of rtPA in severe stroke (NIHSS score >20).<sup>9</sup> The Third International Stroke Trial (IST-3) included 146 patients with NIHSS score >25, and in this prespecified subgroup there was no difference in treatment effect of rtPA compared to the subgroup with lower NIHSS scores. Moreover, the IST-3 showed the greatest benefit for treatment in those with the highest predicted probability of poor outcome.<sup>3</sup> A pooled analysis of 9 rtPA trials revealed no differential treatment effect in the subgroup analysis of patients with NIHSS score >22.<sup>10</sup>

Taking all these data together, an NIHSS score >25 should probably not deter physicians from treating a stroke patient with IV thrombolysis. All efforts must be undertaken to offer rtPA treatment as much as possible to all eligible stroke patients. But IV thrombolysis alone is not enough; further improvement of acute stroke treatment is still necessary, especially in patients with severe stroke because of the poor prognosis. After the recent publication of overwhelming positive studies of endovascular stroke treatment, patients with very severe anterior circulation ischemic stroke should, besides treatment with IV rtPA, also be rapidly screened for proximal intracranial arterial

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occlusions. Those patients with proximal occlusions (frequently the patients with very severe stroke) should be offered a rapid endovascular thrombectomy. Whether these data allow extrapolation to posterior circulation arterial occlusions is a matter of debate. Another question that arises is whether the patients with severe stroke and a proximal intracranial arterial occlusion will do better with primary endovascular treatment without IV thrombolysis, which is the current clinical practice in acute myocardial infarction, or a combined IV rtPA and endovascular thrombectomy approach. A randomized controlled trial that will compare these 2 treatment strategies is currently being planned as a continuation of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN).

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### DISCLOSURE

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