tPA for Stroke
Important Progress in Achieving Faster Treatment

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Intravenous tissue plasminogen activator (tPA) remains the only level 1A treatment for acute ischemic stroke. The results of several prospective randomized trials comparing tPA with standard treatment and pooled analyses confirm the relationship of treatment success with time from symptom onset to initiation of treatment.1-6 However, despite 2 decades of efforts to streamline systems of care including formation of designated stroke centers, placement of CT scanners in emergency departments (EDs), in-house 24/7 stroke teams, and recognition that dedicated neurological ED pathways can speed treatment, only approximately 5% of stroke patients are treated, and most are treated beyond 2 hours from symptom onset when tPA is less effective. The main reason is lack of public recognition of stroke symptoms and failure of patients to quickly seek care at a nearby institution or activate emergency medical services, such as by calling 911. Another important reason within the control of physicians and other health care personnel to reduce the time is the inherent delay caused by ED triage, registration, evaluation, testing, and treatment. The median door-to-needle times for tPA administration in stroke center EDs in the United States has exceeded 60 minutes with little improvement since the drug was first approved in the United States in 1996.7

Two studies in this issue of JAMA report important advances in solving this problem. Fonarow et al8 reported results from 1030 US hospitals contributing to the Get With The Guidelines (GWTG) registry, comparing 27 319 patients treated with tPA from 2003-2009 to 43 850 treated from 2010-2013. In 2010, the American Stroke Association implemented the Target: Stroke quality improvement initiative, which included several important components, including prenotification of hospitals by emergency medical services (EMS), rapid acquisition and interpretation of brain imaging, and rapid feedback on performance, including public recognition of high-performing hospitals. Compared with performance prior to this initiative, median door-to-needle time decreased to 67 minutes (from 77 minutes preintervention), and clinical outcomes also improved, with in-hospital all-cause mortality of 8.25% (vs 9.93% preintervention) and symptomatic hemorrhage rates of 4.68% (vs 5.68% preintervention). Among all patients with ischemic stroke, 8.1% received tPA vs 5.7% preintervention.

Although these types of observational uncontrolled studies have certain important limitations, including quality and consistency of data input before and after the intervention, and the contribution of secular trends toward improved tPA treatment metrics nationally, the study by Fonarow et al8 has many strengths, such as the very large sample size, the sharp positive inflection in the improvement curve seen immediately after the quality improvement initiative began (see Figure 2 in the article), the observation that overall improvement in stroke care for patients not treated with tPA in the same hospitals was much less than tPA-related gains, and adjusted analysis for patient and hospital variables associated with stroke center performance and clinical outcomes. Further analyses will be helpful in identifying which factors of the quality improvement program were most important in contributing to the outcomes observed.

In another report, Ebinger et al9 describe the results of the Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke Study (PHANTOM-S), which tested the effects of a Stroke Emergency Mobile (STEMO) equipped with a computed tomography (CT) scanner; point-of-care laboratory capability; telemedicine connectivity; and physician, paramedic, and CT technician responding to emergency alarms to the Berlin Fire Brigade in parallel with conventional ambulance dispatch. Over a 21-month period, the STEMO was dispatched every other week 1804 times, and 177 patients were treated with tPA in the ambulance prior to transport to the ED. The intervention resulted in a 25-minute reduction in time from alarm to tPA treatment compared with non-STEMO weeks, with 58% of patients treated within 90 minutes of symptom onset (vs 37% in control), low rates of symptomatic intracerebral hemorrhage (2.2%), and notably no instances of CT malfunction. The 25-minute reduction was due to faster alarm-to-imaging intervals and faster imaging-to-treatment intervals. The intervention also resulted in more patients being treated with tPA (33% vs 21% of ischemic strokes). No differences were seen in discharge status, but the study was not powered or designed to assess clinical outcomes other than safety.

It is possible that not all the benefit seen with STEMO was due to having an ambulance equipped with a CT and point-of-care laboratory and that some improvement was due to having a physician present on the ambulance and more efficient triage. However, “standard” management of patients during control weeks in Berlin was excellent, with the median time from stroke symptom onset to treatment of 105 minutes. Also, the study by Ebinger et al9 follows a previous study by Walter et al,10 who were the first to show that, using this mobile stroke...
unit concept, treatment with tPA could be carried out safely and accurately with a median onset to treatment time of 70 to 80 minutes.

With the findings from these 2 reports, the stroke community now has data pointing to how, with some substantial effort and investment, tPA treatment can be administered more quickly. However, several important issues remain.

Perhaps most important is the relationship between faster treatment and improved clinical outcomes for patients with stroke. There are 2 broad ways that more rapid tPA treatment might result in better outcomes. More rapid treatment might increase the absolute number of patients treated with tPA. If all patients are evaluated sooner, more will be treated within the currently recommended 4.5-hour time window. Both studies in this issue confirm such an increase, but neither included reliable outcome data, so such studies are needed. Moreover, when comparing outcomes of groups in which one of these interventions results in earlier treatment vs controls receiving later treatment, it will be necessary to include outcomes of those patients who would have been treated in the intervention group but who, because they were in the control group, were assessed too late to be treated. Another point is that these interventions may have benefit beyond the increased and earlier use of tPA, including earlier blood pressure management or hemo-static therapy for patients with intracerebral hemorrhage and more rapid access to the endovascular suite for intra-arterial mechanical recanalization (IAT). Although recent studies10-13 failed to show an increased benefit for IAT compared with or as an adjunctive approach to tPA, post hoc analysis from the IMS-III study suggests that patients achieving recanalization within 4 to 5 hours from symptom onset may benefit most.11 The interventions described in the reports by Fonarow et al8 and Ebinger et al9 may speed IAT by earlier identification of patients with probable large artery occlusion, out-of-hospital notification and earlier assembly of the endovascular team and angiography suite preparation, and shortening ED delays incurred by acquiring imaging and laboratory data and treating with tPA.

The second potential advantage of faster treatment, and the one most likely to have the greatest effect on patient outcomes, is that more patients will be treated within the first 60 minutes after onset of stroke symptoms when tPA is likely to have its greatest benefit. Considering the randomized prospective controlled studies of tPA that have provided the best evidence of tPA efficacy, among the 302 patients treated within 90 minutes of symptom onset with tPA vs placebo in the NINDS study, only 2 were randomized within 60 minutes of onset (both were randomized to the placebo group), and 41 were randomized between 61 and 80 minutes after onset; the rest (259) were randomized between 81 and 90 minutes (unpublished data from the NINDS tPA Stroke Study database). Only 312 of 3670 patients (8.5%) from the latest pooled data from all randomized tPA trials were randomized within 90 minutes of onset; this pooled data set added only 2 additional patients (total of 4) randomized within the first 60 minutes and 12 additional (total of 53) between 61 and 80 minutes. In addition, considering the large published registries, only 1.6% of patients were treated within 60 minutes of onset in the largest European tPA registry.14

In a study from Helsinki using a streamlined system of stroke triage, 10% of patients were treated within 70 minutes of symptom onset.15 Of 58,353 patients treated with tPA in the GWTG-Stroke Program, fewer than 1000 were treated within 60 minutes of symptom onset.7 Preliminary data from the Berlin group16 indicated that 31% of patients treated with tPA using their STEMO were treated within 60 minutes of onset compared with 4.9% with standard management, and 3 of 12 patients treated by Walter et al10 with their mobile stroke unit were treated within 60 minutes of symptom onset. These rates, although based on relatively small numbers, compare favorably with treatment rates within the first 60 minutes from existing registries and databases.

However, these studies provide little reliable information on how much improvement in clinical outcome will occur with treatment within the first 60 minutes after symptom onset. Virtually all data on outcomes among patients treated with tPA vs placebo in randomized trials are from patients treated 80 to 90 minutes after symptom onset, and the larger registries have no long-term outcome data. Even though data from multiple studies and pooled analyses confirm a strong inverse relation between time to treatment and recovery, the slope and shape of that relationship within the first 90 minutes after stroke symptom onset are uncertain, as reflected in the wide confidence intervals surrounding outcomes in various pooled analyses.2-4 It is possible that, because of collateral blood flow, human penumbral tissue can survive 90 minutes just as well as 30 minutes so that within the 90-minute epoch, there would be little advantage to earlier treatment. However, based on preclinical data and modeling of the scarce available clinical data, it is more likely that the converse is true and that brain tissue dies very quickly, resulting in a steeper, more exponential relationship. Furthermore, tPA might have a greater lytic effect if administered within a shorter time after clot formation. Thus, outcomes with early treatment could be substantially better than projected by a simple linear relationship between time and treatment. Patients treated within the first 60 minutes of onset by the Berlin STEMO had an odds ratio of 1.93 (95% CI, 1.09-3.41) for discharge to home compared with those who received later treatment.16 Similar data from the GWTG database are awaited. However, these data are limited by lack of systematic long-term blinded outcome assessments, lack of comparison controls, and the possibility of confounding variables, so further prospective controlled studies of outcomes after earlier treatment, using out-of-hospital treatment and improved ED management as exemplified in the studies by Fonarow et al8 and Ebinger et al9 are needed.

Whatever benefits occur from interventions to achieve more rapid tPA treatment for patients with acute stroke need to be balanced against the costs to establish and maintain them, both to the payers who will pay for them and the hospital and EMS organizations that will implement and operate them. This issue requires carefully constructed cost-effectiveness studies carried out in the environments...
where the interventions will be implemented; these are likely to differ between cities in the United States and in other countries and between rural and urban areas. One of the first needs for the out-of-hospital environment is to validate the ability of telemedicine on the CT-equipped ambulance to replace the physician to reduce personnel costs, which contribute substantially to maintaining such units in operation. The decision whether to give tPA requires training, experience, and careful judgment. Recent experience with telemedicine has shown it to be a feasible, accurate, and safe way to extend this expertise to hospitals where it is lacking to guide and increase tPA treatment. Wu et al have demonstrated the feasibility and accuracy of telemedicine assessment of actors simulating stroke patients in ambulances using existing technology. However, telemedicine must be tested for treating actual stroke patients with tPA in the out-of-hospital environment. Regarding initial setup costs, purchasing, equipping, and deploying an ambulance with a CT scanner, point-of-care laboratory testing capabilities, telemedicine, and other needed equipment in Houston has cost approximately $600 000. Formal cost analysis would have to balance these costs against the total hospital and long-term care costs to the health care system for each patient with an ischemic stroke, estimated to average approximately $140 000 per patient in 1990s dollars, undoubtedly much higher today.16,19

The studies by Fonarow et al and Ebinger et al in this issue of JAMA indicate exactly where and how to direct efforts in improving treatment outcomes for patients with acute ischemic stroke—namely by reducing time from symptom onset to treatment.

REFERENCES