Eligibility for Intravenous Recombinant Tissue-Type Plasminogen Activator Within a Population

The Effect of the European Cooperative Acute Stroke Study (ECASS) III Trial

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Background and Purpose—The publication of the European Cooperative Acute Stroke Study (ECASS III) expanded the treatment time to thrombolysis for acute ischemic stroke from 3 to 4.5 hours from symptom onset. The impact of the expanded time window on treatment rates has not been comprehensively evaluated in a population-based study.

Methods—All patients with an ischemic stroke presenting to an emergency department during calendar year 2005 in the 17 hospitals that comprise the large 1.3 million Greater Cincinnati/Northern Kentucky population were included in the analysis. Criteria for exclusion from thrombolytic therapy are analyzed retrospectively for both the standard and expanded timeframes with varying door-to-needle times.

Results—During the study period, 1838 ischemic strokes presenting to an emergency department were identified. A small proportion of them arrived in the expanded time window (3.4%) compared with the standard time window (22%). Only 0.5% of those who arrived in this timeframe met eligibility criteria for thrombolysis compared with 5.9% using standard eligibility criteria in the standard timeframe. These results did not vary significantly by repeated analysis varying the door-to-needle time or the expanded time window’s exclusion criteria.

Conclusions—In reality, the expanded time window for thrombolysis in acute ischemic stroke benefits few patients. If we are to improve recombinant tissue-type plasminogen activator administration rates, our focus should be on improving stroke awareness, transport to facilities with ability to administer thrombolysis, and familiarity of physicians with acute stroke treatment guidelines. (Stroke. 2012;43:1591-1595.)

Key Words: acute stroke ■ ECASS ■ epidemiology ■ stroke care ■ thrombolysis

Current US guidelines for the treatment of acute ischemic stroke support early treatment with intravenous (IV) recombinant tissue-type plasminogen activator (rtPA) for patients who meet the necessary criteria. Despite the clinical and economic benefits of giving rtPA to patients with ischemic stroke, few patients actually receive it. National estimates of rtPA use range from 1.8% to 5.2%.[1,2] Some of the efforts to improve rtPA treatment rates have focused on the inclusion criteria for IV rtPA, especially the time window from symptom onset[3-8] and the “door-to-needle time.”[9-15]

A recent breakthrough regarding the time window for IV rtPA use was reported by the European Cooperative Acute Stroke Study (ECASS III), which found that IV rtPA was beneficial to selected patients up to 4.5 hours from stroke onset, thus expanding the time window from the previous guideline of 3 hours. However, the expanded time window included 4 new exclusion criteria that are stricter than the current criteria used in the United States: age >80 years, initial National Institutes of Health Stroke Scale >25, history of both diabetes and prior stroke, or any oral anticoagulant use.[16] The American Heart Association recently updated their 2007 stroke guidelines to include the ECASS III study findings (Class I recommendation, Level of Evidence B).[17]

We sought to determine the potential impact of the extended time window on IV rtPA treatment rates. Previous studies focused on this topic have found only marginal benefits, but these studies had significant limitations. They were either not population-based[18] or analyzed time from stroke onset to presentation at treatment facilities as the only exclusion criteria to thrombolysis.[19] A more comprehensive analysis including all current practice exclusion criteria is required.
Methods

The Greater Cincinnati/Northern Kentucky region includes 2 southern Ohio counties and 3 northern Kentucky counties separated by the Ohio River. This region represents a biracial metropolitan population of 1.3 million. The proportion of blacks and socioeconomic status indicators are similar to the US population in general (Hispanics, however, at 1.1% of the Greater Cincinnati/Northern Kentucky population, are underrepresented, compared with the United States as a whole at 12.5%). Although residents of nearby counties seek care at the 17 acute care hospitals in the study region, only residents of the 5 study area counties are included as cases. This analysis consisted of strokes that occurred from January 1, 2005, to December 31, 2005.

Briefly, study nurses reviewed the medical records of all patients with International Classification of Diseases, Ninth Revision codes 430 to 436 as primary or secondary discharge diagnoses from the 17 acute care hospitals in the study region. Strokes not found by this hospital ascertainment method were ascertained by monitoring all stroke-related visits to the 9 local public health clinics, 7 hospital-based outpatient clinics, and 5 county coroners’ offices. Further monitoring was performed by examining the records of potential stroke cases in a random sample of 51 of 832 primary care physicians’ offices and 26 of 126 nursing homes in the Greater Cincinnati/Northern Kentucky region. Sampling was necessary given the large number of both physician offices and nursing homes in the area. All events were crossexamined within and between sources to prevent double counting. Institutional Review Board approval was obtained at each participating study site during all study periods. Further details on the methodology for screening cases has been described elsewhere.

Once a potential case was identified, a study nurse abstracted data regarding the patient’s demographics and the stroke event from the medical record onto forms specifically designed for the study. Abstracted information and all available neuroimaging were then reviewed by a study physician, who made a final determination as to whether the patient met the case definition of acute stroke. The events were classified as ischemic stroke, transient ischemic attack, intracerebral hemorrhage, or subarachnoid hemorrhage according to definitions adapted from the Classification of Cerebrovascular Diseases III.

Only patients with ischemic stroke who presented to an emergency department (ED) within the study region were included in this analysis. Eligibility was determined based on prospectively collected symptoms and retrospectively abstracted clinical data, not whether thrombolysis was actually prescribed. Eligibility for rtPA administration among patients presenting between 3 and 4.5 hours from symptom onset was defined in 2 ways. The first definition mirrors standard US 2007 guidelines (Table 1). For the purposes of this analysis, we considered ways. The first definition mirrors standard US 2007 guidelines in 2 ways. Therefore, we evaluated the impact of various door-to-needle times on the proportion of eligible cases.

Data were managed and analyzed using SAS Versions 8.02 and 9.2, respectively (SAS Institute, Cary, NC). Percentages were obtained by including the sampling weights in all estimates as dictated by the study design. A weight of 1 was used for all cases except for those ascertained only through screening of a subset of physician’s offices (weight 831/51) and nursing homes (weight 126/26) in our region. Values are reported as raw counts with associated weighted percentages.
During the study period, 2210 ischemic strokes in patients ≥18 years of age were identified, of which 1838 presented to an ED. The remaining 372 patients presented to other sites such as primary care offices or nursing homes or were hospitalized at the time of their stroke. These patients were excluded from this analysis. Demographics of the overall ischemic stroke population and patients with ischemic stroke arriving early after symptom onset are presented in Table 2. The elapsed time from symptom onset (or “time last seen normal” for strokes for which exact time of onset was not known) to arrival at the ED was 4.5 hours for 1377 (74.6%) of the 1838 ED cases; 395 (22.0%) arrived in 3 hours from symptom onset; and 66 (3.4%) arrived in the 3- to 4.5-hour range (Figure).

According to standard eligibility for rtPA criteria, 115 of the 395 who arrived within 3 hours of onset (5.9% of the 1838 ED cases) were eligible for rtPA. With the expansion of the onset-to-arrival time window to 4.5 hours, an additional 9 patients (0.5% of the 1838 ED cases) would have been eligible based on ECASS III criteria.

Contraindications to rtPA administration for those who arrived to the ED within 3 hours and between 3 and 4.5 hours after symptom onset are listed in Table 1. The most frequent reason for nontreatment with rtPA was mild stroke severity (defined as an initial National Institutes of Health Stroke Scale <5), 208 of the 395 patients who presented within 3 hours, and 40 of the 66 who presented between 3 and 4.5 hours. In addition, the ECASS III criterion that requires a patient to be <80 years would result in the exclusion of 15 of the 66 who presented in the expanded time window. Applying standard criteria, rather than the ECASS III criteria, to the expanded time window would have allowed 5 more patients (for a total of 14 patients, 0.8% of the 1838 ED cases) to be eligible for treatment with rtPA.

When a door-to-needle time of 30 minutes was added as a criterion, which effectively reduces the onset-to-arrival window to <2.5 hours for the standard eligibility criteria and reduces the expanded window for ECASS III criteria to 2.5 to 4 hours, the number of cases eligible for rtPA was reduced from 115 to 108 (5.6%) and from 9 to 8 (0.4%), respectively. With a door-to-needle requirement of 60 minutes (the current national guideline recommendation), the number of standard criteria cases (presented within 2 hours of onset) eligible for rtPA was further reduced to 99 (5.4%), but it increased to 11 (0.6%) for ECASS criteria patients (presented 2–3.5 hours after onset). This is summarized in Table 3.

Despite extending the time window to 4.5 hours from symptom onset for IV rtPA administration, few additional patients with ischemic stroke (an additional 0.5%) would have been eligible for treatment within our study population.
This is in part due to the additional exclusion criteria described in the ECASS III trial, which exclude a significant portion of patients with stroke, especially those aged >80 years, which represent 22.7% of those who arrived between 3 and 4.5 hours. This is in accordance with results obtained in previous studies.18,19

Several studies have found a potential benefit of IV rtPA treatment after 3 hours from symptom onset without the additional exclusion criteria delineated in the ECASS III trial.23,24 Unfortunately, analysis using the standard eligibility criteria on the 3- to 4.5-hour group still revealed minimal improvement in treatment rates. Only an additional 0.7% of patients would have been eligible for treatment.

The most important reason why more patients are not eligible in the extended time window is that patients tend not to arrive in the “acute but >3 hours” timeframe. In our population, 22.0% of patients arrived to the ED within 3 hours of onset, but only 3.4% arrived in the 3- to 4.5-hour timeframe. This finding has been demonstrated in multiple other studies, some of which were also population-based.12,19,25,26 Patients with ischemic stroke tend to arrive either very early (<2 hours) or quite late or with unknown onset times (wake-up or found down). Therefore, expecting treatment rates to increase purely by broadening the time window will not likely be successful. Greater efforts are needed to improve the public’s awareness of stroke warning signs and encouraging plans to seek emergency help when symptoms occur.

Contrary to our hypothesis, the extended time window did not substantially improve the eligibility for patients arriving later within the 3-hour window nor did varying the treatment time from 60 minutes to 0 minutes. This does not imply, however, that door-to-needle time is not an important target for quality improvement. Although varying the treatment times <1 hour did not make a significant difference, many experienced stroke centers have difficulty achieving a 1-hour door-to-needle time, and there are many more patients who are missed altogether or have much longer delays in treatment. In fact, keeping the door-to-needle time as an important quality indicator of stroke centers may be even more important now with an extended time window, because physicians tend to respond to time deadlines. Recently, Schwamm et al27 found that within a large quality improvement data set among 30,000+ patients treated with rtPA, time of arrival after onset was inversely proportional to the door-to-needle time, that is, the earlier the patient arrived, the longer it took to get treated.

Given the strong association with time to treatment and good outcome, there is a potential that the extended time window could actually harm more than help.

Our study had limitations that need to be taken into consideration. First of all, retrospective studies rely on past documentation (time of stroke onset and eligibility criteria). In a similar way, we took a conservative approach and excluded from rtPA treatment patients who had a low National Institutes of Health Stroke Scale (<5), abnormal glucose and blood pressure levels, and a positive history of aneurysm, arteriovenous malformation, or brain tumor, all of which are not considered absolute exclusion criteria in clinical practice and guidelines. Also, we were unable to exclude from thrombolysis those patients with rapidly improving symptoms. This might lead to an overestimation of the patients eligible for thrombolysis. However, that is potentially counterbalanced, to some degree, by the underestimation of eligibility for those patients with an National Institutes of Health Stroke Scale <5 but who present with significant or disabling symptoms. Similarly, we did not include in our analysis the patients who were already hospitalized at the time of their stroke. They were excluded because very few patients who present in this setting receive thrombolytics (N=4; 5.5% of all IV thrombolytics prescribed in our population during 2005) and the documentation regarding these events is generally not as detailed as that provided in the ED. Finally, our analysis was performed in 2005, before the publication of the ECASS III or the Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register (SITS-ISTR)28 studies endorsing treatment up to 4.5 hours from symptom onset. Because our study did not determine eligibility based on thrombolysis administered by the treating physician but rather analyzed specific clinical and patient level data, we do not expect this to influence our findings significantly. We cannot, however, rule out changes after the publication of the updated guidelines that may lead to more patients being eligible for thrombolysis such as increased timely transport of patients with stroke in the expanded time window to emergency rooms.

In summary, IV rtPA is of benefit to patients with acute ischemic stroke who present in the 3- to 4.5-hour window, albeit to a small percentage of all patients with ischemic stroke. Care should be taken not to delay treatment due to the new expanded time window. Although reducing the door-to-needle time did not increase the number of patients

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**Table 3. No. (Weighted %) of Patients Eligible for rtPA Using Standard Criteria and Expanded ECASS III Time Window/Criteria Calculated by Varying Treatment Time**

<table>
<thead>
<tr>
<th>Treatment Time</th>
<th>Door-to-Needle Time</th>
<th>Door-to-Needle Time</th>
<th>Door-to-Needle Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0 H (Theoretical)</td>
<td>≤30 Min</td>
<td>≥60 Min*</td>
</tr>
<tr>
<td>Time from symptom onset</td>
<td>0–3 h</td>
<td>3–4.5 h</td>
<td>0–2.5 h</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Standard</td>
<td>ECASS</td>
<td>Standard</td>
</tr>
<tr>
<td>Eligible for rtPA</td>
<td>115 (5.9%)</td>
<td>9 (0.5%)</td>
<td>108 (5.6%)</td>
</tr>
</tbody>
</table>

Data presented as raw No. (weighted percent of the 1838 strokes).

rtPA indicates recombinant tissue-type plasminogen activator; ED, emergency department; ECASS, activated partial thromboplastin time.

*Current national guideline recommendation.22
eligible for thrombolysis, reducing this time leads to improved patient outcomes and remains an important quality control measure. If we are to improve rtPA administration rates, future healthcare resources should be focused on improving stroke awareness, transport to facilities with ability to administer rtPA, and physician awareness of rtPA administration guidelines rather than expanding the treatment window.

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References
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