Letter to the Editor

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Letter by Turc et al Regarding Article, “Defining Clinically Relevant Cerebral Hemorrhage After Thrombolytic Therapy for Stroke: Analysis of the National Institute of Neurological Disorders and Stroke Tissue-Type Plasminogen Activator Trials”

To the Editor:

We read with interest the important article by Rao et al.1 Using publicly available data from the National Institute of Neurological Disorders and Stroke Tissue-Type Plasminogen Activator (NINDS-tPA) trials, the authors compared 4 definitions of intracranial hemorrhage (ICH) after thrombolysis to identify the most clinically relevant. They conclude that the European Cooperative Acute Stroke Study 2 (ECASS-2) and Modified Safe Implementation of Thrombolysis in Stroke-Monitoring Study (mSITS-MOST) definitions best identify tissue-type plasminogen activator hemorrhages that alter final outcome, but that their results favor the ECASS-2 definition, in line with previous reports.

One important feature of the ECASS-2 definition is that it encompasses minor ICH, sometimes unlikely to cause neurological deterioration such as hemorrhagic infarction type 1 or 2. In relation to this, we are puzzled by the fate of the 6 patients (No. 22–27) who had a symptomatic ICH according to ECASS-2 and were all dead at 3 months, yet did not have parenchymal hemorrhage, raising the question whether these patients’ death, and in turn their initial neurological deterioration, was related to the ICH. Another limitation of the ECASS-2 definition is that it does not require a presumed causal relation (unlike ECASS-3) nor a temporal association (unlike NINDS), between the ICH and the deterioration. Patient No. 22 and 23 met the ECASS-2 but not the NINDS definition for symptomatic ICH, raising the question of the temporal association between their ICH and their neurological deterioration.

For the purpose of their study, Rao et al1 slightly modified the ECASS-2 definition, considering the National Institutes of Health Stroke Scale score at 24 hours and the ICH within 36 hours of tissue-type plasminogen activator administration instead of 7 days in the original definition. This modified definition equates to early neurological deterioration (END; generally defined as ≥4 National Institutes of Health Stroke Scale increase within the first 24 hours) with documentation of any ICH. Could patient No. 22 to 27 have another cause of END such as malignant edema, early recurrent ischemic stroke, or seizures, which would question the presumed clinically relevant association between ICH and END? Besides, were no alternative cause to the clinical deterioration documented, END without clear mechanism (unexplained END) could be considered, especially in case of hemorrhagic infarction type 1. We recently reported that unexplained END accounts for two thirds of all END cases.3 The poor outcome in patient No. 22 to 27 does not necessarily imply a causal (as opposed to incidental) link with their ICH. In our database of thrombolized patients, 18 of 22 (85%) unexplained END patients had poor 3-month outcome, defined as modified Rankin Scale ≥2 (odds ratio, 7.06; 95% confidence interval, 2.03–24.51, relative to the no-END group).3 We recently reported that most instances of unexplained END have infarct growth beyond the initial penumbra in the context of proximal arterial occlusion and no 24-hour recanalization.3 Such a hypothesis is unlikely to explain most ENDS in the study by Rao et al, as the authors took into account not only the observed outcome after thrombolysis but also the model-derived expected outcome of each patient had they not received tissue-type plasminogen activator, implying that the above vascular features were adequately controlled. However, proximal arterial occlusion was based on the computed tomography hyperdense artery sign, which is known to often miss true occlusions.

Altogether then, although the ECASS-2 definition has clinical face value because it is straightforward and robustly predicts 3-month poor outcome, it may in fact mix 2 distinct causes of poor outcome, namely true symptomatic ICH and unexplained END associated with asymptomatic hemorrhagic transformation. This stems from the fact that, like the NINDS definition, the ECASS-2 definition accepts as symptomatic any ICH irrespective of its location or radiological characteristics. With a uniform definition of symptomatic ICH as target for future randomized trials, the rigorous methodology proposed by Rao et al should now be used to formally compare the clinical relevance of ECASS-3, ECASS-2, and SITS-MOST definitions, capitalizing for instance on the ECASS-3 trial data set.

Disclosures

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Guillaume Turc, MD
Department of Neurology
Hôpital Sainte-Anne
Université Paris Descartes & INSERM UMR 894
Paris, France

Marie Tissierand, MD
Department of Radiology
Hôpital Sainte-Anne
Paris, France

Pierre Seners, MSc
Department of Neurology
Hôpital Sainte-Anne
Paris, France

Catherine Oppenheim, PhD
Department of Radiology
Hôpital Sainte-Anne
Université Paris Descartes & INSERM UMR 894
Paris, France

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Jean-Claude Baron, ScD
Department of Neurology
Hôpital Sainte-Anne
Université Paris Descartes & INSERM UMR 894
Paris, France

References
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Guillaume Turc, Marie Tisserand, Pierre Seners, Catherine Oppenheim and Jean-Claude Baron

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