Transition of European Cooperative Acute Stroke Study III Results to Clinical Practice Ninety-Day Outcomes in a US Cohort

Carolyn A. Cronin, MD, PhD; Patricia Langenberg, PhD; Tara M. Dutta, MD; Steven J. Kittner, MD

Background and Purpose—The European Cooperative Acute Stroke Study (ECASS) III showed benefit of intravenous tissue-type plasminogen activator for acute ischemic stroke 3 to 4.5 hours from onset in selected patients from Europe, with this extended treatment subsequently recommended by the American Stroke Association. We prospectively enrolled patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator, during the time this recommendation was being applied in clinical practice to determine safety and efficacy in a representative cohort from the United States.

Methods—Patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator were enrolled at 18 primary stroke centers throughout Maryland, including community hospitals and academic medical centers. Patients grouped by time to treatment (≤3 versus 3–4.5 hours) were compared for the presence of exclusion criteria from ECASS III that are not standard practice in the United States for ≤3 hours (age, >80 years; history of stroke and diabetes mellitus; oral anticoagulant treatment; and National Institutes of Health Stroke Scale, >25). Outcomes included good function at 90 days (modified Rankin Scale, 0–1 and 0–2), mortality, and symptomatic intracerebral hemorrhage.

Results—In the 3- to 4.5-hour treatment group, there were significantly fewer patients aged >80 years and no patients with the combination of stroke and diabetes mellitus. There were no statistically significant differences by time to treatment in symptomatic intracerebral hemorrhage, mortality, or functional outcome.

Conclusions—For patients treated with intravenous tissue-type plasminogen activator 3 to 4.5 hours from onset in everyday practice in the United States, there is no evidence for increased risk or worse outcomes compared with standard treatment ≤3 hours. (Stroke. 2013;44:00-00.)

Key Words: ischemic stroke thrombolysis tissue plasminogen activator

The only treatment for acute ischemic stroke approved by the United States Food and Drug Administration is thrombolysis with intravenous tissue-type plasminogen activator (tPA) ≤3 hours of stroke onset. The third European Cooperative Acute Stroke Study (ECASS III), published September 2008, showed benefit of intravenous tPA 3 to 4.5 hours from onset.1 ECASS III used additional exclusion criteria that are not part of standard approved treatment for ≤3 hours in the United States (age, >80 years; history of stroke and diabetes mellitus; oral anticoagulant treatment regardless of prothrombin time; and National Institutes of Health Stroke Scale [NIHSS], >25). Expansion of the treatment window to 4.5 hours was recommended for patients who would have met the ECASS III inclusion criteria by a Scientific Advisory from the American Stroke Association in May 2009.2 As this recommendation was being transitioned into clinical practice, we sought to determine whether exclusion criteria were being strictly followed, and whether the expanded time window was safe and effective in everyday clinical practice using a representative cohort in the United States.

Methods

The Maryland intravenous tPA Stroke Outcomes Study (MITSOS) included 18 primary stroke centers throughout Maryland, ranging from small community hospitals to academic medical centers (study approved by the Institutional Review Board for each site). Consecutive patients were approached during hospitalization, and informed consent was obtained from them or their legally authorized representative. Enrollment occurred between July 2009 and March 2012; however, because of institutional review board schedules, sites became active at different times. During the enrollment period, 544 patients were treated with intravenous tPA for acute ischemic stroke at participating sites. Consent was unable to be obtained from 248 patients, and 296 were enrolled. Of those enrolled, 5 underwent intra-arterial treatment, 13 lost to follow-up, and 1 did not have time of tPA treatment recorded, leaving 277 for analysis.
Patient demographic, treatment, and hospital outcome data were obtained from the Get With The Guidelines performance improvement database at each site (described previously) or from the medical record. Study personnel at University of Maryland blinded to details of hospitalization, including time to tPA treatment, determined 90-day modified Rankin Scale through structured phone interviews.

Functional outcome was evaluated using the 2 definitions most commonly used in stroke clinical trials: modified Rankin Scale 0 to 1 or 0 to 2. Safety outcomes were mortality and symptomatic intracerebral hemorrhage, as entered into Get With The Guidelines by local personnel using National Institute of Neurological Disorders and Stroke (NINDS) criteria. Baseline characteristics and outcomes were compared between the ≤3- and 3- to 4.5-hour groups, using Fisher exact test for proportions, t test for mean, or 2-sample median test. Adjusted analysis with logistic regression was performed to evaluate for confounding by baseline characteristics (see online-only Data Supplement for additional details of analysis). Statistical calculations were performed with SAS (version 9.2).

### Results

Of the remaining 277 patients in the analysis, the majority (183; 66%) were enrolled at community hospitals. However, community hospitals treated a significantly lower proportion of their patients in the later time window compared with academic medical centers (15.8% versus 38.3%; P<0.0001).

Patients treated in the later time window had less severe strokes (median NIHSS, 5 versus 8; P=0.04) and a trend toward younger age (mean, 62.6 versus 66.6 years; P=0.06). There were no other significant differences in demographic characteristics between the groups (Table I in the online-only Data Supplement). Our patients had a higher rate of comorbid conditions compared with patients enrolled in prior randomized clinical trials (notably, diabetes mellitus in 29% versus NINDS 21% and ECASS III 16%; Table II in the online-only Data Supplement).

The additional ECASS III exclusions did seem to influence which patients were treated, as there were significantly fewer patients aged >80 years, and there were no patients with the combination of stroke and diabetes mellitus in the later time window. However, it did not seem that NIHSS >25 or use of anticoagulants were significant factors in treatment (Table I).

There was no significant difference in the proportion of patients with good outcome at 90 days between treatment groups. Treatment ≤4.5 hours also seemed to be safe, as there was no increase in symptomatic intracerebral hemorrhage or mortality.

Logistic regression analysis showed that the odds ratio for good outcome was influenced by age, NIHSS, and the combination of prior stroke, and diabetes mellitus. When corrected for baseline differences, there was still no statistically significant difference in the odds of good outcome in patients treated ≤3 versus 3 to 4.5 hours (Table 2).

We analyzed the limited data available on intravenous tPA-treated patients not enrolled in the study to determine whether our cohort was representative. Non-enrolled patients had more severe strokes (median NIHSS, 12.0 versus 8.0; P<0.0001), and a higher proportion of patients was >80 years (30% versus

### Table 1. Adherence to Additional Exclusion Criteria and Patient Outcomes

<table>
<thead>
<tr>
<th>Additional exclusion criteria, %</th>
<th>≤3 h (n=212)</th>
<th>3–4.5 h (n=65)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80 years</td>
<td>21.20</td>
<td>9.20</td>
<td>0.03</td>
</tr>
<tr>
<td>NIHSS &gt;25</td>
<td>1.00</td>
<td>3.10</td>
<td>0.23</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>8.50</td>
<td>4.60</td>
<td>0.3</td>
</tr>
<tr>
<td>Prior stroke and diabetes mellitus</td>
<td>7.10</td>
<td>0.00</td>
<td>0.03</td>
</tr>
<tr>
<td>Any additional exclusion</td>
<td>32.10</td>
<td>13.90</td>
<td>0.004</td>
</tr>
<tr>
<td>Functional outcome, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–1</td>
<td>36.80</td>
<td>44.60</td>
<td>0.26</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>50.90</td>
<td>53.80</td>
<td>0.68</td>
</tr>
<tr>
<td>Safety, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>6.10</td>
<td>7.70</td>
<td>0.66</td>
</tr>
<tr>
<td>sICH</td>
<td>4.30</td>
<td>3.10</td>
<td>0.67</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracerebral hemorrhage.

### Table 2. ORs for Good Outcome From Logistic Regression Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>3–4.5 vs &lt;3 h</th>
<th>5–8 vs 1–2</th>
<th>12.0 vs 8.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted OR</td>
<td>Adjusted OR</td>
<td>P Value</td>
<td>Unadjusted OR</td>
</tr>
<tr>
<td>Age 10 years older</td>
<td>0.78 (0.66–0.93)</td>
<td>0.006</td>
<td>0.63 (0.52–0.77)</td>
</tr>
<tr>
<td>NIHSS 5 unit higher</td>
<td>0.59 (0.46–0.75)</td>
<td>&lt;0.0001</td>
<td>0.51 (0.34–0.65)</td>
</tr>
<tr>
<td>Prior stroke and DM</td>
<td>0.20 (0.04–0.92)</td>
<td>0.039</td>
<td>0.09 (0.02–0.43)</td>
</tr>
<tr>
<td>Ambulatory at baseline</td>
<td>1.95 (0.72–5.31)</td>
<td>0.190</td>
<td>2.34 (0.87–6.33)</td>
</tr>
</tbody>
</table>

DM indicates diabetes mellitus; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*95% confidence interval. Adjustments are for all other variables in table.
18.4%; \( P = 0.002 \). Notably, there was no difference in the proportion of patients treated 3 to 4.5 hours in the non-enrolled versus enrolled groups (22.6% versus 23.5%; \( P = 0.81 \)) and also no difference in the proportion treated at community hospitals (65% versus 66%).

**Discussion**

In our cohort, there was incomplete adherence to the published treatment guidelines, with 14% of patients treated 3 to 4.5 hours having \( \geq 1 \) of the additional exclusion criteria. Despite this, we found that for patients treated with intravenous tPA for acute ischemic stroke 3 to 4.5 hours from onset in everyday practice in the United States, there was no evidence for increased risk or worse outcome compared with standard treatment \( \leq 3 \) hours from onset. The study limitations include small sample size that may have masked some differences between groups. Because there were no patients with the combination of stroke and diabetes mellitus treated 3 to 4.5 hours, we cannot comment on safety or efficacy of that practice. There were some differences between enrolled and non-enrolled intravenous tPA-treated patients, which may limit the generalizability of findings. However, as there was no difference in the proportion of patients treated in the extended time window, this is unlikely to affect comparisons related to time to treatment.

The history of acute stroke care is marked by randomized clinical trial results that are only slowly adopted into clinical practice. Some of the concerns clinicians have are whether trial results are generalizable to their patients, and whether the risk-benefit profile from trials will hold true in a broader context. To our knowledge, this study is the first to evaluate long-term functional outcomes in patients treated in the extended time window in the United States. It supports the application of the ECASS III results to practice settings within the United States.

**Sources of Funding**

This study was supported by an award from the American Heart Association/American Stroke Association.

**Disclosures**

None.

**References**

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Transition of ECASS III Results to Clinical Practice: 90 Day Outcomes in a US Cohort

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Supplementary Table I. Baseline and clinical characteristics of patients treated ≤3 hr and 3-4.5 hr from symptom onset

<table>
<thead>
<tr>
<th>Baseline Characteristic, %</th>
<th>≤3 N=212</th>
<th>3-4.5 N=65</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; mean(SD)</td>
<td>66.6 (15.2)</td>
<td>62.6 (15.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Male</td>
<td>46.7</td>
<td>52.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Afib</td>
<td>25</td>
<td>15.4</td>
<td>0.11</td>
</tr>
<tr>
<td>CAD</td>
<td>21.7</td>
<td>21.5</td>
<td>0.98</td>
</tr>
<tr>
<td>DM</td>
<td>31.6</td>
<td>24.6</td>
<td>0.28</td>
</tr>
<tr>
<td>HTN</td>
<td>74.1</td>
<td>70.8</td>
<td>0.60</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>18.4</td>
<td>10.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Ambulate independently †</td>
<td>88.9</td>
<td>93.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Antiplatelet at onset</td>
<td>45.3</td>
<td>38.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Anticoagulation at onset</td>
<td>8.5</td>
<td>4.6</td>
<td>0.30</td>
</tr>
<tr>
<td>HgA1C; mean (SD)</td>
<td>6.9 (4.7)</td>
<td>6.3 (1.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>INR; mean (SD)</td>
<td>1.04 (0.17)</td>
<td>1.09 (0.27)</td>
<td>0.15</td>
</tr>
<tr>
<td>BMI; mean (SD)</td>
<td>30.5 (12.6)</td>
<td>29.0 (4.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>NIHSS; median (25-75 %)</td>
<td>8 (5-15)</td>
<td>5 (4-13)</td>
<td>0.04 ‡</td>
</tr>
</tbody>
</table>

* P-values from chi-square (%) or t-tests (means)
† some missing ambulatory data; N=146, 46
‡ P-value from two-sample median test


Supplementary Table II. Comparison of baseline characteristics in MITSOS to prior randomized trials

<table>
<thead>
<tr>
<th>Baseline Characteristic, %</th>
<th>NINDS</th>
<th>ECASS III</th>
<th>MITSOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>67.0</td>
<td>65.2</td>
<td>65.6</td>
</tr>
<tr>
<td>Male</td>
<td>58.2</td>
<td>60.3</td>
<td>44.9</td>
</tr>
<tr>
<td>Afib</td>
<td>18.5</td>
<td>13.1</td>
<td>21.3</td>
</tr>
<tr>
<td>DM</td>
<td>21.1</td>
<td>15.7</td>
<td>28.0</td>
</tr>
<tr>
<td>HTN</td>
<td>66.0</td>
<td>62.6</td>
<td>68.5</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>13.5</td>
<td>10.8</td>
<td>15.5</td>
</tr>
</tbody>
</table>

NINDS: National Institutes of Neurologic Disease and Stroke study
ECASS III: The European Cooperative Acute Stroke Study III
MITSOS: The Maryland IV tPA Stroke Outcomes Study
**Supplementary Methods: Logistic regression analysis:**

All of the patient baseline characteristics listed in Supplementary Table I were considered for inclusion in a logistic regression analysis. We included variables in the final model shown in Table 2 if: the two time groups differed on the variables (by approximately p<0.10), the variable was significantly associated with outcome (mRS) in the model, or inclusion of the variable changed the coefficient value (and OR) of the timing variable by approximately 10%. Despite being one of the specific additional exclusion criteria, we did not find that history of anticoagulation use had any effect on the likelihood of mRS 0-1 or mRS 0-2, and it was therefore not included in the final model.
Supplementary Table III: Participating Sites and Personnel

Anne Arundel Medical Center: Alex Katcheves, Laura Norton
Frederick Memorial Hospital: Shahid Rafiq, Michael McLane, Tom Shupp
Good Samaritan Hospital: David Weisman, Joyce Falkenhan
Greater Baltimore Medical Center: Allan Genut, Kirsten McCracken
Harford Memorial Hospital: Neelupalli Reddy, Barbara Cysyk
Holy Cross Hospital: Andrew Barbash, Sharon Harriston
Howard County General Hospital: Merrill Ansher, Susan Groman
Johns Hopkins Hospital: Victor Urrutia, Brenda Johnson
Meritus Medical Center: Samina Anwar, Lee Fitzpatrick, Jean Thomas
Peninsula Regional Medical Center: Richard Bird, Shernita Boyd
Shore Health System-The Memorial Hospital at Easton: Terry Detrich, Christina Ball
Sinai Hospital of Baltimore: Adrian Goldszmidt, Linda Toral
Southern Maryland Hospital Center: Stuart Goodman, Peggy Murphy, Christie Lapanne
St. Joseph Medical Center: Francis Mwaisela, Ruth Linde
Suburban Hospital: Jose Merino, Teresa Morella
University of Maryland Medical Center: Carolyn Cronin, Kathleen Caubo, Mary J Sparks, Karen Yarbrough, Caitlyn Hegge, Mark Dobbins
Upper Chesapeake Medical Center: Syed Shaukat, Barbara Cysyk
Western Maryland Health System: Riaz Janjua, Toni Quesenberry
Supplementary Discussion: Review of literature related to additional IV tPA exclusion criteria

There is a growing literature on patient outcomes with IV tPA in subgroups of patients who have been excluded from many of the randomized acute stroke treatment trials.\textsuperscript{1,2}

The incidence of stroke increases with age, so the exclusion of the large group of stroke patients >80 years old from treatment has received particular attention in the literature. Multiple observational studies have not found evidence to support withholding thrombolysis based on age.\textsuperscript{3-8} However, until recently there were little data from randomized trials on patients >80 years old. The third International Stroke Trial (IST3) randomized patients for which investigators had equipoise regarding treatment with IV tPA up to 6 hours from onset, including 1617 patients >80 years old. While the elderly patients did have worse outcomes overall compared to younger patients, the benefit of treatment with IV tPA did not seem to be diminished.\textsuperscript{9}

There is concern about treating patients with high NIHSS with thrombolytics, as an increased risk of sICH has been seen in patients with severe deficits at presentation.\textsuperscript{10} As these patients are also the most at risk for poor outcomes if not treated, the possible increased risk of hemorrhage may not shift the risk-benefit analysis away from treatment.\textsuperscript{11}

The combination of stroke and diabetes has not been found to be associated with worse outcome in multiple observational studies.\textsuperscript{8,12,13} However, sICH has been associated with higher serum glucose levels on presentation.\textsuperscript{14} The possible implications in terms of treating hyperglycemia in the acute stroke setting are unclear, and studies such as SHINE (Stroke Hyperglycemia Insulin Network Effort) are ongoing.

Single center observational studies on patients taking warfarin have had conflicting results as to whether there is an increased rate of sICH after treatment with IV tPA.\textsuperscript{8,15} However, large registry studies from the Canadian Stroke Network and GWTG-Stroke did not find an association between preadmission warfarin use and outcome.\textsuperscript{16,17}


(14) Tanne D, Kasner SE, Demchuk AM, Koren-Morag N, Hanson S, Grond M, et al. Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen

