Thrombolysis in the 3- to 4.5-Hour Window
What Do ECASS Skeptics Want?

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Our patient has no contraindications for intravenous thrombolysis and meets the eligibility criteria specified in European Cooperative Acute Stroke Study (ECASS) III. Therefore, at first glance it seems that there is no basis for disagreement or controversy. He should be treated immediately with intravenous recombinant tissue-type plasminogen activator (rtPA) in line with the results of ECASS-III, a blinded, randomized, placebo-controlled trial, and professional guidelines including the American Heart Association/American Stroke Association (class I; Level of Evidence B recommendation). This position is strongly articulated by Drs Schellinger and Köhrmann.

Is it really true that the 4.5-hour window for intravenous rtPA is so firmly established? Dr Wechsler expresses some doubts, and he is not alone. The United States Food and Drug Administration, the largest agency regulating medical products on planet earth, denied an application to extend the time window for intravenous rtPA treatment to 4.5 hours. The details of the application and the reasons behind the Food and Drug Administration’s denial have not been released to the scientific community, leading to speculations that the evidence from ECASS-III and supporting data were not sufficient in the Food and Drug Administration’s opinion.

ECASS-III is a landmark study in the history of stroke therapy. It demonstrated a marginally significant statistical increase in the likelihood of having normal or near-normal recovery (modified Rankin Scale, ≤1) after rtPA treatment; 219/418 (52.4%) patients in the rtPA group had a score ≤1 at day 90 when compared with 182/403 (45.2%) patients in the placebo group (unadjusted odds ratio, 1.34; 95% confidence interval, 1.02–1.76; \( P=0.04 \)). Although the incidence of intracranial hemorrhage was higher with rtPA, mortality did not differ significantly between the groups, leading many to conclude that the risk of symptomatic intracranial hemorrhage is modest and acceptable relative to the benefit. Interestingly, this marginal benefit from rtPA could have been negated if only 218 (instead of 219) patients in the rtPA group and 183 (instead of 182) in the placebo group achieved modified Rankin Scale score ≤1! In addition, the benefit of rtPA was less robust when the global test statistic based on modified Rankin Scale, National Institutes of Health Stroke Scale, Barthel Index, and Glasgow Outcome Score was used as the outcome measure (odds ratio, 1.28; 95% confidence interval, 1.00–1.45; \( P=0.05 \)).

ECASS-III followers cite results from observational studies, such as the Safe Implementation of Treatment in Stroke International Stroke Thrombolysis Register (SITS-ISTR), and national registries, such as the Canadian Alteplase for Stroke Effectiveness Study (CASES), showing similar outcomes in patients treated within 3 to 4.5 hours after stroke when compared with those treated within 3 hours and pooled analyses of data from previous thrombolysis trials supporting the benefit of intravenous rtPA ≤4.5 hours. However, SITS-ISTR patients treated in the 3- to 4.5-hour window had significantly lower stroke severity, were younger, and more likely to have small vessel disease. After adjusting for baseline imbalances, outcomes were slightly better in the 0 to 3-hour group. An updated analysis of the 3- to 4.5-hour cohort of SITS-ISTR patients treated in compliance with the European Union approval criteria showed that the 3-month outcomes were favorable for patients treated within 3 to 4.5-hours when compared with patients treated within 3 hours in the unadjusted analysis but less favorable in the adjusted analysis. In CASES, the rates of symptomatic intracranial hemorrhage and deaths were higher in the 3 to 4.5-hour group and seemed to rise significantly in later time windows, leading the investigators to caution that although patients can be successfully treated with intravenous rtPA in the 3- to 4.5-hour window, later time window treatment may result in greater adverse events.

ECASS-III skeptics state that no other randomized controlled trial has supported the 3- to 4.5-hour window and cite data from the Third International Stroke trial (IST-3), which did not support the benefit of intravenous rtPA between 3 and 4.5 hours, despite randomizing 1177 patients in this time window.
window. ECASS-III had weaknesses as Dr Wechsler points out. Patients with severe strokes were excluded; the placebo group had higher rates of prior stroke, which may have resulted in worsened outcomes; and baseline imbalances in stroke severity favored the rtPA group. Like most other thrombolysis trials, the vast majority of patients had a plain head computed tomographic scan and lacked vascular imaging data, precluding accurate assessment of stroke subtype, or the presence of arterial occlusion. Would a lacunar versus nonlacunar infarct influence the decision making? Most likely, not. However, knowing the distribution of stroke subtypes in ECASS-III and their response to rtPA would be helpful especially for those who argue that lacunar infarcts caused by lipohyalinosis and occlusion of small penetrating arteries do not benefit from thrombolysis. The same applies to the value of vascular imaging. What about penumbral imaging? It is intuitive to think that penumbral imaging would be helpful during this late time window because the salvageable tissue decreases over time. However, Dr Wechsler raises an important practical point, the time it takes to perform advanced imaging during the narrow 3 to 4.5-hour window. Furthermore, the clinical usefulness of penumbral imaging still requires more examination. Analysis of the patients treated within the 3 to 4.5 hours in the ongoing EXTEND trial could provide helpful clues.

Further studies of thrombolysis in the 3- to 4.5-hour window are needed, but will they occur. The stroke community has been longing for ways to extend the narrow 3-hour window for rtPA; ECASS-III delivered what we wished for. The stroke community also deserves to know the details behind the Food and Drug Administration’s refusal to extend the use of intravenous rtPA to 4.5 hours. So, how should we treat our patient? In Spain and most other countries, we would treat him with intravenous rtPA without any delays. In Boston and planet USA, we would thoroughly discuss the risks versus benefit with the patient or his family to make an informed decision, albeit time-consuming, and treat with rtPA if they agree. However, the big question remains as to whether the benefit is firmly established.

**Disclosures**

None.

**References**


**Key Words:** stroke • tissue plasminogen activator
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*Stroke*. 2014;45:916-917; originally published online February 13, 2014;
doi: 10.1161/STRKEAHA.113.004265
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/45/3/916

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