Adherence to Third European Cooperative Acute Stroke Study 3- to 4.5-Hour Exclusions and Association With Outcome

Data From Get With The Guidelines-Stroke

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Background and Purpose—The American Heart Association/American Stroke Association guidelines recommend intravenous tissue-type plasminogen activator (tPA) treatment 3 to 4.5 hours from symptom onset according to criteria used in the Third European Cooperative Acute Stroke Study (ECASS III). However, ECASS III excluded certain patient groups in addition to the standard exclusions used for 0 to 3 hours in the United States: age >80 years, history of stroke and diabetes mellitus, oral anticoagulant treatment, and National Institutes of Health Stroke Scale >25. We investigated adherence to these additional exclusion criteria for patients treated 3 to 4.5 hours from onset and their association with outcome.

Methods—We analyzed data from Get With The Guidelines-Stroke on 32,019 patients with ischemic stroke from 1464 hospitals who were treated with tPA ≤4.5 hours from onset from January 2009 to January 2012, excluding patients transferred from another hospital. The percent of patients meeting versus not meeting each exclusion criterion were compared between treatment time windows.

Results—Overall, 1544 of 4910 (31.5%) patients treated with tPA >3 to 4.5 hours had at least 1 of the additional exclusions, the most common was age >80 years. With the exception of prior stroke and diabetes mellitus, the percent of tPA–treated patients with each exclusion criterion was significantly lower at >3 to 4.5 hours compared with 0 to 3 hours. For each additional exclusion criterion, there was no increased risk of symptomatic intracranial hemorrhage or worse hospital outcome for patients treated >3 to 4.5 hours compared with 0 to 3 hours, after adjusting for baseline differences.

Conclusions—Patients with ECASS III–specific exclusion criteria for the >3 to 4.5 hours window are frequently treated with tPA. The presence of the additional exclusion criteria was not associated with worse outcomes in the >3 to 4.5 hours window compared with the 0 to 3 hours window. (Stroke. 2014;45:2745-2749.)

Key Words: stroke ■ thrombolytic therapy
Health Stroke Scale (NIHSS) >25. However, whether these patient groups are treated with IV tPA at >3 to 4.5 hours in current clinical practice is largely unknown.

We analyzed data from the national Get With The Guidelines (GWTG)-Stroke database to determine the degree of adherence to additional exclusion criteria for patients treated >3 to 4.5 hours from symptom onset in the United States. We also evaluated hospital outcome data to determine if the association of these additional exclusion criteria with outcome is related to time from onset to treatment to address the practical question of whether different exclusion criteria should be used for patients presenting in different time windows.

Methods
Characteristics of the GWTG-Stroke program have been described in prior publications. Briefly, eligible patients are identified by International Classification of Diseases, Ninth Revision billing codes, prospective screening of admission logs, or a combination, and the diagnosis of ischemic stroke is verified by a trained chart abstractor. Data are abstracted from the medical record, including age, race, sex, prespecified medical history variables (including history of prior stroke and diabetes mellitus), anticoagulant use, time of symptom onset and tPA administration, reasons for nontreatment with tPA that were documented in the chart, and in-hospital outcomes including symptomatic intracranial hemorrhage (sICH; defined as a computed tomography <36 hours that shows ICH and physician’s notes indicate clinical deterioration because of hemorrhage), hospital discharge destination, and ambulatory status at discharge. All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data are used primarily at the local site for quality improvement, most sites were granted a waiver of informed consent under the common rule. Quintiles (Cambridge, MA) served as the data collection (through their Patient Management Tool) and registry coordination center for GWTG-Stroke. The Duke Clinical Research Institute (Durham, NC) served as the data analysis center, and institutional review board approval was granted to analyze aggregate, deidentified data for research purposes.

We analyzed data from GWTG-Stroke on 32,019 patients with ischemic stroke from 1,464 hospitals who were treated with IV tPA ≤4.5 hours of symptom onset from January 2009 to January 2012, excluding patients transferred from an outside hospital and strokes that occurred while the patient was already admitted to the hospital. For analyses of discharge outcomes (discharge destination, ambulatory status, and mortality), we excluded 5,287 (16.5%) who were transferred to another acute care hospital or had missing data. For analyses of ambulatory status at discharge, we excluded 9208 (28.7%) with missing data.

We compared characteristics of patients treated at 0 to 3 versus >3 to 4.5 hours, including presence of ECASS III–specific additional exclusion criteria, using the Pearson χ² test for categorical variables and the Wilcoxon rank-sum or Kruskal–Wallis test for continuous variables. For each ECASS III–specific exclusion criterion, we compared the following in-hospital outcomes among patients treated at 0 to 3 versus >3 to 4.5 hours using the Pearson χ² test: sICH, ambulatory status at discharge categorized as ambulatory without needing personal assistance (allowing the use of a walking aid such as a cane or walker), hospital discharge status categorized as home versus other destinations, and mortality. Separate multivariable logistic regression models, one for each of the 4 outcomes of interest, were used to determine whether the associations between the ECASS III–specific additional exclusion criteria and outcome differed in patients treated at 0 to 3 hours versus >3 to 4.5 hours. In these models, time of treatment (0–3 versus >3–4.5 hours) and the ECASS III–specific exclusion criteria were entered as main effects, with interaction terms for time of treatment×exclusion criterion. When the interaction P value was <0.05, we concluded that the association between that exclusion criterion and the outcome differed at 0 to 3 versus >3 to 4.5 hours. The models were adjusted for age, sex, race, stroke severity (NIHSS 0–10, 11–15, 16–25, >25), medical history of atrial fibrillation or flutter, coronary artery disease, history of carotid stenosis, dyslipidemia, hypertension, peripheral vascular disease, smoking, on-time arrival (defined as 7 AM to 5 PM Monday to Friday), hospital size, hospital academic status (teaching hospital versus nonteaching), and hospital geographic region. Hospital characteristics were derived from the American Hospital Association database. Generalized estimating equations were used to account for clustering of patients within hospitals. Data were missing for <10% for each variable except for hospital size (12.9%). Missing data were excluded from univariate analyses and were imputed to the most common category for multivariable analyses. A forest plot was used to provide the adjusted odds ratios for the association of each ECASS III–specific exclusion criterion with the outcome, according to time of treatment category. Post hoc power calculations showed that there was 80% power to detect 1.39- to 1.89-fold differences in sICH rates for each of the ECASS III–specific exclusions. SAS version 9.2 was used for all analyses.

Results
The baseline demographic and clinical characteristics of IV tPA–treated patients are shown in Table 1. Overall, the patients treated in the later time window were younger (mean age, 67.1 versus 69.7 years) and presented with less severe symptoms (NIHSS median 9 versus 11). Medical comorbidities were similar, except that patients treated in the later time window had a lower rate of atrial fibrillation and coronary artery disease and a higher rate of smoking.

Overall, 1544 of 4910 (31.5%) patients treated with IV tPA in the >3 to 4.5 hours window had at least 1 of the additional exclusions (Table 2), compared with 39.8% of patients

Table 1. Demographic Data and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=32,019)</th>
<th>0–3 h (n=27,109)</th>
<th>&gt;3–4.5 h (n=4910)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>69.3 (14.9)</td>
<td>69.7 (14.8)</td>
<td>67.1 (15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>49.3</td>
<td>49.3</td>
<td>49.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71.0</td>
<td>71.4</td>
<td>68.6</td>
<td>0.0004</td>
</tr>
<tr>
<td>Black</td>
<td>14.9</td>
<td>14.5</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.4</td>
<td>7.4</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2.7</td>
<td>2.7</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Other or UTD</td>
<td>3.9</td>
<td>3.9</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>AFib/flutter, %</td>
<td>20.6</td>
<td>21.3</td>
<td>16.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous stroke/TIA, %</td>
<td>23.6</td>
<td>23.6</td>
<td>24.0</td>
<td>0.49</td>
</tr>
<tr>
<td>CAD/prior MI, %</td>
<td>25.3</td>
<td>25.6</td>
<td>23.4</td>
<td>0.0009</td>
</tr>
<tr>
<td>Carotid stenosis, %</td>
<td>2.8</td>
<td>2.9</td>
<td>2.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>24.8</td>
<td>24.6</td>
<td>25.6</td>
<td>0.13</td>
</tr>
<tr>
<td>PVD, %</td>
<td>3.3</td>
<td>3.3</td>
<td>3.2</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>72.3</td>
<td>72.4</td>
<td>71.7</td>
<td>0.30</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>18.5</td>
<td>18.0</td>
<td>21.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>39.4</td>
<td>39.4</td>
<td>39.4</td>
<td>0.99</td>
</tr>
<tr>
<td>HF, %</td>
<td>8.3</td>
<td>8.5</td>
<td>7.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Ambulate independently, %</td>
<td>85.6</td>
<td>85.6</td>
<td>85.7</td>
<td>0.87</td>
</tr>
<tr>
<td>NIHSS, median (25–75%)</td>
<td>11 (6–17)</td>
<td>11 (6–18)</td>
<td>9 (5–15)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AFib indicates atrial fibrillation; CAD, coronary artery disease; HF, heart failure; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease; TIA, transient ischemic attack; and UTD, unable to determine.
treated 0 to 3 hours from onset. The most common additional exclusion among treated patients was age >80 years (20.5%). With the exception of prior stroke and diabetes mellitus, the percent of IV tPA–treated patients with each exclusion criterion was lower at >3 to 4.5 hours compared with 0 to 3 hours. Overall, hospitals treated a lower percent of eligible patients within the 4.5-hour window than they did within the 3-hour window, with greater practice variation in treatment at 3 to 4.5 hours: 0 to 3 hours median 85.7%; interquartile range, 64.6% to 93.6%; 0 to 4.5 hours median 75.0%; interquartile range, 53.8% to 87.3% (see the online-only Data Supplement).

Among all treated patients, with or without the ECASS III–specific exclusion criteria, patients treated in the later window were more likely to be ambulatory and to be discharged home compared with those patients treated at 0 to 3 hours (Table 3). In univariate analysis, there were no significant differences in sICH or hospital outcomes for patients with additional exclusion criteria treated at 0 to 3 versus >3 to 4.5 hours, with the exception of a higher mortality rate in patients with NIHSS >25 treated in the later time window.

The association of each of the additional exclusion criteria with adverse hospital outcomes (sICH, not ambulatory at discharge, not discharged home, and mortality) was analyzed through a multivariable analysis while correcting for all other differences between groups (Figure). NIHSS >25 (versus NIHSS 0–10) was associated with increased odds of all adverse outcomes, but there was no significant difference between the odds of poor outcome between the treatment time windows. Age >80 years was generally associated with worse outcomes, but without significant differences between time windows except that age >80 years was associated with less risk of being nonambulatory in the >3 to 4.5 hours window compared with the 0 to 3 hours window. Similarly, the combination of prior stroke and diabetes mellitus was associated with less risk of being nonambulatory in the >3 to 4.5 hours window versus the 0 to 3 hours window. Anticoagulant use was not associated with increased risk of sICH in either window, nor were there differences in any of the other outcomes between anticoagulated patients treated at >3 to 4.5 versus 0 to 3 hours.

**Discussion**

Despite the American Heart Association/American Stroke Association guideline recommending adherence to the same exclusion criteria used in the ECASS III trial when treating patients with IV tPA in the >3 to 4.5 hours window, we found that patients with the additional exclusion criteria for the >3 to 4.5 hours window are frequently treated with IV tPA in the United States, accounting for approximately one third of the cases in that treatment window. However, patients treated at >3 to 4.5 hours were younger and had milder stroke severity than patients treated at 0 to 3 hours, possibly reflecting partial adherence to ECASS III trial criteria or delayed presentation to hospital.

After correction for baseline differences, the additional exclusion criteria were not associated with worse outcomes in the >3 to 4.5 hours window compared with the 0 to 3 hours window. In some circumstances we found that the additional exclusion criteria were associated with less, not more, risk of poor outcomes in the >3 to 4.5 hours window versus the 0 to 3 hours window—age >80 years and history of prior stroke and diabetes mellitus were associated with less risk of being nonambulatory in patients treated at >3 to 4.5 hours. However, the clinical implications of these findings are unclear. Although age >80 years and history of prior stroke and diabetes mellitus are poor prognostic factors overall, there is no evidence that tPA is less effective in these patient groups, and treatment should not be withheld from these patients in the 0 to 3 hours window.
Our findings are in agreement with prior observational studies investigating outcomes in patients with additional exclusion criteria who have been treated with IV tPA for acute stroke.6–15 There are also now randomized trial data from the Third International Stroke Trial (IST-3), which enrolled patients for whom there was equipoise regarding the benefits of thrombolytic therapy and randomized to treatment with IV tPA versus placebo ≤6 hours from onset.16 This study included 1617 patients aged >80 years and found that although the rate of good outcome in that group was overall lower than younger patients, there was still a significant benefit to treatment with IV tPA.

It should be noted that guidelines to adhere to the ECASS III trial criteria when treating patients in the >3 to 4.5 hours window are based on the certainty that patients meeting the trial criteria will benefit, not that patients meeting exclusion criteria will not benefit or will be at risk for harm. Although our data are not sufficient to provide proof of effectiveness of IV tPA in patients excluded from the ECASS III trial, because our data are drawn from an observational study and not a randomized controlled trial, we do not find any evidence of an increased risk of harm. Given that prior randomized controlled trials show no difference in the tPA effect according to age, stroke severity, or history of diabetes mellitus, and a large observational study showing no increased risk of sICH in patients taking warfarin with international normalized ratio ≤1.7, we suggest that it is reasonable to consider treatment at 3 to 4.5 hours in patients with NIHSS >25, age >80 years, history of prior stroke and diabetes mellitus, or who are using warfarin with international normalized ratio ≤1.7.15–17

A strength of our study is the large size of the cohort, which provides statistical power to analyze outcomes in subgroups of patients. However, there are also limitations. Our findings may have been influenced by practice variation in the use of IV tPA in the >3 to 4.5 hours window, because IV tPA is not Food and Drug Administration–approved for use in this time window in the United States. Patient data are limited to the hospitalization, and 90-day outcomes could not be examined. Program participation in GWTG-Stroke is voluntary; therefore, participating hospitals may not be representative of all US hospitals.

Figure. Odds ratio for adverse outcome adjusted for baseline differences between groups. CI indicates confidence interval; d/c, discharged; DM, diabetes mellitus; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and sICH, symptomatic intracerebral hemorrhage. ⊳, 0–3 h; ♦, >3–4.5 h.
and may not include all stroke patients at participating hospitals although hospitals were instructed to submit consecutive cases; however, a previous study suggests that demographics and comorbidities of GWTG-Stroke patients are similar to US stroke patients overall.\textsuperscript{14} The validity of data in GWTG-Stroke depends on the accuracy of chart documentation and abstraction; however, a previous central validation audit showed good reliability when data were reabstracted.\textsuperscript{19} Finally, because our study was observational, we used regression to control for potential confounders; however, there remains the possibility of residual confounders or unmeasured confounding.

Conclusions

Our data do not support the assumption that strict adherence to clinical trial exclusion criteria is necessary for safe and effective use of IV tPA in the >3 to 4.5 hours window. Based on our results and the randomized trial data from IST-3, we suggest that treatment of patients in the >3 to 4.5 hours window with NISS >25, age >80 years, history of prior stroke and diabetes mellitus, or warfarin use with international normalized ratio ≤1.7 should be considered.

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Disclosures

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References

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Title:

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Supplementary Figure. Percent of Patients treated with IV tPA by site for the 3hr and 4.5hr time windows.
Sites with at least ten IV tPA eligible patients arriving within each time window sorted by the percent of eligible patients treated with IV tPA within the time window.

A. 3hr: 932 hospitals, median 85.7%, IQR 64.6% - 93.6%.  B. 4.5hr: 1054 hospitals, median 75.0%, IQR 53.8% - 87.3%.