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. The evidence 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. 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).

Three other randomized, placebo-controlled trials (A0276g, ECASS, ECASS II) evaluated recombinant tissue plasminogen activator within 3 to 6 hours. 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, 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). The study was summarized as having “no differences” in symptomatic intracerebral hemorrhage and mortality. However, the data suggest worser outcomes in the 3- to 4.5-hour time window group 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

B.S.A. is Editor-in-Chief and C.B.B. is Deputy Editor of DynaMed, an evidence-based clinical reference.

Brian S. Alper, MD, MSPH
Cynthia B. Brown, MD
DynaMed
EBSCO Publishing
Ipswich, Mass


Key Words: stroke management thrombolysis thrombolytic Rx
Expanding Recombinant Tissue Plasminogen Activator Time Window Is Premature
Brian S. Alper and Cynthia B. Brown

Stroke. 2009;40:e632; originally published online October 1, 2009; doi: 10.1161/STROKEAHA.109.560615
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/11/e632

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/