Use of Tissue-Type Plasminogen Activator Before and After Publication of the European Cooperative Acute Stroke Study III in Get With The Guidelines-Stroke

Steven R. Messé, MD; Gregg C. Fonarow, MD; Eric E. Smith, MD, MPH; Lisa Kaltenbach, MS; DaiWai M. Olson, PhD, RN; Scott E. Kasner, MD; Lee H. Schwamm, MD

Background—The European Cooperative Acute Stroke Study (ECASS) III demonstrated benefit to expanding the intravenous tissue-type plasminogen activator (tPA) window from 3 to 4.5 hours for patients with acute ischemic stroke (AIS). We investigated how this trial influenced use of tPA in clinical practice.

Methods and Results—Using the Get With The Guidelines-Stroke data set, we identified 217 692 patients who presented to the hospital within 4.5 hours of AIS from April 2003 to March 2011, 106 113 before and 111 579 after the publication of ECASS III in September 2008. The proportion of patients with AIS who presented within 4.5 hours and were treated with tPA in the 3- to 4.5-hour window increased from 1.2% before ECASS III to 3.5% after (P<0.0001). The proportion of eligible patients with AIS presenting within 3.5 hours and treated within 4.5 hours increased from 19% (18 484/96 208) to 35% (26 888/77 309) (P<0.0001). ECASS III appeared to have no adverse affect on the treatment of patients who presented early because the proportion of eligible patients with AIS presenting within 2 hours and treated within 3 hours increased after ECASS III from 57% to 75% (P<0.0001), whereas median door-to-needle times in patients treated within 3 hours decreased from 79 to 74 minutes (P<0.0001).

Conclusions—Following publication of ECASS III, there has been a significant increase in the use of tPA between 3 and 4.5 hours without adversely affecting treatment of patients in the <3-hour window. However, there remains substantial opportunity to further improve treatment rates in the later time window. (Circ Cardiovasc Qual Outcomes. 2012;5:321-326.)

Key Words: stroke ▪ therapeutic thrombolysis ▪ outcome assessment (health care)

In 1995, the National Institute of Neurological Disorders and Stroke Tissue Plasminogen Activator (tPA) Stroke Study established that intravenous tPA given within 3 hours of the onset of acute ischemic stroke (AIS) improves the likelihood of good outcome.1 However, given the narrow inclusion criteria and limited time window, only a small percentage of patients with AIS are able to receive this medication.2–4 In September 2008, the European Cooperative Acute Stroke Study (ECASS) III randomized controlled trial demonstrated that intravenous tPA given 3 to 4.5 hours after onset of AIS provides a more modest, but still clinically significant improvement in outcome.5 As a result, the American Heart Association/American Stroke Association (AHA/ASA) subsequently published a science advisory recommending treatment of patients with AIS up to 4.5 hours from onset of symptoms who matched the eligibility criteria of the trial.6 It remains uncertain what affect the publication of ECASS III and the subsequent AHA/ASA science advisory has had on the use of intravenous tPA in clinical practice in the United States.

The Get With The Guidelines (GWTG)-Stroke program is a national systems of care quality improvement initiative that was undertaken by the AHA/ASA to improve the treatment of patients with stroke and transient ischemic attack. GWTG-Stroke includes data from >1.5 million patients with stroke treated at >1700 hospitals throughout the United States. We evaluated the use of tPA before and after publication of ECASS III in GWTG-Stroke.

Methods

The GWTG-Stroke data set has been described extensively in prior publications.7–9 Data from hospitals that participated in the program at any time between April 1, 2003, and March 31, 2011, were included in this analysis. All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Outcome Sciences, Inc (Cambridge, MA), served as the registry coordinating center. The Duke Clinical Research Institute (Durham, NC) served as the data analysis center, and institutional review board
WHAT IS KNOWN

- Intravenous tissue-type plasminogen activator given within 3 hours of the onset of acute ischemic stroke improves the likelihood of good outcome, but only a small percentage of patients with acute ischemic stroke are able to receive this medication because of the narrow inclusion criteria and limited time window.
- In September 2008, the European Cooperative Acute Stroke Study III randomized controlled trial demonstrated that intravenous tissue-type plasminogen activator given 3 to 4.5 hours after onset of acute ischemic stroke provides a more modest, but still clinically meaningful improvement in outcome.

WHAT THE STUDY ADDS

- Among hospitals participating in Get With The Guidelines-Stroke program, the use of intravenous tissue-type plasminogen activator has significantly increased since publication of the European Cooperative Acute Stroke Study III in both the traditional 3-hour time window and the expanded 3- to 4.5-hour window without negatively influencing treatment times or clinical outcomes.
- The increased use appeared to be temporally related to both European Cooperative Acute Stroke Study III trial results and publication of the American Heart Association/American Stroke Association science advisory supporting tissue-type plasminogen activator use in the expanded time window, highlighting the importance of practice guidelines and quality care initiatives in facilitating the integration of new information into clinical practice.
- Despite the improvement in tissue-type plasminogen activator treatment rates observed, there remain further opportunities to improve treatment of patients with acute ischemic stroke arriving at the hospital within 4.5 hours of symptom onset.

At the time of publication in September 2008, the results of the ECASS III trial were communicated to GWTG-Stroke-participating hospitals. After the release of the AHA/ASA science advisory in May 2009, the expanded time window recommendations were disseminated to each participating hospital. In addition, a new quality metric of intravenous tPA use in eligible patients with AIS arriving within 3.5 hours and treated within 4.5 hours was added to the program to complement the established performance measure for eligible patients with AIS arriving within 2 hours and treated with intravenous tPA within 3 hours, providing sites a minimum of 60 minutes to treat all potentially eligible patients.

We queried the GWTG-Stroke data set to identify patients with AIS who presented within 4.5 hours from the onset of symptoms. Patients who were missing time of onset, experienced an in-hospital stroke, received an experimental thrombolytic, or received intravenous tPA at an outside non-GWTG-Stroke hospital were excluded. To determine the impact of ECASS III on tPA use in the later time window, we compared the proportion of patients with AIS who were treated with intravenous tPA between 3 and 4.5 hours among those who presented within 4.5 hours of the time they were last known to be well, both before and after publication of ECASS III. We also assessed the GWTG-Stroke quality measure of tPA use in the 4.5-hour time window before and after ECASS III, which was defined as the proportion of eligible patients with AIS who presented within 3.5 hours after symptom onset and were treated with tPA within 4.5 hours. The presence or absence of contraindications to tPA use is recorded in GWTG-Stroke, and patients were considered eligible for tPA treatment if they had no documented contraindications.

To assess trends over time in the proportion of patients with AIS who presented within 3.5 hours of the onset of symptoms and were treated with intravenous tPA by 4.5 hours, we performed a segmented linear regression model with segments before and after ECASS III. The model was constructed to estimate the percentage of patients treated with intravenous tPA at the start of the study period, trends over time in quarters, changes in the percentage treated with intravenous tPA at the start of the after-ECASS III period, and changes in trends after ECASS III. This model specification allowed for directly testing an immediate change in the percentage of patients treated and changes in trends after ECASS III by testing whether each term was equal to 0. We performed a similar analysis for segments before and after the publication of the AHA/ASA science advisory.

Additionally, we compared the hospital characteristics and the clinical characteristics and outcomes of patients with AIS treated with intravenous tPA in the 3- to 4.5-hour time window both before and after publication of ECASS III, using the χ² test for categorical variables and the Kruskal-Wallis test for continuous variables. Multivariate logistic regression modeling was performed to evaluate the affect of ECASS III on intravenous tPA use in the 3- to 4.5-hour window, using generalized estimating equations to account for within-hospital clustering. Multivariate analyses with generalized estimating equations were also performed to compare the time periods before and after ECASS III with clinical outcomes available in GWTG-Stroke, including mortality, discharge home, length of stay ≥4 days, and rate of symptomatic intracranial hemorrhage within 36 hours, among those patients treated in the 3- to 4.5-hour window. Models were adjusted for demographics (age, sex, and race/ethnicity), National Institutes of Health Stroke Scale (NIHSS) (as a continuous variable), comorbidities (atrial fibrillation, prior stroke, coronary artery disease, history of carotid stenosis, diabetes, peripheral vascular disease, hypertension, smoking, and dyslipidemia), arrival during weekday working hours, onset-to-needle time (as a continuous variable), and hospital characteristics (number of beds, academic teaching status, region, number of strokes per year, and number of tPA cases per year). Hospital characteristics were obtained from the American Hospital Association database. Data were missing in <4% of patients except for initial NIHSS (15%), method of arrival (6%), and ambulatory status at discharge (19%). Patients with missing information on age, sex, NIHSS, or hospital characteristics were excluded from the models except where noted, whereas patients with missing medical history information on specific conditions (eg, hypertension) were imputed to absence of that medical condition.

To determine the impact of ECASS III on patients who presented early, we assessed the proportion of patients with AIS who were treated with tPA among those who presented within 3 hours, and we compared the GWTG-Stroke quality measure of tPA use in the 3-hour window (defined as the proportion of eligible patients who presented within 2 hours and were treated within 3 hours) both before and after publication of ECASS III. The treatment times for patients who received tPA within 3 hours were also assessed before and after ECASS III. All statistics were performed using SAS version 9.1 (SAS Institute) software.

Results

The GWTG-Stroke database includes information on 1 568 979 patients admitted to 1711 hospitals between April 2003 and March 2011. Excluding patients without ischemic...
stroke (617 398), patients missing onset-to-door time (537 314), patients with onset-to-door time ≥ 4.5 hours (150 890), patients with onset-to-needle time ≥ 12 hours (431), patients with intravenous tPA given at an outside non-GWTG-Stroke hospital (13 114), patients treated with an experimental thrombolytic therapy (1335), and patients with an in-hospital stroke (15 936), we analyzed 217 692 patients with AIS who presented with AIS within 4.5 hours were treated with IV tPA between 3 and 4.5 hours, whereas after ECASS III, 3.5% (3932/111 570) of all patients treated with IV tPA between 3 and 4.5 hours, all patients who presented with AIS within 4.5 hours were treated by 4.5 hours over time with segmented linear regression lines for before and after ECASS III. The proportion treated with intravenous tPA during the pre-ECASS III

### Table 1. Characteristics of GWTG-Stroke Hospitals Included in the Analysis

<table>
<thead>
<tr>
<th>Region (admissions)</th>
<th>Pre-ECASS III</th>
<th>Post-ECASS III</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
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<td>52</td>
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</tr>
<tr>
<td>Missing</td>
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<td>8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or percent. GWTG indicates Get With The Guidelines; ECASS III, European Cooperative Acute Stroke Study III.

Before publication of ECASS III, 1.2% (1322/106 133) of all patients who presented with AIS within 4.5 hours were treated with intravenous tPA between 3 and 4.5 hours, whereas after ECASS III, 3.5% (3932/111 570) of all patients with AIS who presented within 4.5 hours were treated with intravenous tPA between 3 and 4.5 hours (P<0.0001). Table 2 presents the clinical and demographic data for patients treated with intravenous tPA between 3 and 4.5 hours, dichotomized as pre- or post-ECASS III.

### Table 2. Characteristics of Patients Treated With Intravenous tPA Between 3 and 4.5 Hours Before and After Publication of the ECASS III Results

| Age, y | 72 (58–81) | 68 (56–79) | 0.36 |
| Female sex | 49.5 | 48.7 | 0.62 |
| White race | 73.8 | 69.5 | 0.07 |
| Hypertension | 76.0 | 79.4 | 0.01 |
| Diabetes | 28.7 | 27.5 | 0.40 |
| Dyslipidemia | 34.9 | 43.2 | <0.0001 |
| Atrial fibrillation | 20.1 | 19.0 | 0.40 |
| Coronary artery disease | 28.3 | 25.6 | 0.06 |
| Smoker | 22.0 | 23.2 | 0.40 |
| Prior stroke/TIA | 28.8 | 26.5 | 0.12 |

Data are presented as median (interquartile range) or percent. tPA indicates tissue-type plasminogen activator; ECASS III, European Cooperative Acute Stroke Study III; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; EMS, emergency medical service.

Use of tPA After ECASS III in GWTG-Stroke

The GWTG-Stroke quality measure of the proportion of eligible patients with AIS who presented within 3.5 hours and were treated by 4.5 hours increased at publication period increased at a rate of 0.53% (absolute) per quarter (95% CI, 0.40%–0.66%). After publication of ECASS III, the proportion treated increased at a rate of 2.92% per quarter (95% CI, 2.49%–3.36%; postpublication versus prepublication slope change, P<0.0001). However, in the 3 months immediately after ECASS III was published, the...
change in the rate was not significantly different at −0.22% (95% CI, −3.31.2 to 2.69). When the May 2009 AHA/ASA science advisory was used instead, the prepublication rate was 0.57% per quarter (95% CI, 0.46–0.67%) and the postpublication rate 2.71% per quarter (95% CI, 1.99–3.42%; postpublication versus prepublication slope change, \( P<0.0001 \)). Additionally, there was a significant immediate jump in rate in the 3 months after publication of the AHA/ASA science advisory of 7.25% (95% CI, 4.23–10.27).

A multivariable logistic regression model incorporating all patients who presented within 4.5 hours found that patients who presented after publication of ECASS III were more likely to be treated with intravenous tPA between 3 and 4.5 hours than before publication, after adjusting for the clinical, demographic, and hospital factors described previously (adjusted odds ratio, 1.50; 95% CI, 1.43–1.57; \( P<0.0001 \)). When a logistic regression model was constructed to include only patients who presented within 3 to 4.5 hours, there was an even greater likelihood of tPA use in the post-ECASS III period compared to the pre-ECASS III period (adjusted odds ratio, 6.26; 95% CI, 4.54–8.63; \( P<0.0001 \)).

Table 3 presents the clinical outcomes of interest available in the GWTG-Stroke database for patients treated with intravenous tPA in the 3- to 4.5-hour time window, dichotomized as pre- or post-ECASS III. In univariate analysis, there were modest improvements in discharge destination, ambulatory status at discharge, and length of stay after publication of ECASS III, and there were fewer symptomatic intracranial hemorrhages based on the National Institute of Neurological Disorders and Stroke definition. Table 4 presents the association of the publication of ECASS III with outcomes among patients treated between 3 and 4.5 hours in multivariable logistic regression models. Patients treated after ECASS III compared to those treated before were significantly less likely to develop symptomatic hemorrhages and less likely to have a length of stay of >4 days, after adjusting for potential confounders. There were no significant differences in in-hospital mortality, ambulatory status at discharge, or discharge home.

ECASS III appeared to have no adverse influence on the treatment of patients who presented early because the proportion of all patients who presented within 3 hours and received tPA increased from 18.9% (17 128/90 414) before ECASS III to 24.7% (23 046/93 176) after ECASS III. The GWTG-Stroke quality measure of the proportion of eligible patients with AIS presenting within 2 hours and treated within 3 hours increased after ECASS III from 57% to 75% (\( P<0.0001 \)). Importantly, median door-to-needle times in patients treated within 3 hours decreased after publication of ECASS III (79 minutes; interquartile range, 61–100 minutes) versus before (74 minutes; interquartile range, 57–94 minutes; \( P<0.0001 \)). Door-to-needle times were also shorter among all patients treated with intravenous tPA <4.5 hours from stroke onset (80 versus 76 minutes, \( P<0.0001 \)). Focusing on patients who presented early, the door-to-needle times for intravenous tPA-treated patients who presented <2 hours after stroke onset (including those treated beyond 3 hours)
also decreased after publication of ECASS III (81 versus 78 minutes, \(P<0.0001\)). Finally, when evaluating the time period after ECASS III, door-to-needle times were longer for those patients treated from 3 to 4.5 hours compared to those treated within 3 hours (95 versus 74 minutes, \(P<0.0001\)).

**Discussion**

Intravenous tPA is the only Food and Drug Administration-approved and -proven treatment of AIS, although only a minority of patients receive this medication.\(^4\),\(^10\) One of the major reasons for the limited use of tPA is the narrow time window for treatment.\(^2\),\(^3\) The present analysis of the GWTG-Stroke data set is, to our knowledge, the first large study of tPA treatment in later time windows in clinical practice in the United States. We found that intravenous tPA treatment has increased significantly since the publication of ECASS III both in the 3-hour time window and, to a greater extent, in the 3- to 4.5-hour window, although the rates of treatment of eligible patients in the later window remain relatively low. These results are similar to what was reported by the Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register (SITS-ISTR) assessment of tPA use in Europe, where use expanded in both time windows after ECASS III, suggesting that this study provided further validation for some clinicians regarding the use of thrombolytics in stroke.\(^11\) This GWTG-Stroke analysis was performed after the SITS-ISTR study, which allows for a better understanding of the long-term impact of ECASS III in the present study. We found that use of tPA continued to increase in the 3- to 4.5-hour time window throughout the period studied, without any appearance of a plateau in the most recent quarters. Importantly, there was a striking increase in tPA use in the later time window in the third quarter of 2009 immediately following publication of the AHA/ASA science advisory supporting the use of tPA up to 4.5 hours after stroke onset and its distribution by GWTG-Stroke. This finding highlights the importance of practice guidelines and national quality improvement initiatives that include strategies for the rapid dissemination of new information.

Prior studies of patients with stroke treated with tPA within 3 hours of symptom onset have found that patients who present earlier tend to have longer arrival-to-treatment times.\(^12\),\(^13\) Presumably, when clinicians believe that there is more time before the treatment window closes, there is less urgency to proceed with the evaluation. Alternatively, clinicians may be waiting to see whether the patients improve on their own before proceeding to tPA treatment. Despite this concern that patients might receive treatment more slowly once the time window is expanded to 4.5 hours, we found modest decreases in door-to-needle times after ECASS III was published. Importantly, there was no evidence for increased door-to-needle times in the overall cohort of patients treated within 4.5 hours or among those who presented early at <2 hours after stroke onset. The SITS-ISTR analysis reported that there was no change in the median door-to-needle time for tPA administration after ECASS III was published.\(^11\) However, it is important to note that in both GWTG-Stroke and SITS-ISTR, the door-to-needle time was longer in patients who were treated from 3 to 4.5 hours compared to those treated within 3 hours. It is likely that this finding reflects the fact that some patients who arrive <3 hours from symptom onset cannot be treated in the 3-hour window because they are awaiting laboratory results, head CT interpretation, or critical information regarding the time of onset, but they became eligible for treatment once the time window expanded to 4.5 hours. As was demonstrated previously in the GWTG-Stroke data set for patients treated within 3 hours, we found that the median door-to-needle time in the 3- to 4.5-hour time window was well above the recommended goal of <60 minutes.\(^6\)

We also found that patients treated in the 3- to 4.5-hour time window were less likely to develop symptomatic intracranial hemorrhage after publication of ECASS III, even after adjusting for potential confounders. It is possible that this is because physicians who treated patients within the 3- to 4.5-hour window after ECASS III likely adhered to the additional exclusion criteria used in the study and subsequently recommended by the AHA/ASA (age \(>80\) years, NIHSS score \(\geq 25\), \(>1/3\) middle cerebral artery changes on head CT, and a history of both stroke and diabetes). However, no significant differences in in-hospital mortality, ambulatory status at discharge, or discharge home were observed among the cohort of patients treated after ECASS III compared to before ECASS III.

There are important limitations to this study. The GWTG-Stroke program includes hospitals from every state in the United States, thus providing broad insight into current clinical practices. We did not examine the use of intraarterial tPA or thrombectomy devices, which has been increasing in many stroke centers. During the time period after ECASS III publication, 2.7% of patients who presented within 4.5 hours underwent intraarterial therapy in this cohort. Thus, this report likely underestimates acute stroke interventions overall. However, the GWTG-Stroke program is voluntary, and the participating hospitals are more likely to be larger teaching hospitals with a strong interest in stroke and quality improvement. Thus, the findings may overestimate the change in the use of intravenous tPA in the United States after ECASS III. In addition, it is likely that there was some improvement in treatment rates and times over time because of increased experience, improved organization, and general comfort level with the use of intravenous tPA. Similarly, the increase in use of intravenous tPA in the 3- to 4.5-hour time window after ECASS III may have been influenced by participation in GWTG-Stroke and the dissemination of the ECASS III and AHA/ASA science advisory. However, because there is no concurrent control group of US hospitals, we cannot determine with certainty any independent effect of GWTG-Stroke participation on treatment patterns. It is possible that physicians at participating hospitals were more likely to have been informed of important new clinical trial results independent of their GWTG-Stroke participation. As with other analyses of this cohort, the data depend on the accuracy and completeness of clinical documentation and subsequent chart abstraction. Finally, residual measured and unmeasured confounding variables may have influenced the findings.
Conclusions

Among hospitals participating in the GWTG-Stroke program, the use of intravenous tPA has significantly increased after publication of ECASS III in both the traditional 3-hour time window and the expanded 3- to 4.5-hour window without negatively influencing treatment times or clinical outcomes. Door-to-needle times decreased in all the time frames evaluated, and there was less symptomatic intracerebral hemorrhage in the 3- to 4.5-hour window after ECASS III. The increased use appeared to be temporally related to both ECASS III trial results and the publication of the AHA/ASA science advisory supporting the use in the expanded time window, highlighting the importance of practice guidelines and quality care initiatives in facilitating the integration of new information into clinical practice. Despite the improvement in tPA treatment rates observed, there remain further opportunities to improve treatment of patients with AIS arriving within 4.5 hours of symptom onset.

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Disclosures

Dr Messé has served on the speaker’s bureau for Boehringer Ingelheim (modest), receives research support from the National Institutes of Health (significant) and from W.L. Gore & Associates (modest). Dr Fonarow serves as a member of the GWTG Steering Committee; receives research support from the National Institutes of Health (significant); served as a consultant to Pfizer (modest); and is an employee of the University of California, which holds a patent on retriever devices for stroke (significant). Dr Smith serves as a member of the GWTG Steering Committee and has served on an advisory board for Genentech (modest). Ms Kaltenbach and Dr Olson are members of the Duke Clinical Research Institute, which serves as the GWTG data coordinating center. Dr Kasner serves as a member of the GWTG Steering Committee and the AHA Stroke Scientific Statement Oversight Committee and receives research support from the National Institutes of Health (significant) and W.L. Gore & Associates (significant). Dr Schwamm serves as chair of the GWTG Steering Committee, serves as a consultant to the Research Triangle Institute and Massachusetts Department of Public Health, and serves on the steering committee for Lundbeck’s Dias4 clinical trial.

References

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