The publication of the National Institute of Neurological Diseases and Stroke trial 13 years ago was one of the most exciting events in modern stroke medicine, demonstrating the powerful effect of tissue plasminogen activator (tPA) in acute ischemic stroke within 3 hours of symptom onset. The sound barrier for stroke treatment had been broken. The European Cooperative Acute Stroke Study III (ECASS III) trial of 821 patients is the second positive result using tPA in an individual trial with a 7% absolute improvement in the primary outcome measure of disability at 90 days. The results were remarkably consistent with the predicted benefit from the pooled meta-analysis, which included all the trial data that had been accrued out to 6 hours, showing that efficacy was likely significant until 4.5 hours after stroke onset with diminishing treatment effect over time. This underlined the “time is brain” paradigm. What are the consequences for guidelines and clinical practice with the positive ECASS III results? First, we consider that there is unequivocal support for defining a new time window of 4.5 hours without the need for additional trials. Second, these results should remove any doubt from the skeptics, particularly in emergency medicine, concerning the therapeutic efficacy and relative safety of tPA in ischemic stroke and therefore stimulate the uptake of the therapy both within and beyond 3 hours. Third, the results are another validation of the reperfusion paradigm for treatment of acute brain ischemia and help inform the design of future trials aimed at further extension of the time window in selected patients. Finally, despite the extension of the time window, earlier is better in terms of treatment effect.

The ECASS III results confirm the efficacy and relative safety of tPA. Like any acute stroke trials, heterogeneity of patients and the vagaries of randomization led to some baseline imbalance. There was a somewhat milder population accrued in ECASS III compared with earlier tPA trials and slight baseline imbalance favoring the active arm. Perhaps aware of the controversy in some circles (again mainly emergency medicine) concerning baseline imbalance in the National Institute of Neurological Diseases and Stroke, the investigators performed post hoc baseline adjustment in ECASS III. Similar to the National Institute of Neurological Diseases and Stroke analysis, this made no difference and the results remain clearly and undeniably positive.

Intriguingly, although the link between time and treatment effect is further confirmed by these results, there was no increase in the rate of symptomatic intracerebral hemorrhage beyond 3 hours using a variety of different definitions. The rate was essentially the same as the National Institute of Neurological Diseases and Stroke trial at 7% using the conservative National Institute of Neurological Diseases and Stroke definition. Furthermore, there was no trend to increased mortality with tPA. This was consistent with the earlier meta-analysis, which also showed no significant link between later treatment times and risk of symptomatic intracerebral hemorrhage. The safety of 3- to 4.5-hour tPA was further supported by the recent report from the Safe Implementation of Thrombolysis in Stroke Trialists’ Collaborators (SITS-ISTR) investigators.

This web-based register was instituted as part of the licensing procedure by European Medicines Agency together with the requirement for a further randomized trial beyond 3 hours, initially planned for 4 hours and then extended to 4.5 hours. Inevitably, some patients in clinical practice in Europe were treated beyond the 3-hour time limit and these formed the basis of this SITS-ISTR report. Although a treatment register rather than a rigorously conducted clinical trial, the results add further assurance regarding safety in the longer time window. Given the clearly positive results of ECASS III, supported by the meta-analysis and SITS-ISTR findings, we consider the 4.5-hour window is clearly established with immediate implications for clinical guidelines around the world.

The only other ongoing Phase III trial of tPA is International Stroke Trial 3, randomizing patients up to 6 hours after stroke onset and where there remains uncertainty about eligibility for tPA both within and beyond the established...
time window. These include older patients (>80 years) and those with extensive ischemic change on baseline CT scans. 6 We consider that this trial will provide further valuable data, particularly concerning the 4.5- to 6-hour time window, and should be supported. However, the new guidelines should mandate a new time benchmark of 4.5 hours for most tPA candidates.

Anyone involved in acute stroke therapy over recent years would have to be concerned at the relatively poor uptake of tPA, particularly in less expert settings, despite the overwhelming evidence of benefit, concordant guidelines around the world, numerous editorials in major journals, improved acute stroke systems, and the increasing development of stroke care units. Why should up to 20% patients with ischemic stroke receive tPA in some expert academic centers, yet 1% to 3% in many other hospitals? This might be termed the “tPA paradox.” One significant factor has probably been the scepticism by some emergency physicians, who have clamored for more randomized trial evidence. 7 Involvement of emergency physicians is critical to facilitating use of tPA for stroke. We would hope that the ECASS III results, the second positive pivotal trial of tPA, will resolve this lingering reservation. We predict that the results should accelerate use of tPA both within and beyond 3 hours.

The ECASS III results support the reperfusion paradigm and our current understanding of the ischemic penumbra. Salvageable tissue in the ischemic penumbral is present in many patients well beyond 3 hours, perhaps even up to 24 or 48 hours. 8,9 The clinical results are supported by Phase II imaging studies such as our Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) trial, which showed the biological benefits of tPA at 3 to 6 hours in patients with perfusion–diffusion mismatch on MRI with significantly increased reperfusion, strong trends to infarct growth attenuation, and improved clinical outcomes. 10 There are many important questions for the reperfusion field that need to be addressed. What is the efficacy of intra-arterial therapy or mechanical clot retrieval versus intravenous thrombolysis? What of alternative thrombolytic agents or penumbral selection aimed at enriching the population with potential treatment responders? In Interventional Management of Stroke III, the concept of reduced-dose intravenous tPA followed by catheter angiography and artery reopening with clot retrieval or intra-arterial thrombolysis is being tested. 11 The Desmoteplase in Acute Ischemic Stroke (DIAS) investigators will test the efficacy of desmoteplase up to 9 hours in patients with evidence of baseline arterial occlusion. We are planning to test the hypothesis of online penumbral selection using MRI mismatch in a Phase III design of tPA versus placebo in the 4.5- to 9-hour time window in the Extension of Thrombolysis for Emergency Neurological Defects (EXTEND) trial. An important conclusion from ECASS III is that changed clinical practice must depend on such Phase III trials. This is an important lesson for device manufacturers.

Finally, although the time window for tPA has been extended to 4.5 hours, the single most important principle of acute stroke intervention must not be lost: time is critical. It is better to treat within 3 than 4.5 hours, and even better within 90 minutes, of onset. Earlier treatment is associated with increased therapeutic effect and this should be the goal of all stroke clinicians and underpin the design of acute stroke systems. 12

Disclosures

None.

References


Key Words: acute Rx | acute stroke | clinical trials
4.5 Hours: The New Time Window for Tissue Plasminogen Activator in Stroke
Stephen M. Davis and Geoffrey A. Donnan

*Stroke*. 2009;40:2266-2267; originally published online April 30, 2009;
doi: 10.1161/STROKEAHA.108.544171
*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/40/6/2266

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/