Thrombolytic Therapy for Acute Stroke — Not a Moment to Lose

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Stroke, the most common cause of disability in the world among adults, remains the only neurologic disorder for which physicians are potentially able to completely reverse disabling deficits. Thrombolytic therapy, which can restore neurologic functions if given early enough, not only has stood the test of time, shown benefit in serial community registries on multiple continents, and received approval by every major regulatory authority in the world, but also has now — once again — been shown in a randomized, blinded, placebo-controlled trial to be efficacious. The results of the European Cooperative Acute Stroke Study III (ECASS III) (ClinicalTrials.gov number, NCT00153036), reported in this issue of the Journal, teach us many lessons, some medical and some political, and clearly provide powerful, persuasive evidence that thrombolytic therapy is safe and effective for patients with acute stroke.

The design of ECASS III closely mirrored that of the original National Institute of Neurological Disorders and Stroke (NINDS) trial of recombinant tissue plasminogen activator (rt-PA) for acute stroke, with the important exception that ECASS III enrolled patients who presented between 3 and 4.5 hours after the onset of symptoms, whereas the NINDS trial enrolled patients who presented within 3 hours after the onset of symptoms. Patients in ECASS III also tended to have less severe stroke, and fewer were diabetic, so outcomes in the placebo group in ECASS III were somewhat better than those in the placebo group in the NINDS trial. The rationale for ECASS III arose from a pooled analysis of several previous studies that had differing time windows for enrollment. Analyses from the resulting pooled sample suggested that thrombolytic therapy could be beneficial even when given more than 3 hours after the onset of symptoms, and ECASS III was designed to confirm this hypothesis.

As the authors of this article point out, however, neither their results nor those of the previous pooled analysis suggest that the ideal window for acute thrombolytic therapy is 4.5 hours after the onset of a stroke, because we know that the potential for neurologic rescue declines monotonically with every passing minute. I like to pose this scenario to my trainees: a patient presents to you 30 minutes after the onset of a left hemispheric stroke; how long do you have to initiate thrombolytic therapy? The correct answer is 1 minute, not 2.5 hours, and ECASS III does not now justify an answer of 4 hours. From the moment the patient arrives at the door, every minute counts, and the only justifiable delays would be for performing brain imaging studies to exclude hemorrhage and for obtaining the results of a few simple laboratory tests.

In fact, the very real peril of the ECASS III data is that some may take an even more leisurely approach to treating acute stroke. Nothing could be more wrong, for as we look back on the past decade of thrombolytic therapy for stroke, it is very clear that our focus must remain on the door-to-needle time. Every minute matters during a stroke.

The data in ECASS III offer some surprises and some questions that remain to be answered. The proportion of patients with diabetes was lower than is typical in larger stroke trials, but in other ways, the trial sample clearly and sufficiently represents the population of interest. Are these data generalizable to patients with diabetes? The authors must be criticized for excluding patients with severe stroke (patients with scores of 25 or higher on the National Institutes of...
Health Stroke Scale [NIHSS], in which scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts). No data suggest that treatment fails in such patients, and a subgroup analysis of data from the NINDS trial showed that very old patients with very severe stroke had a better outcome with treatment than without, although the absolute value of the benefit was small.\(^8\) Despite the fact that ECASS III enrolled patients who presented at a later time after the onset of symptoms than patients in other trials, the rate of hemorrhages was similar to that in earlier trials.\(^9\) The rate of death in the group that was treated with rt-PA was less than that in the group that received placebo (although not significantly so), consistent with the results of the NINDS trial.\(^2,8\) Data from very large registries, without controls, suggest a modest beneficial effect on mortality with thrombolytic therapy, but larger studies will be needed to confirm that finding.\(^10\)

To their credit, the investigators allowed the use of small doses of subcutaneous heparin during the 24 hours after thrombolytic therapy, addressing an issue that has engendered much controversy with respect to the proper care of patients with stroke ever since the NINDS trial protocol became part of the regulatory approval document.\(^6,11\) Such therapy is needed to avoid the development of deep venous thrombi, and ECASS III encourages us to use it, but further studies are urgently needed to study the effect of combining antithrombotic agents with thrombolysis for acute stroke, in order to prevent not only venous clots but also reocclusion.\(^12\)

When one reads the ECASS III results and sees the parallels to the NINDS trial — the robust result across multiple trial end points, the statistical power of the end points, and the efficacy despite an increased rate of hemorrhages — one cannot help wondering why thrombolytic therapy has traveled such a long, difficult path to wider clinical use. For one thing, the NINDS trial design and end points — though standard now — were quite novel at the time. Also, the statistical methods used in the NINDS trial came from well-established methodology in the cancer literature but were new and mysterious to many in the field of neurology.\(^13\) Another important phenomenon was the hesitancy of neurologists to weigh risks against benefits; most decision making regarding neurologic conditions before 1995 involved establishing a diagnosis or at worst choosing among antiepileptic medications with varying side-effect profiles. Very few neurologists came to the emergency department with any training in or familiarity with making time-pressured decisions involving relatively high benefits and risks.

Now the field of vascular neurology includes such training,\(^11,14\) and it is quite clear that the risk of withholding rt-PA from patients with acute stroke greatly exceeds the risk of giving it. The inclusion and exclusion criteria of ECASS III are broad, and in general, patients who present with acute stroke will qualify for treatment. Furthermore, we know that some patients who present to our emergency departments with stroke are being inappropriately excluded from receiving rt-PA therapy.\(^15\) When data are collected properly, the evidence consistently shows that roughly one third of all patients with stroke come to an emergency department within the appropriate time window and satisfy the criteria for acute thrombolytic therapy.\(^15,16\) The frequently quoted statistic that only 4% of all patients with stroke receive rt-PA must be viewed as an important indictment of our health care system and of the field of neurology in particular. The patients are coming in, but we are not. The real lesson of ECASS III is not that we can wait longer before treating; the lesson is that systems such as the Joint Commission criteria for accreditation of a hospital as a Primary Stroke Center must be widely adopted. Policies and procedures must be instituted to ensure that patients are promptly identified and treated, quality outcome data must be used to select and designate treatment centers of excellence for patients with acute stroke, and patients should be diverted to these centers.\(^17\) The public expects no less, and given the past decade of distortion of the NINDS study findings and delay in implementing thrombolytic therapy for acute stroke, we have not a minute to lose.

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Calcific Aortic Stenosis — Time to Look More Closely at the Valve
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Calcific aortic stenosis is a progressive disease that results in stiff valve leaflets with eventual obstruction to left ventricular outflow. Once symptoms occur, valve replacement is the only effective treatment, and there are no known therapies to prevent disease progression. However, several lines of evidence suggest that calcific valve disease is not simply due to age-related degeneration but, rather, is an active disease process with identifiable initiating factors, clinical and genetic risk factors, and cellular and molecular pathways that mediate disease progression.

The key initiating factor in the development of calcific aortic stenosis appears to be mechanical stress. Specifically, a congenitally bicuspid valve, which is present in about 0.5 to 0.8% of the population, is the underlying anatomy in the majority of valve replacements for aortic stenosis. Blood-flow dynamics may also play a role, since early lesions are located on the aortic side of the valve in regions with low shear stress.

Clinical factors that are associated with the presence of calcific valve disease include older age, male sex, elevated serum levels of low-density lipoprotein and lipoprotein(a), smoking, hypertension, diabetes, and the metabolic syndrome. The presence of mild valve changes, even in the absence of obstruction to blood flow, is associated with an increase of 50% in the risk of myocardial infarction and death from cardiovascular causes during the next 5 years. Genetic factors are difficult to study in a disease that often is not evident until the sixth or seventh decade of life. However, in a subgroup of families, a bicuspid valve appears to be inherited in an autosomal dominant pattern. In one study in France, familial clustering of calcific disease in trileaflet valves also was shown. Mutations in the signaling and transcriptional regulator NOTCH1 gene have been identified in families with bicuspid aortic valves and leaflet calcification. Case–control studies have suggested an association between calcific aortic stenosis and genetic polymorphisms in the vitamin D receptor, estrogen receptor, apolipoprotein E4, and interleukin-10 alleles.

Our understanding of disease progression at the tissue level is based on human valve studies of either early lesions or end-stage disease, with the assumption that these processes represent the ends of a disease spectrum (Fig. 1). Experimental models support this assumption, with the demonstration that valve lesions occur in the...