Expanding Recombinant Tissue Plasminogen Activator Time Window Is Premature

To the Editor:

The American Heart Association/American Stroke Association has expanded the time window for recombinant tissue plasminogen activator from 3 hours to 4.5 hours after stroke onset for many patients.1 The evidence2–7 does not support a Class I recommendation (which will impact clinical care, quality measures, and medicolegal decisions), and we urge the American Heart Association/American Stroke Association to reconsider.

The new recommendation is based on the European Cooperative Acute Stroke Study III (ECASS III), a high-quality trial in 821 patients.2 ECASS III found recombinant tissue plasminogen activator within 3 to 4.5 hours after stroke onset to reduce the risk of death or dependency at 90 days (47.6% versus 54.8%, *P* = 0.04, number needed to treat 14) despite an increase in any intracranial hemorrhage (27% versus 17.6% using the National Institute of Neurological Diseases and Stroke definition, *P* = 0.001, number needed to harm 10) and in symptomatic intracranial hemorrhage (7.9% versus 3.5%, *P* = 0.006, number needed to harm 22). In isolation, the ECASS III trial supports the recommendation.

However, there are 4 other randomized, placebo-controlled trials to consider. The Alteplase Thrombolysis in Ischemic Stroke (ATLANTIS) trial, a high-quality placebo-controlled trial in 613 patients, found recombinant tissue plasminogen activator within 3 to 5 hours after stroke onset had no significant differences in death or dependency at 90 days (66.2% versus 68%), a nonsignificant increase in mortality (11% versus 6.9%, *P* = 0.09), and a significant increase in symptomatic intracranial hemorrhage (7% versus 1.1%, *P* < 0.001, number needed to harm 17).3 Three other randomized, placebo-controlled trials (A0276g, ECASS, ECASS II) evaluated recombinant tissue plasminogen activator within 3 to 6 hours.4–6 Increases in intracranial hemorrhage were fairly consistent, but decreases in death or dependency were inconsistent.

Although a single pooled analysis of results from previous trials was reported,1 inconsistencies in the populations, outcome definitions, and results do not support a single pooled analysis. Additional support for the new recommendation used an observational study of patients treated 3 to 4.5 hours (n = 664) compared with patients treated within 3 hours after symptom onset (n = 11 865).7 The study was summarized as having “no differences” in symptomatic intracerebral hemorrhage and mortality. However, the data suggest worse outcomes in the 3- to 4.5-hour time window for symptomatic intracerebral hemorrhage (2.2% versus 1.6%, *P* = 0.052) and mortality (12.7% versus 12.2%, *P* = 0.053). A distinction must be made between “no differences” and “no statistically significant differences.” A trend toward harm that approaches the traditional threshold for statistical significance does not establish safety or equivalence.

With clear harms consistent across trials and inconsistent evidence for benefit, a Class I recommendation is not warranted. Further research establishing benefit in another high-quality randomized, placebo-controlled trial should be completed before making recombinant tissue plasminogen activator 3 to 4.5 hours after stroke onset a standard of care.

Disclosures

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