The Ethics of Thrombolytic Trials Beyond 3 (or 4.5) Hours
Randomized Controlled Trials Are Required to Change Clinical Practice
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For several decades, clinicians across all fields of internal medicine have embraced the concept of practice guidelines based on levels of evidence. Medical practice in our careers has been transformed from opinion-driven behavior to a reliance on carefully assessed evidence, ranked according to its strength. Ultimately, we expect level 1 evidence for any new therapy, namely adequately powered and conducted randomized, prospective clinical trials. This has facilitated a universal benchmark for clinical practice throughout the world, with only minor regional variations. In acute stroke, this has led to the recommended use of intravenous tissue plasminogen activator within 3 hours, aspirin within 48 hours, management in stroke care units, and, more recently, hemicraniectomy in selected cases of malignant cerebral edema.1

How, then, does this principle apply to the current controversy concerning the ethics of using a placebo arm in reperfusion trials in the 3- to 6-hour time window. In other words, the essence of the debate relates to the conduct of clinical trials—not to the clinical decision in an individual patient, in which the physician is aware that level 1 evidence may not yet be available to inform a clinical decision. Until recently, there had been no level 1 evidence in the form of a randomized controlled trial with primary clinical outcome measures for intravenous tissue plasminogen activator (or indeed clot retrieval) beyond 3 hours. Since the preparation of this Controversy, the positive results of the ECASS 3 trial have been published, extending the time window to 4.5 hours for intravenous tissue plasminogen activator.2 Furthermore, we consider that there is strong evidence for intra-arterial thrombolysis in middle cerebral artery occlusion up to 6 hours, based on the PROACT II results.3

Concerning imaging-based selection of patients for thrombolytic therapy, there is no phase III trial as yet indicating that the use of MR mismatch in select patients beyond 3 hours significantly improves clinical outcomes, although there is accumulating evidence in support of this hypothesis. Our recently published EPITHET trial showed that intravenous tissue plasminogen activator, in the presence of mismatch in the 3- to 6-hour time window, was associated with significantly increased reperfusion and strong trends to infarct growth attenuation.4 There was a 15% absolute increase in excellent outcomes (modified Rankin Scale score, 0,1) in this group. Whereas this trend did not achieve statistical significance, the results suggest that only 200 patients per arm would be required for a phase III trial of tissue plasminogen activator vs placebo in patients with MR mismatch beyond 3 hours after stroke onset.

Does this mean that individual clinicians should not consider intravenous tissue plasminogen activator (or other reperfusion therapies) in patients with MR mismatch in the 3 (or now 4.5)-to 6-hour time window? Here we accept a pluralistic approach, emphasizing that there is, indeed, an art as well as science in medicine, and stroke neurology is no exception. In other words, we support the view that stroke clinicians might reasonably treat individuals in some circumstances while we await more definitive evidence. For us, this is a situation of classical clinical equipoise. Fortunately, the uncertainty principle for the conduct of clinical trials is alive and well, and a sufficient number of clinicians worldwide would be prepared to randomize such patients. Based on the available data, and particularly the recent results of EPITHET, we strongly consider that a pivotal phase III clinical trial of intravenous tissue plasminogen activator beyond 4.5 hours, using the MR mismatch selection principle, must now proceed. Despite the accumulating evidence that supports the strategy of reperfusion beyond the established time window, we consider that phase III randomized controlled trial evidence is required to change clinical practice. We are, therefore, planning to conduct the EXTEND Trial (extended time for thrombolysis in emergency neurological deficits) using online selection of patients with MR mismatch and a 4.5- to 9-hour time window.

Disclosures
None.

References
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