Analysis of Tissue Plasminogen Activator Eligibility by Sex in the Greater Cincinnati/Northern Kentucky Stroke Study

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Background and Purpose—Sex differences in recombinant tissue-type plasminogen activator (r-tPA) administration are present in some populations. It is unknown whether this is because of eligibility differences or the modifiable exclusion criterion of severe hypertension. Our aim was to investigate sex differences in r-tPA eligibility, in individual exclusion criteria, and in the modifiable exclusion criterion, hypertension.

Methods—We included all ischemic stroke patients ≥18 years among residents of the Greater Cincinnati/Northern Kentucky region who presented to 16-area emergency departments in 2005. Eligibility for r-tPA and individual exclusion criteria were determined using 2013 American Heart Association (AHA) and European Cooperative Acute Stroke Study (ECASS) III guidelines.

Results—Of 1837 ischemic strokes, 58% were women, 24% were black. Mean age in years was 72.2 for women and 66.1 for men. Eligibility for r-tPA was similar by sex (6.8% men and 6.1% women; P=0.55), even after adjusting for age (7.0% and 5.9%; P=0.32). Similar proportions of women and men arrived beyond 3- and 4.5-hour time windows, but more women had severe hypertension. There were no sex differences in blood pressure treatment rates among those with severe hypertension (14.6% women and 20.8% men; P=0.21). More women were >80 years and had National Institutes of Health Stroke Scale (NIHSS) >25.

Conclusions—Within a large, biracial population, eligibility for r-tPA was similar by sex. Women were more likely to have the modifiable exclusion criterion of severe hypertension but were not more likely to be treated. Women were more likely to have 2 of the 5 ECASS III exclusion criteria. Undertreatment of hypertension in women is a potentially modifiable contributor to reported differences in r-tPA administration. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.006737.)

Key Words: healthcare disparities ▪ hypertension ▪ sex characteristics ▪ stroke ▪ thrombolytic therapy

In some study populations, women are less likely to receive intravenous (IV) recombinant tissue-type plasminogen activator (r-tPA) compared with men. In a meta-analysis of hospital-based studies, women were 22% less likely to receive IV r-tPA. This difference decreased when only the patients eligible for r-tPA were considered. Previous investigations of the contributors to these treatment differences have not led to a clear understanding of the problem or to feasible strategies to eliminate the disparities. Specifically, outside the time from symptom onset to arrival, the role of individual elements of r-tPA eligibility as a contributor to sex differences in thrombolytic treatment rates is unknown.

Overall r-tPA eligibility rates are known to be low, but data on sex- and race-specific rates are lacking. In previous work, we found that only 5.9% and 6.4% of patients who presented to an emergency department (ED) with acute ischemic stroke were eligible for IV r-tPA based on standard criteria and European Cooperative Acute Stroke Study (ECASS) III criteria, respectively. In addition to estimates of overall eligibility, individual exclusion criteria for IV r-tPA have not been systematically reported by sex. Although most of these criteria are not modifiable at the individual patient level, severe hypertension (systolic blood pressure [BP] >185 or diastolic BP >110) is 1 factor that is treatable in the acute setting. Knowledge of sex differences in the modifiable exclusion criterion of severe hypertension might lead to specific strategies to increase r-tPA eligibility rates in the acute setting.

Our primary study objectives were to determine whether there are sex differences in (1) overall IV r-tPA eligibility by standard and ECASS III criteria, and (2) individual IV r-tPA exclusion criteria as per standard American Heart Association
(AHA) guidelines and ECASS III. Our secondary study objective was to explore sex differences in the potentially modifiable r-tPA exclusion criterion, severe hypertension.

Methods

Study Design/Study Population

This was a retrospective, population-based study of all adults (age ≥18 years) with acute ischemic stroke among residents of a 5-county region of Southwest Ohio and Northern Kentucky who presented to 1 of the 16-area hospital EDs during the calendar year 2005. This represents a large, biracial, metropolitan population that is representative of the United States population in general with respect to median age and median income, as well as percentage of those who are black, women, below the poverty line, and high school graduates. Methodology from this study, the Greater Cincinnati/Northern Kentucky Stroke Study, has been published in detail elsewhere.7

Data Abstraction

In brief, strokes were ascertained by both in-hospital and out-of-hospital methodology. Data relevant to r-tPA exclusion criteria per the 2013 American Heart Association8 and ECASS III Guidelines9 were abstracted by study nurses and reviewed by study physicians. Because of the retrospective nature of the study, relative and absolute exclusion criteria as per Jauch et al10 were both analyzed. In addition, the ECASS III criterion of infarct involving more than one third of the middle cerebral artery territory was not included because imaging was not reviewed during the study period. ED BPs were used for analysis of the severe hypertension exclusion criterion. When BP treatment was administered, the first 3 doses of antihypertensive medications given were recorded, along with the post-treatment BPs. Although both the initial BP and the lowest (post-treatment) BP were reported, the lowest recorded BP was used for exclusion purposes because a clinician would not likely use initial BP to exclude a patient from receiving r-tPA; rather, the clinician would treat the patient with antihypertensive agents and would consider treating the patient with r-tPA (if there were no other exclusion criteria) if the post-treatment BP was not >185/110.

Primary Outcomes

Primary outcomes analyzed by sex were (1) r-tPA eligibility by standard and ECASS III criteria and (2) individual r-tPA exclusion criteria, both standard and ECASS III.

Secondary Outcomes

Our secondary outcome was the use of antihypertensive medications in the ED among patients with severe hypertension.

Data Analysis

For individual r-tPA exclusion criteria, data were analyzed using generalized linear models to account for study design, specifically inclusion of repeat strokes and sampling methodology, which requires weighting of the out-of-hospital ascertained strokes. Data pertaining to the severe hypertension criterion were also analyzed by adjusting for age because of a concern for a potential relationship between BP and age, as well as the significant age difference between women and men in our population.

Generalized linear models were used to analyze ED BP treatment rates among those with severe hypertension who arrived within 4.5 hours of symptom onset. After unadjusted analyses of BP treatment rates, BP treatment rates were adjusted for age, race, and NIH Stroke Scale (NIHSS) score.

Among patients who arrived within 4.5 hours of symptom onset and who had severe hypertension as their only exclusion criterion, descriptive statistics were used to report the number that were treated with antihypertensive agents, the agents used, and the change in systolic BP after treatment by sex. Further analysis was not attempted because of a small sample size.

For overall eligibility by both standard and ECASS III criteria, and then by only absolute exclusion criteria, data were again analyzed using generalized linear models. All data are presented as raw frequencies and weighted percentages or means with standard errors because of the out-of-hospital sampling methodology. All data analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

There were 1837 strokes included; 1041 (58%) were women. Women and men were similar with regard to race (23.9% versus 24.9% black), but women were older than men (72.2±0.54 versus 66.1±0.66; P<0.001). Women had slightly higher median NIHSS scores at baseline (4, interquartile range 2–8 versus 3, interquartile range 2–6; P=0.03).

There were individual r-tPA exclusion criteria that differed between women and men within both standard and ECASS III guidelines (Table 1). First, regardless of the presence of other exclusion criteria, women were more likely to be severely hypertensive using post-treatment and lowest ED BPs (17.1%, n=176 versus 12.4%, n=101; P=0.02). Severe hypertension did not differ significantly by race, with 19.8% of black women versus 16.2% of white women meeting hypertension criteria (P=0.29). Of note, more women also had severe hypertension using first recorded ED BP (24.3% versus 18.5%; P=0.01).

Only 16.8% (n=49) of patients meeting the exclusion criteria for hypertension (n=277) were treated in the ED with antihypertensive medications. In addition, despite more women meeting the exclusion criterion of severe hypertension, there were no sex differences in BP treatment rates among those with hypertension (14.6% of women, n=28 versus 20.8% of men, n=21; P=0.21). After restricting the analysis to those arriving within 4.5 hours of stroke onset and adjusting BP treatment rates for age, race, and NIHSS, women and men were equally likely to receive antihypertensives (adjusted odds ratio, 0.76; 95% confidence interval, 0.24–2.38; Table 2). None of the independent variables in this model were statistically significant, although this may be because of lack of power (n=68; Table 2).

Of those arriving within 4.5 hours, there were 20 patients who had severe hypertension as their only exclusion criterion; 11 were women and 9 were men. Of the 11 women, 4 were treated with antihypertensive medications and all received multiple agents. Medications included nitroglycerin paste, continuous nitroglycerin infusions, enalapril, labetalol, and lisinopril. The average decrease in systolic BP after treatment was 22.5 mm Hg. Of the 9 men, 2 received BP medications and 1 received multiple agents. Medications included labetalol and nitroglycerin infusions. The average decrease in systolic BP was 30 mm Hg.

In terms of other comparisons in individual exclusion criteria between women and men, there were no sex differences in patients who arrived after 3 hours (79.1%, n=822 versus 76.5%, n=620; P=0.35) or 4.5 hours (75.8%, n=785 versus 73.1%, n=592; P=0.33) from symptom onset. There were, however, sex differences in 2 of the 5 ECASS III exclusion criteria: women were more likely to be >80 years old (35.0%, n=358 versus 17.4%, n=138; P<0.0001) and have NIHSS scores >25 (2.8%, n=32 versus 1.2%, n=10; P=0.01; Table 1).
Despite differences in individual exclusion criteria, there were no differences in sex in overall r-tPA eligibility as defined by standard or ECASS III criteria; combining both sets of criteria, 6.1% of women compared with 6.8% of men were found to be eligible for IV r-tPA ($P=0.55$). When using only absolute exclusion criteria to determine eligibility, 16.0% of women compared with 17.7% of men were eligible for r-tPA ($P=0.38$; Table 3).

**Table 1. Individual Exclusion Criteria by Sex**

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>Overall (n=1837)</th>
<th>Women (n=1041, 58%)</th>
<th>Men (n=797, 42%)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrival &gt;3 h</td>
<td>1442 (78.0%)</td>
<td>822 (79.1%)</td>
<td>620 (76.5%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Minor symptoms (NIHSS &lt;5)</td>
<td>1083 (60.1%)</td>
<td>596 (60.0%)</td>
<td>487 (60.2%)</td>
<td>0.93</td>
</tr>
<tr>
<td>SBP &gt;185 mm Hg or DBP &gt;110 mm Hg*</td>
<td>277 (15.1%)</td>
<td>176 (17.1%)</td>
<td>101 (12.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke/head trauma in previous 3 mo*</td>
<td>75 (5.4%)</td>
<td>47 (5.6%)</td>
<td>28 (3.5%)</td>
<td>0.92</td>
</tr>
<tr>
<td>INR &gt;1.7*</td>
<td>99 (7.5%)</td>
<td>56 (9.1%)</td>
<td>43 (5.3%)</td>
<td>0.13</td>
</tr>
<tr>
<td>aPTT value &gt;40 s*</td>
<td>100 (6.0%)</td>
<td>60 (6.7%)</td>
<td>40 (4.9%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Seizure at presentation</td>
<td>36 (1.9%)</td>
<td>18 (1.6%)</td>
<td>18 (2.2%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Major surgery in preceding 14 days</td>
<td>35 (1.8%)</td>
<td>13 (1.2%)</td>
<td>22 (2.7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous ICH*</td>
<td>23 (1.2%)</td>
<td>14 (1.2%)</td>
<td>9 (1.1%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Aneurysm*</td>
<td>20 (1.0%)</td>
<td>11 (1.0%)</td>
<td>9 (1.1%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Platelets &lt;100000*</td>
<td>28 (1.4%)</td>
<td>13 (1.2%)</td>
<td>15 (1.8%)</td>
<td>0.23</td>
</tr>
<tr>
<td>MI in previous 3 mo</td>
<td>10 (0.5%)</td>
<td>3 (0.3%)</td>
<td>7 (0.9%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Gl/urinary tract hemorrhage in previous 21 days</td>
<td>1 (0.05%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Serum glucose &lt;50 mg/dL*</td>
<td>1 (0.05%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Brain tumor*</td>
<td>6 (0.3%)</td>
<td>4 (0.4%)</td>
<td>2 (0.2%)</td>
<td>0.65</td>
</tr>
<tr>
<td>AVM*</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Active bleeding/acute trauma*</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Noncompressible arterial puncture previous 7 days*</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>ECASS III criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrival &gt;4.5 h*</td>
<td>1377 (74.7%)</td>
<td>785 (75.8%)</td>
<td>592 (73.1%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Age &gt;80 y</td>
<td>456 (24.6%)</td>
<td>358 (35.0%)</td>
<td>138 (17.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of DM and prior stroke</td>
<td>216 (11.9%)</td>
<td>118 (11.9%)</td>
<td>98 (12.0%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Any oral anticoagulant use or heparin use with aPTT &gt;40*</td>
<td>237 (13.8%)</td>
<td>134 (14.7%)</td>
<td>103 (12.6%)</td>
<td>0.39</td>
</tr>
<tr>
<td>NIHSS &gt;25</td>
<td>42 (2.2%)</td>
<td>32 (2.8%)</td>
<td>10 (1.2%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are reported as raw counts and weighted percentages. Generalized linear models were used for analysis to account for the study design. AVM indicates arteriovenous malformation; DBP, diastolic blood pressure; DM, diabetes mellitus; GI, gastrointestinal; ICH, intracerebral hemorrhage; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PTT, partial thromboplastin time; and SBP, systolic blood pressure.

*Absolute exclusion criteria.

**Table 2. Predictors of Treatment With Antihypertensive Medication Among Those With Severe Hypertension Arriving Within 4.5 h of Stroke Onset**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>0.76 (0.24, 2.38)</td>
<td>0.64</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.00 (0.96, 1.05)</td>
<td>0.97</td>
</tr>
<tr>
<td>Black</td>
<td>2.10 (0.61, 7.26)</td>
<td>0.24</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.03 (0.94, 1.13)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Adjusted odds ratios are reported. Generalized linear models were used for analysis to account for the study design. CI indicates confidence interval; and NIHSS, National Institutes of Health Stroke Scale.

**Discussion**

In summary, we found sex differences in only 1 individual exclusion criterion for IV r-tPA, as described within the US Food and Drug Administration label: severe hypertension. With the additional ECASS III criteria, we found that women were older and had more severe strokes as reasons for exclusion within the extended time window. Sex differences in severe hypertension are especially relevant to the acute care of ischemic stroke patients because BP is modifiable; conversely, sex differences in those aged >80 years and NIHSS >25 may affect the impact of the extended r-tPA time window in women but are nonmodifiable. Despite differences in individual r-tPA exclusion criteria, overall r-tPA eligibility rates were similar between women and men.
Overall, women were more likely to meet the exclusion criterion of severe hypertension. Despite this, there was no sex difference in treatment with antihypertensive medications. One potential explanation for the similar BP treatment rates between women and men, despite higher rates of severe hypertension in women, is that other r-tPA exclusion criteria were present, making BP treatment not indicated. Alternatively, these results may represent less aggressive care in women compared with that in men. These hypotheses are purely speculative and require further investigation. Although our study is novel in its investigation of sex differences in severe hypertension as an r-tPA exclusion criterion, our findings are consistent with previous literature showing that women presenting with acute stroke are more acutely hypertensive.10,11 Our results suggest that women may be at higher risk for being excluded from r-tPA because of severely elevated BP. In addition, if untreated, higher BPs in women may lead to worse outcomes in both r-tPA–treated and untreated patients.12

Our analysis of ED practice patterns for severe hypertension in stroke is limited, given the cross-sectional nature of the data and the small number of patients with hypertension as their only exclusion criterion for r-tPA. We did, however, intend for our analysis of ED BP treatment to be hypothesis generating only. Further research should be conducted on predictors of treatment of severe hypertension in those with no additional exclusion criteria using a larger study sample. In addition, because of the structure of the study institution’s stroke team coverage (a single stroke team covers the entire population for r-tPA treatments), r-tPA administration rates are not generalizable to other study populations, and this is why we did not present actual treatments within this population. Outcome data from our study population is also limited to only the outcome at discharge. As a result, these hypotheses should be analyzed in future studies in larger populations. Our findings also suggest the need for more research on the practice patterns among physicians treating severe hypertension in patients with acute stroke, especially as it relates to r-tPA eligibility.

Sex differences in age >80 years and NIHSS >25, although nonmodifiable, have clinical implications as they may affect the impact of the extended r-tPA time window in women. Findings from the ECASS III study were used to extend the IV r-tPA time window from 3 to 4.5 hours,5 but AHA/American Stroke Association (ASA) guidelines recommend that additional exclusion criteria are applied to patients who receive r-tPA during this extended window.13 Our findings that 2 of these exclusion criteria, age and NIHSS, disproportionately affect women suggest that women may benefit less from the extended r-tPA time window. Our analysis of overall eligibility by ECASS III criteria did not confirm this, but the number of additional patients eligible as a result of the extended time window was small. This is an important direction for future research, especially given recent data demonstrating the safety of IV r-tPA in patients >80 years.14–16 Observational data suggest that age >80 years is not a predictor of hemorrhagic transformation14,15 or in-hospital mortality16 after treatment with IV r-tPA. Although age is a nonmodifiable factor, providers could use these data to inform treatment decisions for patients >80 years; based on our eligibility data, treating more patients >80 years with IV r-tPA has the potential to benefit women even more so than men.

Our findings of similar overall IV r-tPA eligibility in women and men suggest that eligibility is not a major contributor to the sex disparities in IV r-tPA use described in previous literature,1,2,4 something that was previously unknown. Future studies should investigate whether sex disparities in the use of IV r-tPA continue to exist or whether they are decreasing over time. If disparities in the use of IV r-tPA do still exist, continued efforts should be made to identify contributing factors and eliminate the disparities. Eligibility differences should also be considered in other demographic groups at risk for treatment disparities, including nonwhite patients.

Conclusions

In conclusion, overall eligibility for IV r-tPA is similar in men and women, but women were more likely to have the modifiable r-tPA exclusion criterion of severe hypertension. Future work should focus on strategies to address modifiable exclusion criteria to potentially increase r-tPA eligibility in women, a group at risk for receiving less aggressive care. In addition, epidemiological data on eligibility and exclusion criteria should be used to develop strategies to increase the number of patients eligible for r-tPA.

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Disclosures

Dr Kleindorfer is a consultant at Genentech (modest level of COI). Dr De Los Rios La Rosa is a member of Boehringer Ingelheim speakers bureau (mild COI). Dr Khatri’s Department of Neurology at University of Cincinnati received financial support for her research-related activities from Genentech (PRISMS Trial Lead PI), Penumbra (THERAPY Trial Neurology PI), and Biogen (DSMB member).

References


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