

# Sex-Based Differences in Response to Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke

## A Pooled Analysis of Randomized Clinical Trials

David M. Kent, MD, MS; Lori Lyn Price, MS; Peter Ringleb, MD;  
Michael D. Hill, MD; Harry P. Selker, MD, MSPH

**Background and Purpose**—Women experience worse outcomes after stroke compared with men. Prior work has suggested sex-based differences in coagulation and fibrinolysis markers in subjects with acute stroke. We explored whether sex might modify the effect of recombinant tissue plasminogen activator (rtPA) on outcomes in patients with acute ischemic stroke.

**Methods**—Using a combined database including subjects from the National Institute of Neurological Disorders and Stroke (NINDS), Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A and B, and the Second European Cooperative Acute Stroke Study (ECASS II) trials, we examined 90-day outcomes in patients randomized to rtPA versus placebo by sex. We used logistic regression to control for potential confounders.

**Results**—Among 988 women treated between 0 and 6 hours from symptom onset, patients receiving rtPA were significantly more likely than those receiving placebo to have a modified Rankin Score  $\leq 1$  (40.5% versus 30.3%,  $P < 0.0008$ ). Among 1190 men, the trend toward benefit in the overall group did not reach statistical significance (38.5% versus 36.7%,  $P = 0.52$ ). An unadjusted analysis showed that women were significantly more likely to benefit from rtPA compared with men ( $P = 0.04$ ). Controlling for age, baseline National Institutes of Health Stroke Scale, diabetes, symptom onset to treatment time, prior stroke, systolic blood pressure, extent of hypoattenuation on baseline computed tomography scan and several significant interaction terms (including onset to treatment time–by-treatment and systolic blood pressure–by treatment) did not substantially change the strength of the interaction between gender and rtPA treatment ( $P = 0.04$ ).

**Conclusions**—In this pooled analysis of rtPA in acute ischemic stroke, women benefited more than men, and the usual gender difference in outcome favoring men was not observed in the thrombolytic therapy group. For patients presenting at later time intervals, when the risks and benefits of rtPA are more finely balanced, sex may be an important variable to consider for patient selection. (*Stroke*. 2005;36:62-65.)

**Key Words:** clinical trials ■ outcome ■ thrombolytic therapy ■ sex factors ■ stroke, acute

Prior studies have shown that, over their lifetime, women are more likely than men to have a stroke, and those that do are more likely to be functionally dependent and institutionalized as a result.<sup>1-3</sup> Prior work has also demonstrated sex-based differences in coagulation and fibrinolysis in subjects with acute stroke.<sup>4-6</sup> A preliminary analysis suggested that sex may influence response to therapy with recombinant tissue plasminogen activator (rtPA).<sup>7</sup> In this article, we explore the effect of sex on the response to rtPA in patients with acute ischemic stroke using a database of combined clinical trials.

### Methods

Using a combined database including the National Institute for Neurological Disorders and Stroke (NINDS) rtPA Trial,<sup>8</sup> Alteplase

Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A<sup>9</sup> and B<sup>10</sup> Trials, and the Second European-Australasian Acute Stroke Study (ECASS II),<sup>11</sup> we examined the likelihood of a normal or near-normal outcome at 90 days (modified Rankin Scores [mRS]  $\leq 1$ ) in patients randomized to rtPA versus placebo by sex. These trials are described in detail in their original report and the important differences between the databases are reviewed in a recent individual patient meta-analysis.<sup>8-12</sup> We used step-wise logistic regression to control for prognostically important clinical and radiological variables, using a threshold  $P$  value of 0.05 for inclusion in the model. To validate our results, we performed the same analysis using generalized estimating equations to examine the treatment-by-sex effects simultaneously across different outcome scales (the mRS, the Barthel Index and the National Institute of Health Stroke Scale [NIHSS]), also referred to as the “global outcome.”<sup>13</sup>

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From the Institute for Clinical Research and Health Policy Studies (D.M.K., L.L.P., H.P.S.), Tufts–New England Medical Center Boston, Mass; the Department of Neurology (P.R.), University of Heidelberg, Germany; and the Department of Clinical Neuroscience (M.D.H.), Foothills Medical Centre, University of Calgary, Canada.

Correspondence to Dr David M. Kent, Institute for Clinical Research and Health Policy Studies, Tufts–New England Medical Center, 750 Washington Street, #63, Boston, MA, 02111. E-mail dkent1@tufts-nemc.org

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**Baseline Characteristics of Men Versus Women in the ATLANTIS/ECASS II/NINDS Combined Database**

	Men (n=1190)	Women (n=988)	P
Age (mean, SD)	65.4 (11.3)	66.5 (11.5)	0.02
SBP, mm Hg (mean, SD)	151.6 (20.2)	153.7 (20.4)	0.02
Symptom OTT, min (median, interquartile range [IQR])	245 (168–292)	220 (135–285)	<0.0001
NIHSS (mean, SD)	13.0 (6.8)	13.0 (6.4)	0.89
Glucose, mmol/l (median, IQR)	6.7 (5.8–8.4)	6.8 (5.8–8.8)	0.34
Diabetes, %	21.0	21.1	0.94
Prior stroke, %	16.9	16.3	0.72
Hypertension, %	56.3	61.6	0.01
Atrial fibrillation, %	17.9	19.7	0.27
Ischemic heart disease, %	24.5	23.9	0.76
Congestive heart failure, %	11.7	12.7	0.46
Findings on baseline computed tomography scan			
ASPECTS (median, IQR)	9 (7–10)	9 (7–10)	0.71
Hypoattenuation by location, %			
Internal capsule	0.6	0.3	0.32
Lentiform	26.8	27.3	0.77
Caudate	14.3	16.0	0.29
Insular cortex	34.0	30.1	0.05
MCA1	15.7	13.4	0.12
MCA2	23.6	21.5	0.25
MCA3	7.3	8.1	0.52
MCA4	10.5	11.4	0.49
MCA5	25.4	27.1	0.38
MCA6	7.2	8.4	0.32
Hypoattenuation: cortical vs subcortical,* %			0.07
Cortical only	23.6	21.1	
Subcortical only	5.2	7.7	
Both	22.9	21.4	

MCA indicates middle cerebral artery.

\*Cortical areas include the insular cortex and MCA1 to MCA6; subcortical areas include caudate lentiform and internal capsule

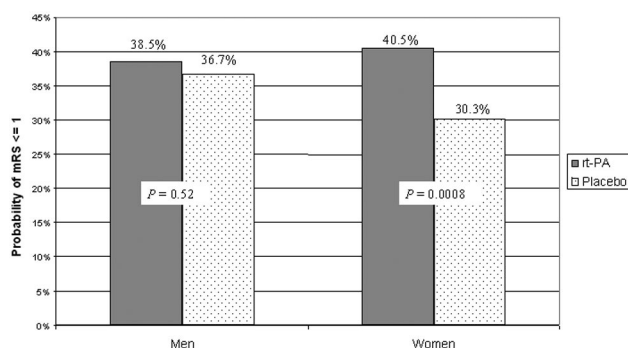
## Results

Of the 2178 patients in the combined database, 55% (1190) were men and 45% (988) were women (Table). Women, on average, were slightly older, more often had a history of hypertension, had slightly higher systolic blood pressure (SBP) on presentation, and were treated 25 minutes earlier after symptom onset than were men. They were also somewhat more likely to have a history of hypertension than men. Otherwise, baseline characteristics were similar between men and women. In particular, there was no difference in baseline stroke severity, as measured by NIHSS, or in the extent or location of hypoattenuation on baseline computed tomography scan, as measured by the Alberta Stroke Program Early CT Score (ASPECTS).<sup>14,15</sup>

Overall, 90-day outcomes were similar in men and women (mRS≤1: 37.7% versus 35.4%, respectively;  $P=0.28$ ). However, there was a considerable difference in response to therapy (Figure 1). Among men treated within 6 hours of symptom onset, there was no overall difference

between the rtPA- and placebo-treated patients in the proportion of patients with normal or near-normal outcome (mRS≤1: 38.5% versus 36.7%, respectively;  $P=0.52$ ). However, among women treated within 6 hours of symptom onset, those receiving rtPA were significantly more likely than those receiving placebo to have a normal or near-normal outcome; the margin of benefit was ≈10% (mRS≤1: 40.5% versus 30.3%,  $P<0.001$ ). An unadjusted analysis showed that women were significantly more likely to benefit from rtPA compared with men ( $P=0.04$ ). The apparent difference in treatment-effect was not because of any difference in the thrombolytic-related symptomatic intracranial hemorrhage rate (7.9% for women versus 7.8% for men,  $P=0.97$ ).

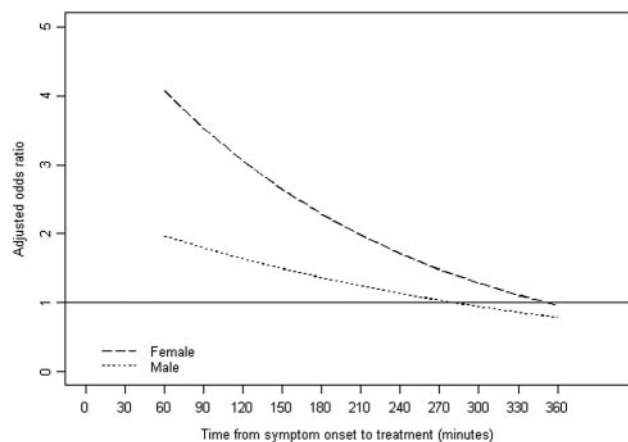
As can be seen in Figure 1, among patients treated with placebo, outcomes among women were considerably worse than men ( $P=0.03$ ). There was no significant difference in outcomes between men and women among those treated with rtPA ( $P=0.50$ ).



**Figure 1.** Outcomes in men and women treated or not treated with thrombolytic therapy. Graph depicts the probability of a normal or near-normal outcome in men and women treated or not treated with rtPA. Overall, outcomes between the 2 treatment groups are similar in men ( $P=0.52$ ), whereas women receiving rtPA have considerably better outcomes than those receiving placebo ( $P=0.0008$ ). The effect of rtPA on outcome is significantly different between the 2 subgroups ( $P=0.04$ ). Among placebo-treated patients (light bars), women had a significantly worse outcome than men ( $P=0.03$ ). However, among those treated with rtPA (dark bars), there was no significant difference in outcomes between men and women ( $P=0.50$ ).

Using logistic regression to control for age, baseline NIHSS, diabetes, symptom onset to treatment time (OTT), systolic blood pressure, ASPECT score and also controlling for the effects of OTT on treatment and the effects of SBP on treatment, as well as an interaction term between diabetes and OTT, did not substantially alter the significance of the interaction between sex and rtPA treatment ( $P=0.04$ ). Figure 2 demonstrates the effect of rtPA in men and women over time, measured by the odds of having a mRS≤1, controlling for the same covariates. There was no significant sex-by-OTT interaction, nor was there a significant sex-by-treatment-by-OTT interaction, indicating that the influence of sex on treatment was consistent across time.

The influence of sex on treatment-effect did not reach statistical significance in any of the individual trials and there



**Figure 2.** Odds ratio for a normal or near-normal outcome (mRS≤1) with rtPA in men and women. Graph depicts the odds ratio for a normal or near-normal outcome at 90 days with thrombolytic therapy for men and women across different symptom OTTs. The estimated effect is adjusted for differences in age, baseline NIHSS, the presence of diabetes, ASPECTS, baseline SBP, and the following interactions: SBP and treatment, diabetes and OTT, and age and NIHSS.

was no significant heterogeneity across trials in the sex-by-treatment interaction. When generalized estimating equations were used to test whether a similar interaction was observed when the global outcome was used, the trend was similar but not as extreme as with the modified Rankin outcome ( $P=0.09$ ).

## Discussion

In this pooled analysis, we found that women with acute ischemic stroke appear to get significantly more benefit from rtPA than men. To date, we are aware of only 2 other factors that have been shown to modify the effects of rtPA: time from symptom onset to treatment<sup>16</sup> and the presence of an ApoE2 phenotype.<sup>17</sup> Factors that modify the effects of rtPA may be important in selecting patients with a favorable treatment profile, because the benefits of rtPA treatment need to be balanced against its risks.<sup>18</sup>

It is interesting to note that there is no appreciable effect of gender on outcome in rtPA-treated patients. Among placebo-treated patients, however, the outcome in women was significantly worse than men. These results are consistent with several prior reports demonstrating that women with stroke generally have worse functional outcomes than men (ie, in the absence of thrombolytics).<sup>19–22</sup> Our results indicate that rtPA may nullify this gender difference in stroke outcomes.

There are several possible explanations for the relationship between sex and rtPA response, including chance. In our analyses and the analyses of others on similar databases,<sup>7,11,23</sup> several clinical variables were examined for treatment-effect interactions; multiple post hoc analyses increase the likelihood of reporting a chance interaction. However, the effect appears to be large enough so as to be clinically significant. Further, there have been multiple reports demonstrating sex-based differences in functional outcome in stroke,<sup>19–22</sup> and there may be plausible mechanisms that might explain the association of gender with treatment benefit. Although the mechanisms are not currently clear, factors associated with sex might affect either (1) the likelihood of reperfusion or (2) the response of the brain to ischemia and reperfusion.

Regarding the first of these mechanisms, sex-based differences in coagulation and fibrinolysis have been described in patients with acute stroke. For example, at least 2 reports have found significantly higher levels of plasminogen activator inhibitor-1 in females with acute stroke compared with males.<sup>4,5</sup> However, plasminogen activator inhibitor-1 levels have been shown to correlate inversely with the likelihood of reperfusion in stroke,<sup>24</sup> which would seem to bias against the sex-effect seen in our study.

Regarding the second potential mechanism, estrogen has been shown to be a potent neuroprotective agent in animal models.<sup>25,26</sup> Because the great majority of women in our study were postmenopausal, the direct effect of estrogen is an unlikely explanation, unless there are yet-to-be-described longer-lasting “preconditioning” or organizational effects of hormones.

Sex may also play a role in the vascular anatomy of stroke (distal versus proximal) or in stroke subtype (eg, women may have a higher rate of cardioembolic strokes and men a higher rate of atheroembolic and lacunar strokes).<sup>27</sup> However, in our

study, there was no difference across sex in stroke severity, in the extent or location of hypoattenuation on baseline computed tomography scan (except for a small excess involvement of insular cortex of marginal statistical significance) or in the rate of atrial fibrillation or other heart disease. One can still speculate that sex-based differences in cerebrovascular anatomy may cause differences in collateral flow, preserving threatened ischemic tissue longer in women than men, or that the generally smaller vessels in women may correspond to a smaller clot burden, more vulnerable to lysis.

The possible role of sex on the treatment-effect of rtPA is potentially important in the context of other gender-based differences in acute stroke. One report has shown that women are more likely than men to present with nontraditional stroke symptoms (such as pain or altered level of consciousness),<sup>28</sup> and another has demonstrated a trend suggesting women are less likely than men to receive IV thrombolytic therapy.<sup>29</sup> In this regard, it is interesting that women appeared to be somewhat underrepresented in these trials, despite the fact that the overall lifetime risk of stroke is higher in women.<sup>30,31</sup> Such a gender-based treatment-bias may result in the (reverse) targeting of treatment to patients who are actually less likely to benefit from therapy (ie, men). Our results suggest that female gender may be an important clinical marker for patients who may be more likely to benefit from rtPA, especially at later times when the risks and benefits are more evenly balanced.

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