Outcomes of Intravenous Recombinant Tissue Plasminogen Activator Therapy According to Gender
A Clinical Registry Study and Systematic Review

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Background and Purpose—The natural history of stroke is worse in women than in men. Controversial data have been published on the efficacy of thrombolysis with recombinant tissue plasminogen activator (rtPA) according to gender. We evaluated gender differences in the efficacy and safety outcomes of intravenous rtPA using a clinical registry and systematic review.

Methods—Since January 2002, we collected baseline characteristics and efficacy and safety outcomes for patients who received intravenous rtPA in our center. We performed a systematic PubMed literature search for previous observational studies that examined gender effects on outcomes after intravenous rtPA treatment.

Results—No gender difference in good outcome at 3 months (adjusted OR for women, 1.41; 95% CI, 0.76 to 2.60) and in 90-day mortality (adjusted OR, 1.38; 95% CI, 0.59 to 3.19) was found in our registry. We identified 16 studies that evaluated the gender effect among intravenous rtPA-treated patients. None of these studies supported a gender difference in favorable outcome, and one suggested an increased risk of mortality in men. In unadjusted partial meta-analysis in 4074 women and 5840 men including our registry data, we found a trend toward a lower risk of symptomatic intracranial hemorrhage in women (crude OR, 0.87; 95% CI, 0.68 to 1.10).

Conclusions—These results suggest no gender difference in outcome among patients treated with intravenous rtPA. (Stroke. 2009;40:2104-2110.)

Key Words: acute cerebral infarction ■ thrombolysis

Recombinant tissue plasminogen activator (rtPA), administered intravenously within 3 hours of symptom onset, is the only approved treatment for acute brain infarction (BI). A pooled analysis of 3 trials of intravenous rtPA (IV rtPA) suggested an interaction between gender and thrombolytic therapy that impacted functional outcome after BI. This interaction was explained by a gender difference in outcome among the control group, which was consistent with previous reports supporting worse functional outcomes in women compared with men with acute ischemic stroke. These studies suggested that thrombolysis using IV rtPA could nullify the usual gender difference in functional outcomes after stroke. A post hoc analysis from the Glycine Antagonist in Neuroprotection (GAIN) study, restricted to patients with BI treated with IV rtPA found that men were more likely than women to display a good functional outcome. In contrast, a recent post hoc analysis from the Canadian Alteplase for Stroke Effectiveness Study (CASES) registry found no difference in outcomes, except for a lower risk of symptomatic intracerebral hemorrhage (sICH) in women. Two other studies reported a gender difference that favored women, one on neurological improvement and the other on the rate of arterial recanalization. No systematic review is available, however, on the outcomes of thrombolysis according to gender. We therefore studied gender differences in efficacy and safety outcomes of patients treated with IV rtPA based on a systematic review of published observational studies and from data from our prospective clinical registry.

Materials and Methods

Bichat Stroke Program

Patients were treated with IV rtPA according to the National Institute of Neurological Disorders and Stroke criteria with the following additional restrictions: early signs of infarct in more than one third of the middle cerebral artery territory on CT scan and/or severely impaired consciousness. We had no age limit for IV rtPA. Starting in April 2007, patients with a documented arterial occlusion that was still present after IV administration of rtPA (0.6 mg/kg) received an additional dose by...
the intra-arterial route (through a microcatheter at the site of the thrombus up to a total dose of 22 mg).

Data Collection
Since January 2002, we have used a structured questionnaire to collect prospective data on patient demographics, clinical and radiological data, and efficacy and safety outcomes of all patients with BI treated with rtPA. Age, gender, vascular risk factors, laboratory findings, vital signs before treatment, and severity of BI were recorded at admission. The severity of the BI was assessed using the National Institutes of Health Stroke Scale (NIHSS). Subsequent NIHSS recordings were made 1, 3, and 24 hours after initiation of thrombolysis. Time from symptom onset (or from last seen in a normal condition) to initiation of thrombolysis was also recorded. All patients had a follow-up CT or MRI scan 24 hours after starting thrombolysis. Hemorrhagic complications were classified according to the European Cooperative Acute Stroke Study I classification: hemorrhagic infarction (1 and 2) and parenchyma hematoma (1 and 2). Ninety-day outcome was assessed, using the modified Rankin scale (mRS), by a senior vascular neurologist in a follow-up visit and, when that was not possible, by phone (E.M. and M.M.).

Outcome Definitions
The primary study outcome was the percent of patients who achieved a 90-day favorable outcome, defined as a mRS score of 0 to 1. Secondary outcomes included early major neurological improvement (defined as an NIHSS score of 0 to 1 at 24 hours or a decrease of ≥8 points in NIHSS score at 24 hours), 90-day mortality, and symptomatic intracerebral hemorrhage (defined as a hemorrhage on the follow-up CT/MRI scan associated with an increase of ≥4 points in NIHSS score).

Systematic Review
We performed a computerized PubMed search of articles published between January 1996 and September 2008 to identify all observational studies that investigated the effect of gender on efficacy and/or safety outcomes of patients treated with IV rtPA. We used the search terms [“thrombolysis” OR “thrombolytic” OR “fibrinolysis” OR “tissue plasminogen activator”] AND “stroke.” Searches were restricted to studies published in English and conducted in humans. One author (J.L.) selected potentially relevant articles based on the title and abstract and obtained the full text for detailed review. We also searched the reference lists of retrieved articles and published review articles for additional studies.

Studies were selected using the following criteria: (1) involving subjects aged ≥18 years; (2) that reported a statistical analysis on the relationship between gender and efficacy and/or safety outcomes; and (3) that reported a consecutive series of patients with BI treated with IV rtPA within 3 hours of symptom onset. We did not select studies according to the reported outcome definitions. Associations between gender and different outcomes in the same populations, available in separate publications, were included. When both individual and pooled analyses were published, only the publication on the combined samples was included. In other cases of duplicate publication (eg, report of extended study period, subgroup analysis), only the report with the most complete data were included.

Data Extraction
Data were extracted by one author (J.L.) and were reviewed by a second (E.M.). We did not contact the authors of the studies to request incomplete or unpublished data. The following data were collected: report characteristics (first author’s name, journal, year of publication), study sample (country, study period, sample size, age, sex, admission NIHSS score), time to treatment, outcome definitions, statistical methods, direction of association between gender and outcome, and a measure of the strength of the associations.

Statistical Analysis
Statistical testing was done at the 2-tailed α level of 0.05, except in tests for homogeneity in which an α level of 0.10 was used.

Bichat Clinical Registry
Comparison of baseline characteristics and outcomes between both genders were made using χ² tests for categorical variables and Student t test for continuous variables; the Mann–Whitney U-test was used for non-Gaussian distributions. We investigated the effect of gender on primary and secondary outcomes using a logistic regression model adjusted for prespecified confounding factors known to be related to postthrombolysis outcomes (age, hypertension, glucose, atrial fibrillation, baseline NIHSS). Additional adjustments were made for other characteristics associated with gender (unadjusted P<0.05). A sensitivity analysis was performed by excluding patients treated with an additional rtPA dose by the intra-arterial route. Data were analyzed using SAS software version 9.1 (SAS Institute, Cary, NC).

Pooled Analysis
When data were available, we calculated for each individual study (including the Bichat clinical registry), crude ORs, and 95% CIs for favorable outcome, mortality, and sICH using men as the reference group. Although the study outcomes were not sufficiently homogeneous to allow a reliable quantitative synthesis, we pooled our registry data with that from the observational studies using all available data to increase the statistical power to detect any gender difference. After the assumption of homogeneity was examined using the Breslow-Day test, we calculated the combined unadjusted OR for favorable outcome, mortality, and sICH using the Mantel-Haenszel fixed-effect model. We performed a sensitivity analysis by excluding data from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), because we cannot exclude the possibility that several of the studies in our meta-analysis may have participated in SITS-MOST and would therefore have included the same patient populations. The partial meta-analysis was done using the Cochrane Collaboration’s Review Manager software package (RevMan), edition 4.2.7.

Results
Bichat Clinical Registry
From January 2002 to June 2008, 278 consecutive patients with BI were treated with IV rtPA within the 3-hour therapeutic window. Three men and one woman <69 years were excluded because they were lost to follow-up after discharge. None of the 4 excluded patients had hemorrhagic complications. Of the 274 patients included, 36 received an additional dose of rtPA through the intra-arterial approach.

Baseline Characteristics
Of the 274 patients studied, 111 (41%) were women. Women were older and had a more frequent history of hypertension and atrial fibrillation than men (Table 1). Women had lower diastolic blood pressure levels and were less likely to be current smokers and have a history of myocardial infarction. Baseline stroke severity, assessed by the NIHSS, and frequency of a definite cardiac source of embolism were significantly higher in women. No significant differences in time to treatment from symptom onset and in rate of protocol violations were found. Any protocol violations occurred in 18%. Causes were blood pressure >185/110 mm Hg (n=8), Alberta Stroke Program Early CT Score (ASPECTS) score <7 (n=10), time over 3 hours (n=22), and NIHSS >22 (n=13).

Outcomes
No gender difference was found in the primary end point with a 90-day favorable outcome observed in 33.3% of women and 34.4% of men (Table 2). The 90-day mortality rate was...
Table 1. Bichat Clinical Registry: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Men (n=163)</th>
<th>Women (n=111)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±SD</td>
<td>62.7±13.9</td>
<td>70.6±16.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>89 (54.6)</td>
<td>74 (66.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28 (17.2)</td>
<td>12 (10.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>76 (46.6)</td>
<td>44 (39.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Current smokers</td>
<td>40 (24.5)</td>
<td>13 (11.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>38 (23.3)</td>
<td>39 (35.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>23 (14.1)</td>
<td>7 (6.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Clinical measure</td>
<td></td>
<td></td>
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<tr>
<td>Blood glucose level, mmol/L, mean±SD</td>
<td>7.0±2.2</td>
<td>7.4±2.3</td>
<td>0.16</td>
</tr>
<tr>
<td>SBP, mm Hg, mean±SD</td>
<td>148±20</td>
<td>147±23</td>
<td>0.66</td>
</tr>
<tr>
<td>DBP, mm Hg, mean±SD</td>
<td>82±12</td>
<td>77±14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>12 (7–17)</td>
<td>15 (9–19)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Documented arterial occlusion, n (%)</td>
<td>99 (60.7)</td>
<td>71 (64.0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Cardioembolic stroke etiology, n (%)</td>
<td>58 (35.6)</td>
<td>61 (55.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Onset to treatment time, minutes, median (IQR)</td>
<td>150 (123–175)</td>
<td>150 (122–175)</td>
<td>0.79</td>
</tr>
<tr>
<td>Protocol violations, n (%)</td>
<td>30 (18.4)</td>
<td>16 (16.8)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; IQR, interquartile range.

Table 2. Bichat Clinical Registry: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Men (n=163)</th>
<th>Women (n=111)</th>
<th>P</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-day favorable outcome</td>
<td>56 (34.4)</td>
<td>37 (33.3)</td>
<td>0.86</td>
<td>1.41 (0.76–2.60)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>17 (10.4)</td>
<td>22 (19.8)</td>
<td>0.03</td>
<td>1.38 (0.59–3.19)</td>
</tr>
<tr>
<td>Early major neurological improvement</td>
<td>50 (30.7)</td>
<td>34 (30.6)</td>
<td>0.99</td>
<td>1.10 (0.62–1.97)</td>
</tr>
<tr>
<td>sICH</td>
<td>15 (9.2)</td>
<td>8 (7.2)</td>
<td>0.56</td>
<td>0.32 (0.10–1.04)</td>
</tr>
<tr>
<td>Sensitivity analysis‡, n (%)</td>
<td>(n=143)</td>
<td>(n=95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-day favorable outcome</td>
<td>53 (37.6)</td>
<td>32 (34.0)</td>
<td>0.58</td>
<td>1.30 (0.67–2.51)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>13 (9.2)</td>
<td>18 (19.2)</td>
<td>0.03</td>
<td>1.33 (0.52–3.44)</td>
</tr>
<tr>
<td>Early major neurological improvement</td>
<td>44 (31.2)</td>
<td>28 (29.8)</td>
<td>0.82</td>
<td>1.09 (0.58–2.05)</td>
</tr>
<tr>
<td>sICH</td>
<td>11 (7.8)</td>
<td>8 (8.5)</td>
<td>0.85</td>
<td>0.50 (0.15–1.68)</td>
</tr>
</tbody>
</table>

*χ² test. Favorable outcomes are defined as mRs 0–1.
†The ORs given were calculated by comparing the odds of each outcomes in women with those in men and were adjusted on prespecified confounders (age, glucose, hypertension, atrial fibrillation, and baseline NIHSS) and other gender differences (smoking, admission diastolic blood pressure, history of myocardial infarction, and cardioembolism etiology).
‡After exclusion of patients who received additional intra-arterial rtPA infusion.

Significantly higher in women than in men (19.8% versus 10.4%, P=0.028), but this difference disappeared after adjustment (OR, 1.38; 95% CI, 0.59 to 3.19). The rate of sICH and early major improvement were similar between men and women. In multivariable analysis, a nonsignificant trend toward a lower risk of sICH for women was noted (adjusted OR, 0.32; 95% CI, 0.10 to 1.04). Similar results were found after exclusion of the 36 patients who received an additional dose of rtPA through the intra-arterial approach.

Systematic Review

The literature search identified 5951 citations, of which 60 full articles were read and 16 were judged eligible for inclusion.5–9,11–13,20–24 A recent analysis of the SITS-MOST study25 was also included in this systematic review. Of the 44 excluded articles, 6 were excluded due to patient selection5,26–30 and 3 because of overlap with a study already included (which used the same outcome definition in the analysis).31–33 Except for a positive association between female gender and major neurological improvement reported in one article,6 none of these excluded articles reported signifcant differences in outcomes between genders.

Study Characteristics

The proportion of women ranged from 36% to 53% with a mean age of 69 years (Table 3). Two studies that described baseline characteristics reported significant differences between men and women. In both, women were more likely to be older and have atrial fibrillation and were less likely to have coronary heart disease. One reported a higher prevalence of hypertension and a lower prevalence of dyslipidemia in women,5 whereas the other reported more severe BI in women.13 The difference in age between genders was also reported in 2 studies.10,11

Outcomes

Eleven studies evaluated the effect of gender on favorable outcome, 5 on mortality (4 at 90 days and one at discharge), 7 on sICH, and one on neurological improvement.18,20 As shown in Table 3, several outcome definitions were used. One study defined favorable outcome using the Barthel Index assessed at a mean follow-up of 5 months.24 All of the remaining studies used 90-day mRS; of these, favorable outcome was defined as a mRS score of 0 to 1 in 4 studies.5,11,21,23 Regarding the definition of sICH, 3 studies...
<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Country Study Period</th>
<th>Sample Size</th>
<th>Age,* years</th>
<th>Women n (%)</th>
<th>Baseline NIHSS</th>
<th>Time to Treatment, minutes</th>
<th>Outcome Definitions n (%)</th>
<th>Direction of Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahlgren, 2008</td>
<td>European Union (multicenter) 2002–2006</td>
<td>6483</td>
<td>68</td>
<td>2581 (40)</td>
<td>12</td>
<td>136</td>
<td>90-day functional outcome: mRS 0–2</td>
<td>3362 (55)</td>
</tr>
<tr>
<td>Gómez-Choco, 2008</td>
<td>Spain (single center) 2001–2007</td>
<td>157</td>
<td>72</td>
<td>67 (43)</td>
<td>Men: 11 Women: 15</td>
<td>137</td>
<td>90-day functional outcome: mRS 0–1*</td>
<td>51 (32)</td>
</tr>
<tr>
<td>Kent, 2008</td>
<td>Canada (multicenter) 1999–2001§</td>
<td>1120</td>
<td>70</td>
<td>505 (45)</td>
<td>14</td>
<td>155</td>
<td>90-day functional outcome: mRS 0–1</td>
<td>404 (37)</td>
</tr>
<tr>
<td>Uyttenboogaart, 2008</td>
<td>Netherlands (single center) 2002–2006</td>
<td>301</td>
<td>68</td>
<td>143 (48)</td>
<td>13</td>
<td>175</td>
<td>90-day functional outcome: mRS 0–2</td>
<td>140 (47)</td>
</tr>
<tr>
<td>Caso, 2007</td>
<td>Italy (single center) 2001–2004</td>
<td>73</td>
<td>71</td>
<td>29 (40)</td>
<td>10</td>
<td>160</td>
<td>90-day functional outcome: mRS 0–2</td>
<td>37 (51)</td>
</tr>
<tr>
<td>Martí-Fabregas, 2007</td>
<td>Spain (multicenter) 1999–2004</td>
<td>347</td>
<td>68</td>
<td>154 (44)</td>
<td>15</td>
<td>142</td>
<td>90-day functional outcome: mRS 0–2$</td>
<td>34 (34)</td>
</tr>
<tr>
<td>Ernon, 2006</td>
<td>Belgium (single center) 2000–2005</td>
<td>100</td>
<td>73</td>
<td>42 (42)</td>
<td>16</td>
<td>142</td>
<td>90-day functional outcome: mRS 0–2‡</td>
<td>34 (34)</td>
</tr>
<tr>
<td>Georgiadis, 2006</td>
<td>Switzerland (multicenter) 2001–2004§</td>
<td>341</td>
<td>66</td>
<td>130 (48)</td>
<td>—</td>
<td>—</td>
<td>90-day functional outcome: mRS 0–1</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Berrouschot, 2005</td>
<td>Germany (multicenter) 2000–2004§</td>
<td>228</td>
<td>≥80,17%</td>
<td>89 (39)</td>
<td>14</td>
<td>≥3 hours, 22% (n=50)</td>
<td>90-day functional outcome: mRS 0–1</td>
<td>99 (43)</td>
</tr>
<tr>
<td>Engelter, 2005</td>
<td>Switzerland (multicenter) 1998–2003§</td>
<td>325</td>
<td>65</td>
<td>118 (36)</td>
<td>14</td>
<td>158</td>
<td>90-day functional outcome: mRS 0–1</td>
<td>118 (36)</td>
</tr>
<tr>
<td>Heuschman, 2004</td>
<td>Germany (multicenter) 2000–2002§</td>
<td>1658</td>
<td>70</td>
<td>697 (42)</td>
<td>—</td>
<td>≥3 hours, 9% (n=150)</td>
<td>Hospital mortality</td>
<td>166 (10)</td>
</tr>
<tr>
<td>Saposnik, 2005</td>
<td>Canada (single center) 1999–2003§</td>
<td>216</td>
<td>72</td>
<td>107 (50)</td>
<td>13</td>
<td>157</td>
<td>Neurological improvement: Significant: ≥4-point decrease in NIHSS score at 24 hours</td>
<td>101 (48)</td>
</tr>
<tr>
<td>Mendizabal, 2001</td>
<td>USA (single center) 1996–1999</td>
<td>36</td>
<td>64</td>
<td>19 (53)</td>
<td>13</td>
<td>≥3 hours, 2.8% (n=1)</td>
<td>Major: ≥8-point decrease in NIHSS score at 24 hours‡</td>
<td>61 (28)</td>
</tr>
</tbody>
</table>

0 indicates no association; + indicates a significant positive association between women and outcome; – indicates a significant inverse association between women and outcome.

*mRS = 2 if patient had an estimate mRS equal to before qualifying event.

†NIHSS equal to 0 or 1 at 24 hours.

§According to the baseline NIHSS score (mRS 0 if NIHSS <8, mRS 0–1 if NIHSS 8–14, mRS 0–2 if NIHSS >14).

§Overlapping samples.
defined sICH as clinical neurological deterioration temporally related to intracerebral hemorrhage and 3 as a ≥4-point increase in NIHSS associated with intracerebral hemorrhage; the definition was unclear in the remaining studies. Only of the largest studies (SIS-MOTS) reported a lower incidence of favorable outcome in women in comparison to men in univariate analysis. This difference disappeared after adjustment for confounding factors; none of the identified studies reported a significant gender difference in favorable outcome in the “fully adjusted” model. Two studies reported a significantly higher rate of favorable outcome in men in univariate analysis, which disappeared after adjustment for confounders, including admission stroke severity. One study reported an increased risk of mortality in men (adjusted OR, 1.23; 95% CI, 1.02 to 1.47) and another reported a decreased risk of sICH in women. The study on neurological improvement (24 hours after symptom onset) reported a significant gender effect on clinical improvement in one analysis, but this was not significant in another.

The available unadjusted estimates of gender effect on favorable outcome, mortality, and sICH in individual and combined studies are shown in the Figure. Combining our results with those of the 7 studies that reported functional outcome at 3 months, the incidence of favorable outcome was lower in women and men with a crude OR of 0.89 (95% CI, 0.81 to 0.97). This unadjusted difference disappeared after exclusion of data from SITS-MOTS (crude OR, 0.95; 95% CI, 0.79 to 1.14), which contributed to 77% of combined data. No unadjusted difference was found for mortality. When combining our results with those of the 7 observational studies that reported safety outcome, we found a trend toward a lower incidence of sICH in women (crude OR, 0.87; 95% CI, 0.68 to 1.10) with no evidence of heterogeneity across studies (P=0.43). A similar trend was found after exclu-

![Figure. Crude odds ratios for (A) 90-day favorable outcome; (B) symptomatic intracranial hemorrhage; and (C) 90-day mortality associated with women in individual and combined observational studies.](http://stroke.ahajournals.org/externalgraphics/FIG-2108.Figure.png)
sion of data from SITS-MOTS (crude OR, 0.75; 95% CI, 0.55 to 1.02).

Discussion

This systematic review, including our registry data, showed no evidence of gender differences in outcomes after IV rtPA therapy despite well-known gender differences in untreated subjects.2,3

In our clinical registry, the incidence of a favorable outcome at 3 months (mRs 0 to 1) was similar between genders despite more deaths in women (20% versus 10%). This difference in mortality rate disappeared after adjustment for potential confounders, including baseline gender differences such as higher NIHSS, older age, more frequent arterial hypertension and atrial fibrillation, and less frequent history of myocardial infarction in women.3,34 These factors are known to impact the prognosis significantly.9–12 In partial unadjusted analysis including all available data, an unadjusted difference in favorable outcome was observed due to the largest study,25 which contributed to 77% of data. Only this study reported an unadjusted gender difference in favorable outcome, which disappeared in multivariate analysis including others predictor factors. The same study showed a higher mortality rate within 90 days in men compared with women in the fully adjusted model. This conflicting result could be explained partially by the selection criteria on age, because patients >80 years were excluded. Saposnik et al18 found that early major neurological improvement (decrease of ≥8 points in the NIHSS score or an NIHSS score of 0 or 1 at 24 hours) was more frequent in women. This fact was not replicated in our series. Thus, the weight of evidence in this systematic review, including our registry data, favors a nongender difference in main outcomes after IV rtPA thrombolysis. This finding was consistent with an individual meta-analysis of randomized trials1 and with the post hoc subgroup analysis of the Pro-Urokinase for Acute Cerebral Thromboembolism (PROACT-2) trial15 reporting, respectively, a significant gender heterogeneity in response to IV rtPA and intra-arterial prourokinase therapy.

Unfortunately, our clinical registry as well as previous observational studies did not have a control group of untreated subjects and could not replicate this finding. Studies of the natural history of patients with stroke have shown that women have a worse prognosis than men, higher mortality, and are more frequently discharged to a nursing home.2,3 The reversal of outcome after IV rtPA treatment suggest that the effect of IV rtPA could be greater in women than in men after adjustment for baseline differences.

Gender differences in coagulation and fibrinolytic factors have been reported in acute ischemic stroke,36,37 but their clinical significance does not appear relevant to our results. Some authors suggested that women have smaller arteries, resulting in smaller clot volumes, which could facilitate a thrombolytic effect;32 this size effect is likely to be counterbalanced by weight-adjusted doses of rtPA. In animal models, estrogens have been shown to be neuroprotective,38 but most women in this analysis were postmenopausal. In addition, most studies do not present data on menopausal status and hormonal replacement therapy.

In our registry, a nonsignificant trend toward a lower risk of sICH appeared after adjusting for gender differences. In the systematic review, one study reported a lower risk of sICH in women compared with men, which was significant only after adjustment.3 In partial meta-analysis, there was a trend toward a lower risk of sICH for women compared with men (crude OR, 0.87; 95% CI, 0.68 to 1.10). Because confounders such as age, glucose concentration, and baseline stroke severity favored men, adjustment for these important factors might well result in a significantly lower rate of sICH in women than in men, and therefore further investigations in large studies or meta-analysis on individual data are needed.

The major limitation in our registry is the inadequate statistical power to detect a difference, especially for sICH outcome. Based on our sample size, we could detect an OR of 2.9 with 80% power, 5% α level (2-tailed), assuming a prevalence of 8% in women. We therefore combined our data with previous observational studies. The major limitation of this combined analysis is the lack of adjustment on baseline differences, which biased the comparisons as shown in the largest study.25 Finally, some relevant studies may not have been included in our review, because our search was limited to published reports in English and included in the PubMed database.

In summary, on the basis of the available literature, including data from our registry, there were no relevant gender differences in outcome after IV rtPA treatment. Additional large studies are warranted to establish firmly and to better understand these findings.

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