Sex Differences in the Use of Intravenous rt-PA Thrombolysis Treatment for Acute Ischemic Stroke
A Meta-Analysis

Mathew Reeves, PhD; Archit Bhatt, MD; Peter Jajou, BS; Michael Brown, MD; Lynda Lisabeth, PhD

Background and Purpose—Some studies report that women are less likely to receive IV rt-PA treatment for stroke than men. We undertook a meta-analysis to determine whether a sex disparity existed.

Methods—We identified studies that reported sex-specific IV rt-PA treatment rates for acute stroke. Eligible studies included acute stroke admissions from single or multiple hospitals, registries, or administrative databases. Random effects odds ratios (OR) and 95% confidence intervals (CI) were generated to quantify sex differences (females versus males) among all ischemic stroke admissions and among the eligible subgroup who arrived within 3 hours without contraindications. Study design and geographic location were explored as sources of heterogeneity.

Results—Eighteen studies were included. Study designs included single hospitals (n=5), multiple hospitals (n=6), registries (n=4), and administrative databases (n=3). The summary OR was 0.70 (95% CI=0.55 to 0.88) indicating that women had a 30% lower odds of receiving rt-PA treatment than men. However, substantial between-study variability existed. Among 13 hospital-based studies, the summary OR was 0.78 (95% CI=0.71 to 0.86) with no significant heterogeneity. Among the 3 administrative studies, the OR was 0.55 (95% CI=0.34 to 0.90) but with significant heterogeneity. Among 4 studies that included data on the eligible subgroup, women had a nonsignificant lower odds of treatment (OR=0.81, 95% CI=0.58 to 1.13).

Conclusions—Despite the presence of significant between-study variation, women with acute stroke were consistently less likely to receive thrombolysis treatment compared with men. Further studies to explore the origins of this sex disparity are warranted. (Stroke. 2009;40:1743-1749.)

Key Words: acute stroke □ thrombolysis □ quality of health care □ sex disparity

There is growing recognition of the clinical and public health importance of stroke in women.1,2 Stroke affects a greater number of women than men because of their increased longevity coupled with the fact that stroke rates increase dramatically in the oldest age groups. After stroke functional outcomes and quality of life are consistently poorer in women than in men.2

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) was first approved as a treatment for acute ischemic stroke in the mid 1990s.3 However, low treatment rates have remained a problem in all countries where it is available; for example, only about 3% to 4% of all ischemic stroke admissions in the United States receive IV rt-PA treatment.4 Several studies that have reported on the frequency of IV rt-PA use in both men and women have shown a trend toward women being less likely to receive treatment. These reports have included a wide range of study designs including prospective studies from academic medical centers,5,6 or community-based hospitals,7 retrospective studies from community-based hospitals,8,9 stroke registries,10–12 and administrative databases.13,14 Although previous reviews have suggested that the use of IV rt-PA is lower in women,15 as far as we are aware, no systematic review or meta-analysis has been conducted to determine whether there is a gender-based disparity in the use of IV rt-PA for acute ischemic stroke, and whether such a discrepancy is a consistent finding across studies.

Methods

Study Inclusion Criteria and Initial Identification
A written systematic review protocol was first developed and reviewed by all of the authors and included predefined subgroup analyses. Studies of primary interest were those that reported on the use of intravenous (IV) rt-PA in women and men with acute ischemic stroke in typical hospital settings. Typical hospital settings included community-based and academic referral hospitals, and could involve single or multiple sites, or regional or national registries. Studies that used administrative data sources, ie, hospital discharge billing data were also included. Eligible studies must have reported separate data on the IV rt-PA treatment rates in female and male acute stroke.
patients (or the study must have provided sufficient data so that these rates could be calculated). Eligible studies must also have been based on a representative hospital-based population of acute stroke admissions from a defined time period.

We searched MEDLINE, EMBASE, and the ISI Web of Science databases for relevant articles published between January 1995 and March 2008 using the following combination of terms:

1. cerebrovascular accident [MeSH] or stroke, AND
2. r-PA or tPA or thrombolytics or thrombolysis, AND
3. sex, sex factors, sex ratio or sex distribution

Two authors (M.R., P.J.) independently reviewed the title and abstract of each “hit” to determine whether the study could potentially meet the final inclusion criteria (ie, relevancy screen). Disagreement was resolved at consensus meetings or with the assistance of a third party (A.B.) when necessary. The reference lists of the articles that met final inclusion criteria were also screened to identify other potentially relevant studies. Because not all articles that contain relevant sex-specific data will be identified using this search strategy, we also reviewed any article that reported on IV rt-PA use for acute stroke in hospital settings.

Final Study Selection and Data Abstraction

For those studies identified in the initial relevancy screen, the full manuscript was reviewed by 2 independent reviewers (M.R., P.J.) to determine whether the study met eligibility criteria. Any potentially eligible study published in non-English was translated into English for full review. Disagreements between the reviewers in terms of the final selection of studies were resolved at consensus meetings. All final selected studies then underwent data abstraction. If some but not all the data necessary to calculate sex-specific treatment rates were presented we attempted to contact the authors to obtain the required data. To avoid data duplication, if two articles used the same study population only the study that used the more recent or larger dataset was included.

The following data were abstracted: country of origin, time period, study design (single hospital, multiple hospital, registry, or administrative data), case ascertainment (prospective or retrospective), method used to define denominator population (chart review or ICD-9 codes), eligible populations (defined as either all ischemic stroke [AIS] cases, or those that arrived within 3 hours of onset with no documented contraindications [ie, ≤3 hour, no CI]), sex-specific numerators and denominators for rt-PA treatment, crude or adjusted odds ratios (OR) with 95% confidence intervals (CI) for sex difference in rt-PA treatment, and variables included in adjusted analyses. We attempted to abstract information on the demographics of the male and female study population (ie, age, gender, race), although these were recorded inconsistently. Because of the wide range of study designs included we were unable to apply the study quality criteria outlined in our review protocol.

Statistical Analysis

The primary outcome measure of interest was the unadjusted OR comparing IV rt-PA treatment (defined as the proportion of the eligible population who received treatment) in women versus men. All meta-analyses were conducted using STATA (STATA Corporation). Statistical significance and marginal statistical significance were defined as P<0.05, and 0.10<P<0.05, respectively. Given the variability in size and design of the individual studies we chose to report only random effect estimates based on the DerSimonian and Laird method. Heterogeneity across studies was assessed using the Mantel Haenzel Q statistic and the I² statistic—the latter being the proportion of between study variation not attributable to chance (range 0% to 100%). Where significant heterogeneity existed (probability value <0.05), we conducted subgroup analyses to explore the possible sources of between-study variation. A priori subgroup analyses included:

1. Study design (single hospital, multiple hospital, registry, or administrative data)
2. Location (North America, Europe, or Other)
3. Subgroup of patients eligible for rt-PA treatment (≤3 hour, no CI)

To determine whether there were individual studies that had undue influence on the overall results (because of size or magnitude of effect), we conducted a posthoc influence analysis using the METANINF command in STATA. The procedure systematically excludes each study from the analysis and reestimates the summary OR; influential studies are identified by a large change in the summary OR after exclusion. Because of the wide variability in study designs we did not assess publication bias. Finally, for studies that reported adjusted ORs with 95% CI for the sex difference in IV rt-PA use, we analyzed this measure using the inverse variance method.

Results

Forty-seven studies passed the relevancy screen and underwent full review, and of these 24 were deemed to be eligible and underwent data abstraction. Of these 24 studies, 3 studies were excluded because they included duplicative data, and 3 were excluded because the denominator data required to calculate sex-specific estimates was not available for 2 studies this fact was confirmed by the author. The 18 studies that were included in this review are shown in the Table. Sixteen of the studies included data on all AIS admissions, whereas 4 studies provided data on the eligible subgroup of cases who arrived within 3 hours of onset with no documented contraindications, ie, ≤3 hour, no CI. The studies covered the time period between 1997 and 2006; 10 of the studies were from North America, 6 from Europe, 1 from Australia, and 1 from Israel. The study designs included single hospitals (n=5), multiple hospitals (n=6), registries (n=4), or administrative datasets (n=3). Of the 15 hospital-based studies (ie, that did not rely on administrative data), 11 used chart reviews to identify eligible cases, 3 used ICD-9 or ICD-10 codes, and 1 used a combination of both. Most of the hospital-based studies used prospective case ascertainment methods, although 4 relied in part or solely on retrospective methods.

The forest plot of the 16 studies that provided data on all AIS admissions is shown in Figure 1. The overall summary OR was 0.70 (95% CI=0.55 to 0.88) indicating that women had a statistically significant 30% lower odds of receiving IV rt-PA treatment than men. However, the Q statistic demonstrated significant heterogeneity between individual study estimates (P<0.001); the I² statistic was 97% indicating substantial between study variability. To explore the origins of this heterogeneity we conducted a priori subgroup analyses based on study design and location. There were 13 reports that were hospital-based studies as opposed to 3 studies that used administrative data. Subgroup analysis of the 13 hospital-based studies showed a summary OR of 0.78 (95% CI=0.71 to 0.86) with no significant heterogeneity (P=0.13, I²=1.2%; Figure 2). Among the 3 administrative studies, the summary OR was 0.55 (95% CI=0.34 to 0.90), but there was still substantial heterogeneity present (P=<0.001, I²=99%; Figure 2). Examination of the study-specific ORs among these 3 administrative studies suggested that one study was the cause of the heterogeneity, because its OR estimate was much lower (ie, 0.39) compared to the other 2 studies (0.67 and 0.71), and because it is extremely large (over 1.8 million
observations). After deleting this study, the summary OR changed from 0.70 to 0.75 (95% CI = 0.69 to 0.82). Further subgroup analysis of the 13 hospital-based studies confirmed that women were significantly less likely to be treated with rt-PA compared to men among the 5 single hospital sites (OR = 0.64; 95% CI = 0.43 to 0.96) and among the 3 registry sites (OR = 0.79; 95% CI = 0.71 to 0.86). However, among the 5 multiple hospital studies the odds of rt-PA use in women was marginally significantly lower compared to men (OR = 0.86; 95% CI = 0.73 to 1.01). There was no statistically significant heterogeneity identified in any of these 3 subgroup analyses.

Table. Characteristics of the Final Included Studies: All Ischemic Stroke (AIS; n = 16 studies) and Subgroup of Eligible Subjects Who Arrived Within 3 Hours of Onset With No Documented Contraindications (≤3 Hours, no CI; n = 4 Studies)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Time Period</th>
<th>Study Design</th>
<th>Denominator Identification</th>
<th>Male n rt-PA (Treated Cases)</th>
<th>Male n Denominator (Eligible Cases)</th>
<th>Female n rt-PA (Treated Cases)</th>
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Figure 1. Forest plot of the unadjusted OR of IV–rt-PA use in women compared to men in all acute ischemic stroke admissions. Random effects model (n = 16 studies). OR<1 indicates lower rt-PA use in women compared to men.
Subgroup analysis of the 16 AIS studies by geographic location (ie, North America versus Europe) found that women were less likely to receive IV rt-PA treatment in both regions, although significant heterogeneity was present in both groups. Among the 8 North American studies, the summary OR was 0.64 (95% CI 0.46 to 0.89) with significant heterogeneity (P<0.001, I²=98%; Figure 3). However, the presence of significant heterogeneity was not surprising given that this subgroup included the previously identified influential administrative data study.13 Among the 6 European studies, the summary OR was 0.78 (95% CI 0.69 to 0.90), but again there was substantial heterogeneity (P=0.04, I²=58%; Figure 3).

There were only 4 studies which included data on the rt-PA eligible subgroup ie, ≤3 hours, no CI (Figure 4). The summary OR was 0.81 (95% CI 0.58 to 1.13) indicating that women had a nonsignificant 19% lower odds of receiving rt-PA treatment than men. The Q statistic demonstrated no significant heterogeneity (P=0.15). The influence analysis suggested that the study by Foerch11 was very influential. This study, which included more than 5000 observations, found no evidence of a gender difference in IV rt-PA use (OR=0.97); when deleted the summary OR was reduced to a marginally significant 0.67 (95% CI=0.44 to 1.02), suggesting a trend toward a gender difference in IV rt-PA use among the 3 remaining North American studies.5,8,12 Finally, 6 studies5,6,9,10,14,25 included OR estimates of the sex difference in IV–rt-PA use after adjusting for a variety of factors that included age, stroke severity, or comorbidities. The summary OR for these 6 studies was 0.77 (95% CI 0.69 to 0.85) with no statistical evidence of heterogeneity (P=0.29).

### Discussion
This study found consistent evidence that women with acute ischemic stroke were less likely to receive IV rt-PA treatment than men. The summary OR across 16 studies indicated that the odds of treatment was 30% lower in women compared to men. This conclusion was tempered by the presence of...
significant between-study variation, but subsequent influence analyses indicated that the primary source of this heterogeneity was a single very large administrative database study. After elimination of this study, the overall OR was 0.75 (95% CI 0.69 to 0.82), indicating that women were 25% less likely to receive treatment compared to men. Subgroup analysis of the 13 hospital-based studies indicated that the odds of treatment was 22% lower in women compared to men.

Among 4 studies that included data on patients who arrived within 3 hours of onset with no contraindications, we observed a 19% lower odds of treatment in women (although this difference was not statistically significant). Subsequent analysis identified a large German registry-based study as being influential because of its large size and the fact that it found no evidence of a sex disparity (OR=0.97). After removing this study, the analysis of the remaining 3 studies resulted in a marginally significant OR of 0.67; the magnitude of this OR suggested that a substantial sex disparity remains after taking into account patient eligibility. Given the potential for differences in the administration of IV rt-PA between different health care delivery systems, we also conducted a subgroup analysis based on geographic location. A sex disparity was observed in both European (OR=0.78) and North American (OR=0.64) studies, although there was significant heterogeneity in both subgroups. Finally, a significant sex disparity was observed among the 6 studies that provided adjusted OR estimates generated after controlling for confounders including age, stroke severity, and comorbidities.

Reasons for the observed sex disparity in IV rt-PA stroke treatment are unknown. To be eligible for IV rt-PA treatment patients must be adults, have a measurable neurological deficit, and have an established symptom onset time within 180 minutes of hospital arrival.26 Sex differences in these eligibility criteria, particularly arrival time, may impact treatment decisions for women. Although some studies have found longer out-of-hospital delays in women with stroke,27 most have not, indicating that women are not more likely
to arrive outside the treatment window than men. Compared with men, women with stroke are older, and are more likely to be widowed and to live alone, and so may have more unwitnessed stroke events making it difficult to establish symptom onset time and perhaps to obtain consent for treatment. It has also been reported that women with acute stroke are more likely to present with nontraditional stroke symptoms or non-neurological symptoms such as chest pain and shortness of breath. The presence of more atypical symptoms in women could result in a delayed diagnosis, longer in-hospital delays, and ultimately less rt-PA treatment in women.

Aside from eligibility criteria, there are numerous contraindications for IV rt-PA, which if there are sex differences in their frequency, may contribute to lower treatment rates in women. For example, use of anticoagulants or an INR of >1.7 is a contraindication for IV rt-PA, and some studies have shown an increased prevalence of atrial fibrillation and cardioembolic stroke in women. Although several hypotheses surrounding sex differences in eligibility and contraindications can be raised, analysis of the 4 studies that provided data on eligible patients (ie, arrived within 3 hours of onset with no contraindications) still found that women were less likely to receive IV rt-PA.

Apart from formal contraindications for IV-tPA, there are also several warnings surrounding its use. For example, in the acute stroke guidelines, there is a caution about treating patients with major strokes (NIHSS >22) with tPA given the risk of hemorrhage. Although studies have not consistently demonstrated greater stroke severity in women, several studies have documented that women with stroke present more frequently with coma or altered consciousness, which, in turn, may lead clinicians to be more cautious about rt-PA treatment in such women. Further, although older age is not a strict contraindication for IV-tPA treatment, the package insert cautions its use in those ≥75 years. We identified 6 studies that estimated the adjusted OR for rt-PA use in women, after accounting for age and other confounders; however, a significant sex disparity was still found (OR = 0.77).

This study is subject to several limitations. First, our ability to control for potential confounding effects attributable to baseline difference between men and women was very limited because detailed data were not provided in these studies. This lack of data also limited our ability to explore the origins of between-study heterogeneity. Second, even though all of our subgroup analyses were prespecified, we conducted a relatively large number raising the possibility of type 1 statistical errors. However, it should be noted that all of the subgroup analyses conducted had an OR <1.0, indicating that that the odds of treatment in women was less than that of men. Finally, although the inclusion of several different study designs contributed to the problem of heterogeneity, the demonstration of consistent sex disparities across this wide spectrum of studies increases the generalizability of our findings.

In summary, we found that women with acute stroke were consistently less likely to receive thrombolytic treatment. Clearly, more research is needed to understand the barriers to acute stroke therapy in women so this critical health disparity can be eliminated. The development of a consistent set of operational definitions for defining IV rt-PA treatment eligibility, and for documenting the presence of contraindications would greatly facilitate this effort.

Disclosures

None.

References


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