On September 26, 2008, the New England Journal of Medicine published the results of the European Cooperative Stroke Study (ECASS) III,¹ the first randomized, placebo-controlled trial to demonstrate safe and effective use of intravenous recombinant tissue plasminogen activator (rtPA) to treat patients with acute ischemic stroke (AIS) beyond 3 hours from stroke onset. The ECASS investigators studied the safety and efficacy of administering intravenous rtPA to patients with AIS 3 to 4.5 hours after AIS onset. Using the modified Rankin Scale score at 90 days after stroke occurrence as the primary end point of the study, the investigators demonstrated a modest, statistically significant increase in the likelihood of having normal or near normal recovery (modified Rankin Scale=0 or 1) in favor of rtPA treatment compared with placebo (unadjusted OR, 1.34; 95% CI, 1.02 to 1.76; P=0.04).

So, what impact will the results of the study have on acute stroke management and stroke research in the United States and elsewhere? With regard to the first part of the question, the answer is complex. First, the ECASS III results will hopefully help to increase the number of thrombolysis eligible patients with AIS who receive rtPA. Twelve years after the US Food and Drug Administration approved the management of AIS within 3 hours of symptom onset as an indication for the use of intravenous rtPA, less than 5% of patients with AIS are being treated worldwide with rtPA within 3 hours of stroke onset. One of the major factors contributing to this parlous state of affairs has been disagreement among healthcare professionals about the validity of the results of the National Institutes of Neurological Disorders and Stroke (NINDS) trial of rtPA for acute stroke.² In the late 1990s, the stroke community unexpectedly encountered attitudes ranging from ambivalence to overt hostility regarding the use of rtPA in the treatment of AIS from healthcare professionals both within neurology and in other disciplines. Although this resistance has lessened over time, there are still some healthcare professionals, and professional organizations, who do not advocate the use of rtPA in the treatment of AIS.³ One of the major concerns raised by those who question the use of rtPA to treat patients with AIS is that the NINDS trial results have not been confirmed by other clinical trials. Although ECASS III studied rtPA treatment for patients with AIS 3 to 4.5 hours after symptom onset, the results are consistent with the positive results of the NINDS trial, which documented better outcomes for patients with AIS treated with intravenous rtPA within 3 hours of stroke onset. The ECASS III results should put to rest any lingering doubt about using rtPA to treat appropriately selected patients with AIS within 3 hours of stroke onset.

Second, the results of ECASS III emphasize the importance of early treatment of patients with AIS with rtPA. The ECASS III findings are consistent with the results of the 2004 pooled analysis of the Alteplase Thrombolysis for acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), ECASS, and NINDS rtPA stroke trials,⁴ which documented that although intravenous rtPA treatment could potentially be given effectively as late as 4.5 hours after AIS onset, the number of patients with AIS likely to benefit from rtPA treatment declined over time. The pooled analysis documented significant, but declining, unadjusted global ORs of 1.96 (95% CI, 1.30 to 2.95), 1.65 (95% CI, 1.23 to 2.22), and 1.34 (95% CI, 1.04 to 1.72) for the time periods from stroke onset to treatment of 0 to 90 minutes, 91 to 180 minutes, and 181 to 270 minutes, respectively. In ECASS III, the unadjusted global OR for the stroke onset to treatment period of 181 to 270 minutes was 1.28 (95% CI, 1.00 to 1.45; P=0.05). Clearly, the earlier we treat patients with AIS with intravenous rtPA, the better the outcome. The results of ECASS III reinforce the simple, but effective, mantra that “time is brain” and we should continue to focus our efforts to develop stroke systems of care to insure that stroke onset-to-ED and door-to-needle times for patients with AIS are as short as possible.

Third, the ECASS III results raise the question of whether treatment guidelines should be changed to extend the time window from 3 hours out to 4.5 hours for treating patients with AIS with intravenous rtPA. Although it may be tempting to quickly implement changes to the American Stroke Association’s AIS treatment guidelines,⁵ a cautious approach is war-

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rented and the ECASS III data deserves close scrutiny before any extension in the rtPA treatment time window is considered. Among a range of issues to consider is that the positive findings in ECASS III are at odds with the negative results of the 3 studies (ATLANTIS, ECASS, and ECASS II) that previously evaluated intravenous rtPA treatment in patients with AIS beyond 3 hours after stroke onset. Although the ECASS III results are concordant with the results of the pooled analysis showing better outcomes for patients with AIS treated with rtPA in the 3- to 4.5-hour time window, the fact remains that no other randomized study has demonstrated safe and effective use of rtPA in the treatment of AIS beyond 3 hours. There are many potential reasons for the discrepancy in these results, including different time windows in the studies, differences in stroke severity among treatment groups, and the possibility that patients in ECASS III were the recipients of better care because they were treated when the resources devoted to stroke care had improved. Also, we should carefully compare the methodologies of the ECASS III and NINDS rtPA in acute stroke trials. Differences between the 2 studies include the ECASS III study excluded subjects over the age of 80 years as well as patients with diabetes and a history of prior stroke; the primary end points in the ECASS and NINDS studies are different with ECASS III using the modified Rankin Scale score at 90 days after stroke occurrence and NINDS using the global test statistic based on 4 different outcome measures (modified Rankin Scale, National Institute of Health Stroke Scale, Barthel Index, and the Glasgow Outcome Score) assessed at 90 days after stroke occurrence; and, like there was in the NINDS trial, ECASS III had an imbalance between the placebo and rtPA treatment groups in baseline stroke severity with the treatment group having, on average, less severe strokes. Finally, additional areas of analysis to consider undertaking include a time to treatment analysis, inclusion of age in the adjusted analysis of the primary end point, and calculation of an adjusted global OR. If the use of rtPA to treat patients with AIS in the United States is extended out 4.5 hours after stroke onset, there will likely be caveats in the 3- to 4.5-hour time period such as restricting the use of rtPA to a subgroup of patients with AIS who are ≤80 years of age with no history of diabetes and prior stroke.

The positive findings from ECASS III should provide a significant stimulus to AIS treatment research to help determine the time window for treating patients with AIS both effectively and safely with reperfusion therapies and other acute stroke treatments such as neuroprotection. Although ECASS III studied a 3- to 4.5-hour time window for reperfusing patients with AIS, 4.5 hours is almost certainly not the upper time limit for treating patients with AIS. Trials are currently underway evaluating whether there is clinical usefulness in using the penumbra concept in the evaluation of patients with AIS ≥3 hours after stroke onset, and other studies are assessing the safety and efficacy of reperfusion strategies out to ≥9 hours after stroke onset.

As we look forward beyond the ECASS III trial, we should also look back because the use of rtPA in the treatment of AIS has a troubled history and we should learn from the past to avoid repeating our mistakes. The last 12 years have taught the stroke community at least 3 important lessons. First, we now better understand that the stroke systems of care that are needed to provide care to patients with AIS are complex and take time to develop. Second, it is necessary to involve a broad range of healthcare professionals and professional organizations before changes in AIS management can be implemented. If the time window for administering rtPA to patients with AIS is extended out to 4.5 hours, we will have to be mindful of the impact that this change will have on the different components of stroke systems of care, including dispatchers, emergency medicine service training programs, emergency medicine service providers, and hospitals as well as remembering that resources will need to devoted to educating the public about the change. Consideration of the impact of AIS treatment changes on stroke systems of care, combined with discussions with a broad spectrum of stroke healthcare professionals and their professional organizations, will greatly improve the chances of any changes being widely accepted.

Finally, the ECASS investigators are to be congratulated for completing this important study, which could lead to a change in the time window for using rtPA to treat patients with AIS, and should stimulate research in AIS treatment and increase the number of patients receiving acute stroke treatment in the shortest time possible.

Disclosures
None.

References

Key Words: acute Rx  acute stroke  clinical trials