The 4.5-Hour Time Window for Intravenous Thrombolysis With Intravenous Tissue-Type Plasminogen Activator Is Not Firmly Established

Lawrence R. Wechsler, MD

Most stroke neurologists would likely choose to treat this patient with intravenous tissue-type plasminogen activator (IV tPA) assuming the treatment could be initiated within 4.5 hours from stroke onset. In fact, the American Heart Association and European Stroke Organization guidelines both recommend treatment of selected patients in the 3- to 4.5-hour time window. IV tPA is approved in this time window in 15 countries in Europe and several other countries around the world. In the United States, however, the Food and Drug Administration declined an application by Genentech to extend the time window for treatment beyond 3 hours. The evidence supporting the benefit of treatment in the 3- to 4.5-hour time window includes the results of European Cooperative Acute Stroke Study (ECASS) III, a randomized controlled trial enrolling 821 patients. Three prior randomized controlled trials (ECASS, ECASS II, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS]) and 1 subsequent trial (Third International Stroke Trial [IST-3]) attempting to extend the time window for IV tPA beyond 3 hours failed to show significant benefit. In addition, an updated meta-analysis of 7012 patients in 12 IV tPA trials found that the major benefit occurred in patients treated within 3 hours with no significant effect of IV tPA in almost 5000 patients treated 3 to 6 hours after stroke onset (odds ratio, 1.07; 95% confidence interval, 0.96–1.20). Given these conflicting results, how sure are we that patients in general and this patient specifically benefit from IV tPA in the 3- to 4.5-hour time window?

Before ECASS III, 3 randomized controlled trials enrolled patients ≤6 hours from stroke onset and were negative based on the primary prespecified end point. One of the studies (ECASS II) would have been positive based on a post hoc analysis using a different end point, but both ECASS and ATLANTIS showed no suggestion of benefit. These studies were powered to detect differences between groups of ≥10% and were underpowered to detect a smaller effect size. A subsequent pooled analysis combining all 3 studies with the National Institute of Neurological Disorders and Stroke (NINDS) IV tPA trial of patients within 3 hours of stroke onset first suggested that a lesser but significant benefit of IV tPA might be present out to 4.5 hours from stroke onset. The results of ECASS III confirmed this conclusion demonstrating a 7% absolute increase in good outcomes (modified Rankin Scale ≤2; 52.4% versus 45.2%) at 90 days in patients treated between 3 and 4.5 hours. Like all studies, ECASS III had weaknesses. A significant 1 point difference in median National Institutes of Health Stroke Scale (NIHSS) scores favored the treatment group. Although the results remained significant after adjustment for all imbalances, such adjustments do not always account for unknown or unmeasured biases. In addition, good outcomes in the control patients were more frequent than most prior IV tPA trials, suggesting these patients might represent a selected population. Patients aged >80 years, with prior stroke and diabetes mellitus, high NIHSS score, or on oral anticoagulants were excluded from ECASS III. Although reaching significance, the odds ratio of 1.34 and P value of 0.04 for the unadjusted analysis in ECASS III are not robust. Given the baseline imbalances and less than robust statistical significance, support from additional trials would be desirable. Unfortunately, the other randomized controlled trials do not provide confirmatory evidence in support of this single positive trial.

The ATLANTIS Part B study of patients treated 3 to 5 hours after stroke enrolled a comparable population to ECASS III with similar exclusions and median NIHSS scores. ATLANTIS was a smaller trial that underwent several protocol revisions and was powered to detect a larger difference than that found in ECASS III. The study was terminated early for futility, and the overall results do not suggest that a larger trial would have had a different outcome. It is unclear why ATLANTIS and ECASS III found such divergent results. There were a few exclusions in ECASS III not included in ATLANTIS, and better outcomes were achieved in the control group of ECASS III despite similar baseline NIHSS scores, but it is difficult to explain the discrepant results based on these factors.
The design of IST-3 was different from ECASS III and included a much broader range of patients with fewer exclusions.\(^4\) Patients were enrolled who would not have qualified for ECASS III such as those aged >80 years and with severe strokes. However, IST-3 was the largest randomized trial of IV tPA to date and included 1177 patients between 3 and 4.5 hours from stroke onset, more than the entire ECASS III trial. Because of the differences in patient characteristics and trial design, the results cannot be directly compared with ECASS III. However, there was no suggestion of benefit of IV tPA in the IST-3 cohort treated between 3 and 4.5 hours that might support the results of ECASS III (Oxford Handicap Score, 0–2; 32% tPA versus 38% placebo).

Then what about this specific patient and consideration of IV tPA utilization? The moderate NIHSS of 8 raises a question regarding benefit because in ECASS III the greatest effect of IV tPA was found in those with more severe strokes.\(^5\) It is unclear whether all strokes respond equally to IV tPA regardless of etiology. Although limited studies to date have not demonstrated any lack of benefit for lacunar strokes, there is reason to think such strokes which are often caused by occlusion of small penetrating end vessels without collateral would not be helped by reperfusion particularly in a longer time window. In a later time window with narrow therapeutic efficacy, advanced imaging to define extent of infarct core and penumbra help with the decision to treat with IV tPA? It is difficult to obtain additional imaging in the 3- to 4.5-hour time window and remain within this limited time frame. In addition, given the strong association between greater benefit and earlier treatment, it is unclear whether imaging contributes sufficiently to justify even a 20- to 30-minute delay in starting treatment. Imaging might contribute by helping to exclude large established strokes prone to hemorrhage or edema with reperfusion, but whether perfusion studies are superior to plain computed tomography in this regard requires further examination. The recent Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial did not find that a favorable penumbral pattern predicted better outcomes with endovascular therapy compared with standard acute stroke care. This might reflect the population studied with larger strokes at a later time and with relatively low rates of reperfusion. The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 2 trial, although nonrandomized, suggests that penumbra imaging still has promise as a selection tool and deserves further study. The goal must remain treating patients as early as possible after stroke onset with careful selection of patients beyond 3 hours who are more likely to benefit from IV tPA.

**Disclosures**

Dr. Wechsler serves as a consultant for Lundbeck.

**References**


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