Sex-Based Differences in the Effect of Intra-Arterial Treatment of Stroke
Analysis of the PROACT-2 Study

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Background and Purpose—Sex influences outcome after intravenous thrombolysis. In a combined analysis of the tissue plasminogen activator clinical trials, a sex-by-treatment interaction was observed. We sought to confirm that observation in an independent data set.

Methods—Data were from the Pro-Urokinase for Acute Cerebral Thromboembolism-2 (PROACT-2) trial. Baseline factors were compared by sex. The primary outcome was an assessment of a sex-by-treatment interaction term within a logistic regression model, using a modified Rankin Scale score ≤2 at 90 days as the binary outcome. We also assessed whether there were differences in CT-scan appearance and recanalization at 2 hours post-treatment.

Results—In the PROACT-2 study of intra-arterial stroke thrombolysis, in both women and men, prourokinase resulted in better outcomes than control. A sex by prourokinase treatment interaction was observed, with women showing a larger treatment effect (20% absolute benefit) compared with men (10% absolute benefit). The reason for this interaction is that thrombolytic treatment nullifies the worse outcome for untreated women compared with men. The reasons for effect modification do not include improved recanalization at 2 hours among women.

Conclusions—Women with middle cerebral artery ischemic stroke benefit more from intra-arterial therapy. Further study of how sex affects stroke outcome is needed. (Stroke. 2006;37:2322-2325.)

Key Words: gender ■ stroke ■ thrombolysis

Several studies have reported that treatment and outcomes differ between women and men for general stroke care.¹⁻⁴ Reasons for this result may include social factors, age or perhaps true differences in biology.⁵⁻⁷ Analysis of pooled results of the intravenous tissue plasminogen activator (tPA) trials in acute ischemic stroke revealed surprising evidence that women may benefit more than men from intravenous thrombolysis.⁸ This analysis was consistent with previously cited studies in that nonthrombolysed women fared worse than nonthrombolysed men. Among tPA–treated patients, the sex-effect was absent, and this resulted in female sex being a significant modifier of treatment-effect. However, this analysis was a post-hoc assessment and the association could have been the result of chance. We sought to confirm this result in an independent data set.

Methods

The Pro-Urokinase for Acute Cerebral Thromboembolism-2 (PROACT-2) study has been previously reported.⁹ In brief, the study was a randomized, controlled, open-label clinical trial with blinded outcome evaluation, enrolling 180 patients with angiographically proven middle cerebral artery occlusion, randomized in a 2:1 ratio to intra-arterial prourokinase or heparin control. The study demonstrated a 15% absolute benefit in functional independence at 90-days (modified Rankin Score 0 to 2) accruing to patients receiving treatment with prourokinase. In this analysis we used data from the study to evaluate the hypothesis that sex influences outcome after treatment with prourokinase with a greater treatment effect among females.

Clinical trial data and outcomes were collected by the PROACT-2 study group. Assessment of recanalization and angiograms was conducted centrally by the PROACT-2 angiography reading committee. CT Alberta Stroke Program Early CT Score (ASPECTS) scores for both baseline and follow-up scans were assessed separately by a panel of 3 readers (H.R., A.M.B., M.D.H.).¹⁰

Statistical Methods

Baseline variables were examined by sex. Comparisons were made using Fisher exact test for proportions, 2-sample t test for normally or near-normally distributed continuous variables and Mann Whitney U test for ordinal or categorical variables. The primary outcome was a modified Rankin Scale score of 0 to 2 (independent functional outcome) at 90 days compared with a score of 3 to 6 (dependence or death). This outcome was the prespecified primary outcome in the PROACT-2 study and is thought to be the most appropriate outcome for large ischemic strokes. Secondary outcomes included the 90-day modified Rankin Scale score 0 to 1, National Institutes of Health Stroke Scale (NIHSS)

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score 0 to 1, Barthel index 95 to 100, symptomatic intracerebral hemorrhage, 24-hour ASPECTS scores and recanalization at 2 hours from the start of treatment. The main hypothesis was tested using logistic regression analysis with a multiplicative interaction term—sex by proUK indicates prourokinase; MAP, mean arterial pressure; ASA, acetylsalicylic acid; TIA, transient ischemic attack; IQR, interquartile range.

We assessed a simple unadjusted model first using only sex, treatment assignment and the interaction between the 2. Subsequently, we used logistic regression to determine whether recanalization was different between men and women after adjusting for baseline differences. The likelihood ratio test was used to assess interaction terms.

### Results

Of 180 patients enrolled in the study, 106 (59%) were men. There were differences in some baseline risk factors by sex (Table 1); these were baseline blood pressure, history of hypertension and stroke use. Overall, men achieved an independent functional outcome 38% of the time compared with 31% in women, but this difference was not statistically significant.

Using a simple logistic regression model (unadjusted model) using only treatment, sex and the interaction between treatment and sex, the interaction term was not statistically significant (P=0.459). Nevertheless, the direction of effect favored a larger treatment effect size among women. After inclusion of age and baseline NIHSS score, both the main effect variable, sex (P=0.025), and the interaction term (P=0.021) were statistically significant. The reason for this effect modification is that untreated women fared worse than untreated men (17% versus 31%, modified Rankin Scale score 0 to 2 at 90 days), even after adjusting for baseline stroke severity. When examining only the untreated group, women were younger than the men (mean age 60 versus 67, P=0.044) and the men were more likely to have had a past myocardial infarction (36% versus 4%, P=0.001).

With treatment, women and men did equally well (Table 2 and the Figure). In the same model, there was no evidence of confounding and no other significant main effects when other important prognostic variables (diabetes, stroke type, baseline serum glucose and baseline characteristic differences in hypertension, baseline mean arterial pressure, tobacco use and stroke mechanism) were included in the model. Therefore, in the final model only age and baseline NIHSS score were included as covariables. Among 155 patients who had ASPECTS scores available, there was no evidence of confounding by ASPECTS on the sex effect modification. Similarly, the degree of collateral

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Male %, (n=106)</th>
<th>Female %, (n=74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, IQR)</td>
<td>66 (54–75)</td>
<td>70 (59–76)</td>
<td>0.372</td>
</tr>
<tr>
<td>White</td>
<td>80% (85)</td>
<td>80% (59)</td>
<td>1.000</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assigned to proUK</td>
<td>66% (70)</td>
<td>69% (51)</td>
<td>0.748</td>
</tr>
<tr>
<td>NIHSS (median, IQR)</td>
<td>17 (13–20)</td>
<td>17 (13–20)</td>
<td>0.742</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>56% (50)</td>
<td>58% (43)</td>
<td>0.762</td>
</tr>
<tr>
<td>Glucose (mean, SD) (mg/dL)</td>
<td>138 (52)</td>
<td>141 (62)</td>
<td>0.789</td>
</tr>
<tr>
<td>MAP (mm Hg) (mean, SD)</td>
<td>103 (16)</td>
<td>98 (15)</td>
<td>0.041</td>
</tr>
<tr>
<td>M1 occlusion</td>
<td>66% (70)</td>
<td>55% (41)</td>
<td>0.163</td>
</tr>
<tr>
<td>Onset-to-treatment time (hours) (mean, SD)</td>
<td>5.0 (0.9)</td>
<td>5.2 (1.0)</td>
<td>0.241</td>
</tr>
<tr>
<td>ASPECTS (median, IQR)</td>
<td>7 (6–7)</td>
<td>7 (6–9)</td>
<td>0.494</td>
</tr>
</tbody>
</table>

### Table 2. Unadjusted Comparisons of Outcomes Between Men and Women by Treatment Allocation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ProUK (proportion and 95% CI)</th>
<th>Control (proportion and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–2, 90 days</td>
<td>0.41 (0.30–0.54)</td>
<td>0.37 (0.24–0.52)</td>
</tr>
<tr>
<td>Recanalization at 2 hours</td>
<td>0.66 (0.53–0.77)</td>
<td>0.61 (0.46–0.75)</td>
</tr>
<tr>
<td>24-hour ASPECTS (median, IQR)*</td>
<td>4 (1–6)</td>
<td>5 (2–6)</td>
</tr>
</tbody>
</table>

*note n=154 for ASPECTS comparisons.

mRS indicates modified Rankin Scale; ProUK, prourokinase; IQR, interquartile range.
circulation present at the baseline angiogram was not a confounder on the sex by prourokinase treatment interaction.

Using secondary outcomes and the same logistic regression model with age and baseline NIHSS as covariables, the strength of the association as assessed by the interaction term using the Barthel Index $\geq 95$ ($P=0.055$) and NIHSS 0 to 1 ($P=0.065$) was similar. Using excellent functional outcome as modified Rankin Scale score 0 to 1 ($P=0.195$), death ($P=0.587$), or severe disability and death as modified Rankin Scale score 5 to 6 ($P=0.289$) and symptomatic intracerebral hemorrhage ($P=0.636$), no interaction effect was seen. On the modified Rankin Scale score 0 to 1 outcome, a treatment effect was present but there was no significant difference in treatment effect for men (9.1% benefit) and women (8.5% benefit).

To explore this interaction further, we examined whether sex was associated with recanalization. In a logistic regression model using any thrombolysis in myocardial ischemic (TIMI) grade 2 or TIMI grade 3 recanalization at 120 minutes as the outcome, there was no evidence of a sex by prourokinase treatment interaction, even after adjustment of important prognostic variables as described above.

**Discussion**

Our analysis is consistent with the previously reported effect modification of sex on outcome after thrombolysis for stroke. The direction of effect and magnitude of effect (20% risk benefit for women and 10% for men) are similar and the reasons for the interaction are the same: women do worse after ischemic stroke than men but this sex-difference in natural history is nullified with thrombolysis.

Intriguingly, like previous assessments, there was no main effect of sex on outcome in a simple model without adjustment for stroke severity and age. The interaction is only evident when it is specifically looked for and would have been easily missed if interactions among only variables with significant main effects were examined. Furthermore, like onset-to-treatment time, the baseline stroke severity and age were masking confounders. Only after inclusion of these variables in the model does the sex by prourokinase treatment interaction emerge.

In contrast to the intravenous tPA trials, the PROACT-2 trial was angiographically controlled. Therefore, we were able to assess whether differences in outcome were attributable to differences in recanalization between men and women. It has been postulated that differences in coagulation parameters might be important. However, we found no evidence that the probability of recanalization was different between men and women, although differences in the rapidity of recanalization or in late recanalizations conceivably may have been missed given the standardized assessment of angiographic patency at 2 hours. This is in direct contrast to a recent single-center case series which noted much greater recanalization among women compared with men after intravenous tPA.

Sex bias in the assessment of outcome scales, such as the modified Rankin Scale score or the Barthel Index should not have produced this result because patients were randomly allocated to treatment. There was no evidence that women had less severe stroke as shown on their baseline CT scans, measured both clinically (using NIHSS) and radiologically (using ASPECTS).

One possibility is that recovery or rehabilitation are different among men and women and that this can be affected by acute treatment. Meanwhile, studies of women show that they may present with atypical stroke symptoms such as headache and many case series and clinical trials of thrombolysis show that they are under-represented.

It is important to recognize that caution is warranted in interpreting these findings. Why the interaction effect is present using modified Rankin Scale score 0 to 2 as the outcome and not for modified Rankin Scale score 0 to 1 remains unclear. Small numbers may have prevented more precise estimates. Secondary analyses such as this one should be backed up by further study.

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**Disclosures**

None.

**References**

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