Gender Differences in Acute Ischemic Stroke
Etiology, Stroke Patterns and Response to Thrombolysis

Alex Förster, MD; Achim Gass, MD; Rolf Kern, MD; Marc E. Wolf, MD; Caroline Ottomeyer, MD; Katrin Zohsel, PsyD; Michael Hennerici, MD; Kristina Szabo, MD

Background and Purpose—Differences between women and men in relation to stroke are increasingly being recognized.

Methods—From July 2004 until June 2007, 237 acute ischemic stroke (AIS) patients were treated with recombinant tissue plasminogen activator (rtPA) within 3 hours after onset of symptoms in our stroke unit. Baseline characteristics, etiology, CT/MRI stroke patterns, clinical outcome, and complications of women were compared to those of men.

Results—Of 237 AIS patients (mean age 70.7 years), 111 (46.8%) were women and 126 (53.2%) were men. Women were older (P<0.001), but history of hyperlipidemia (P=0.03), smoking (P=0.03), and coronary heart disease (P<0.001) was less frequent than in men. Internal carotid artery disease occurred more often in men (P=0.02), whereas atrial fibrillation was observed more often in women (P=0.002). In men borderzone/small embolic and lacunar stroke was found more frequently (39.7 versus 27.2%), whereas women showed a higher percentage of large territorial stroke (72.8 versus 60.3%, P=0.09). Baseline National Institute of Health Stroke Scale scores (12.5 versus 11.3), NIHSS score at discharge (11.0 versus 9.5), 3-month-outcome modified Rankin Scale score, thrombolysis-related (17.1% versus 13.5%) or independent complications (32.4% versus 30.2%), and mortality after 3 months (13.5% versus 9.5%) were similar.

Conclusion—Differences of stroke lesion patterns in genders are paralleled by differences in etiology and risk factor profiles (women, cardioembolism; men, large and small vessel disease). Baseline characteristics, rates of rtPA-related and independent complications, as well as clinical outcomes were not different between women and men with AIS.

Key Words: gender ■ female ■ stroke ■ thrombolysis

Stroke is one of the leading causes of death and the main cause of long-term disability in the Western society.1 Differences between women and men in relation to stroke are increasingly being recognized. Women not only have a higher lifetime risk of stroke2 but also a higher poststroke mortality, rate of disability, depression, and dementia compared to men.3–6 This has been attributed to their higher life expectancy, consistent with the fact that age is the strongest independent risk factor for stroke and also a negative predictor for clinical outcome.2 Cohort studies indicate that women and men have differences in risk factor profiles,6–8 acute stroke presentation,7–9 and stroke etiology.10 With regard to treatment of stroke with recombinant tissue plasminogen activator (rtPA), it is still under debate whether women benefit more from acute therapy as pooled data analysis of randomized clinical trials indicated.11,12 Women and men treated with rtPA had similar outcomes, whereas women in the placebo group had less favorable clinical outcomes. In this context the results of another study reporting on a higher recanalization rate in women compared to men with acute ischemic stroke (AIS) treated with rtPA13 underline the question of a possible higher efficacy of acute treatment in women. In contrast to these findings, a posthoc analysis of the Glycine Antagonist in Neuroprotection for patients with Acute Stroke Americas (GAIN) Trial could not demonstrate such an effect.14 Differences in the imaging patterns of stroke in women, and especially the question whether these in combination with the gender-specific risk profiles may account for a differential thrombolytic effect among women with ischemic stroke, have not yet been studied in detail.

In this study we analyzed baseline data, stroke etiology, complications, and 3-month outcome in women and men with AIS receiving thrombolysis with special emphasis on gender-based differences in acute patterns of infarction and persistent vessel pathology.

Materials and Methods

Between July 2004 and June 2007, 1678 patients with CT- or MRI-proven AIS were treated in our stroke center. A total of 237/1678 (14.1%) received rtPA in the 3-hour time window. All clinical data and technical investigations were recorded and documented according to a standardized acute stroke care protocol: detailed physical and neurological examinations, length of time from onset of symptoms to initiation of rtPA treatment, assessment of cerebrovascular risk factors, CT or MRI scan, Doppler and duplex...
sonography of the extracranial vessels, transcranial Doppler sonography, transthoracic or transesophageal echocardiography, 24-hour ECG and blood pressure monitoring, oxygen saturation (pulse oximeter), and laboratory tests. Data included regular clinical monitoring according to stroke unit standard requirements in Germany. Modified Rankin Scale (mRS) score at 3 months was assessed according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) protocol. Treatment of stroke patients over the age of 80 years was performed on an individual off-label use basis with informed consent according to ethics committee communication.

Probable stroke cause was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification with the following categories: (1) cardioembolism, (2) large vessel disease, (3) small vessel disease, (4) other determined cause, and (5) undetermined cause. Stroke patterns on CT or MRI scan were classified in territorial, embolic, and lacunar stroke as well as borderzone infarction (see Figure 1) as implemented earlier. In a subset of patients, those without MRI scan because of contraindications or inconclusive CT findings, stroke localization and pattern were classified as uncertain. Complications were categorized into 3 categories: (1) those most likely rtPA-associated (eg, symptomatic intracranial or systemic hemorrhage as well as allergic reactions), (2) those not primarily linked to thrombolysis such as pneumonia, cardiovascular events, poststroke-delirium, respiratory insufficiency, seizures, recurrent AIS, or transient ischemic attack (TIA), (3) death after 3 months. Statistical analysis for gender differences was carried out using SPSS 16.0. Descriptive data were analyzed using either t tests, the rank-sum test, or χ²-based tests as appropriate. Group statistics for single time-point measurements on the National Institute of Health Stroke Scale (NIHSS) were performed using t tests, on the mRS using rank-sum tests. We examined the influence of gender on the likeliness of a favorable clinical outcome defined as mRS score ≤2 (independent functional outcome). Multivariable logistic regression analysis was used to control for prognostically important clinical (initial NIHSS score and risk factors like arterial hypertension and hyperlipidemia) and radiological variables (stroke pattern and persistent vessel pathology), including also the interaction term for stroke pattern and gender.

Results

Baseline Characteristics

Of the 237 AIS patients (mean age 70.7 years, range 19 to 97 years), 126 (53.2%) were men, and 111 (46.8%) were women. Table 1 shows the baseline characteristics. Compared to men, women were older (P=0.001) and showed a worse pretreatment mRS (P=0.001) but similar NIHSS scores at onset and a similar latency from symptom onset to treatment times (OTT). Common vascular risk factors like hyperlipidemia (P=0.03) and a history of smoking (P=0.03) were more frequent in men, and also the incidence of coronary heart disease was significantly higher (P<0.001). Pretreatment medications were not different with regard to platelet inhibitors or anticoagulants.

Table 1. Baseline Data of Patients

<table>
<thead>
<tr>
<th></th>
<th>Femalen=111</th>
<th>M aluminum=126</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>73.9 (15.1)</td>
<td>67.8 (11.9)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS, mean (SD)</td>
<td>12.5 (5.6)</td>
<td>11.3 (5.2)</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment mRS&gt;0</td>
<td>29 (26.1)</td>
<td>5 (4.0)</td>
<td>6.58</td>
<td>2.64–16.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline mRS, median (IQR)</td>
<td>5 (4–5)</td>
<td>5 (4–5)</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>93 (83.8)</td>
<td>98 (77.8)</td>
<td>1.08</td>
<td>0.95–1.22</td>
<td>0.24</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35 (31.5)</td>
<td>29 (23.0)</td>
<td>1.37</td>
<td>0.90–2.09</td>
<td>0.14</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>32 (28.8)</td>
<td>53 (42.1)</td>
<td>0.69</td>
<td>0.48–0.98</td>
<td>0.03</td>
</tr>
<tr>
<td>History of smoking</td>
<td>10 (9.0)</td>
<td>24 (19.0)</td>
<td>0.47</td>
<td>0.24–0.95</td>
<td>0.03</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>9 (8.1)</td>
<td>34 (27.0)</td>
<td>0.30</td>
<td>0.15–0.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21 (18.9)</td>
<td>18 (14.3)</td>
<td>1.32</td>
<td>0.74–2.35</td>
<td>0.34</td>
</tr>
<tr>
<td>PVD</td>
<td>2 (1.8)</td>
<td>6 (4.8)</td>
<td>0.57</td>
<td>0.15–2.22</td>
<td>0.41</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>13 (11.7)</td>
<td>18 (14.3)</td>
<td>0.82</td>
<td>0.42–1.60</td>
<td>0.56</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>4 (3.6)</td>
<td>3 (2.4)</td>
<td>1.51</td>
<td>0.35–6.61</td>
<td>0.58</td>
</tr>
<tr>
<td>Pretreatment with</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>39 (35.1)</td>
<td>55 (43.7)</td>
<td>0.80</td>
<td>0.58–1.11</td>
<td>0.18</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>1 (0.9%)</td>
<td>5 (4.0%)</td>
<td>0.23</td>
<td>0.03–1.91</td>
<td>0.14</td>
</tr>
<tr>
<td>Onset to needle time (min), mean (SD)</td>
<td>143.4 (31.4)</td>
<td>143.1 (28.6)</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stroke Etiology and Stroke Pattern

The definite/probable cause of AIS could be identified in only 65.4% of all patients (see Figure 2). Large vessel disease (26.2% versus 9.9%, RR 0.37, 95% CI 0.19 to 0.71, \( P = 0.002 \)) and hereof internal carotid artery (ICA) disease (19.0% versus 8.1%, RR 0.43, 95% CI 0.21 to 0.88, \( P = 0.02 \)) were observed more often in men, whereas cardioembolism (44.1% versus 27.8%, RR 1.47, 95% CI 1.04 to 2.08, \( P = 0.03 \)) and hereof atrial fibrillation (AF; 41.4% versus 23.0%, RR 1.80, 95% CI 1.22 to 2.66, \( P = 0.002 \)) were found more frequently in women. Correspondingly the rate of known and newly diagnosed atrial fibrillation was significantly higher in women compared to men (41.4% versus 23.8%, RR 1.74, 95% CI 1.19 to 2.55, \( P = 0.004 \)), whereas the rate of previously known atrial fibrillation (atrial fibrillation at baseline) did not differ significantly (see Table 1).

Prevalence of atherosclerosis did not differ between women and men, but women were less likely to have asymptomatic or symptomatic high grade or subtotal ICA stenosis or occlusion (8.6% versus 24.6%, RR 0.35, 95% CI 0.17 to 0.70, \( P = 0.001 \)). Furthermore women showed a significantly lower rate of persistent vessel pathology as diagnosed with MR-Angiography or transcranial Doppler ultrasound between days 1 to 3 postthrombolysis (20.7% versus 34.0%, RR 0.61, 95% CI 0.37 to 1.01, \( P = 0.05 \)).

A total of 188 patients (79.3%) received a standardized stroke MRI workup. Most frequent cause not to perform an MRI was a rapid clinical deterioration (46.9%) or pacemaker implantation (22.4%). There was no significant difference between women (74.8%) and men (83.3%, RR 0.90, 95% CI 0.79 to 1.03, \( P = 0.1 \)) concerning the percentage of a MRI assessment. With regard to stroke patterns there was no statistically significant difference between women and men, but a trend (\( \chi^2 = 6.46, P = 0.09 \)). The frequency of specific stroke patterns reflects the etiologic findings: females had more territorial strokes (72.8% versus 60.3%), whereas males had higher numbers of borderzone (2.5% versus 0.0%) and lacunar strokes (15.7% versus 9.7%; see Figure 3).

With regard to stroke etiology, persistent vessel occlusion was found more often in large vessel disease (51.2%) compared to cardioembolism (27.9%) or stroke of undetermined cause (14.5%, \( \chi^2 = 20.89, P < 0.001 \)). With regard to stroke pattern, persistent vessel occlusion was found to be associated more often with territorial infarctions (35.4%) compared to embolic and borderzone infarctions (12.5%, \( \chi^2 = 8.76, P = 0.01 \)).

Complications and Clinical Outcome

Thrombolysis-associated complications were not different in women and men. The same holds true for thrombolysis...
ICA stenosis or occlusion as compared to women. This often asymptomatic or symptomatic high grade or subtotal of smoking in men. Correspondingly, male patients had more prevalence of risk factors such as hyperlipidemia and history higher, which is not surprising with regard to the higher patients with symptomatic ICA disease was significantly AIS.19,20 This might explain the higher number of territorial AF in accordance with earlier studies demonstrating that stroke etiology, women showed a significantly higher rate of borderzone and lacunar infarctions in women. With regard to MRI scan with higher rates of territorial and lower rates of embolic as well as lacunar stroke in women, which are also reflected in different frequencies of stroke patterns on CT or bolics as well as lacunar stroke in women, which are also percentiles of cardioembolic and lower rates of thromboem-

Table 2. Clinical Outcome and Complications

<table>
<thead>
<tr>
<th>Clinical scores</th>
<th>Female n=111</th>
<th>Male n=126</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS at discharge, mean (SD)</td>
<td>11.0 (6.2)</td>
<td>9.5 (5.5)</td>
<td>0.91</td>
<td>0.72 to 1.14</td>
<td>0.13</td>
</tr>
<tr>
<td>mRS at discharge, median (IQR)</td>
<td>4 (2–5)</td>
<td>4 (1–5)</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS at 3 months, median (IQR)</td>
<td>4 (1–5)</td>
<td>3 (1–4)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS ≥ 2 at 3 months*</td>
<td>34 (37.4)</td>
<td>49 (46.7)</td>
<td>0.80</td>
<td>0.57–1.12</td>
<td>0.19</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rtPA-associated complications</td>
<td>19 (17.1)</td>
<td>17 (13.5)</td>
<td>1.27</td>
<td>0.69–2.32</td>
<td>0.44</td>
</tr>
<tr>
<td>SICH</td>
<td>3 (2.7)</td>
<td>5 (4.0)</td>
<td>0.69</td>
<td>0.17–2.81</td>
<td>0.73</td>
</tr>
<tr>
<td>Systemic hemorrhage</td>
<td>16 (14.2)</td>
<td>12 (9.5)</td>
<td>1.51</td>
<td>0.75–3.06</td>
<td>0.24</td>
</tr>
<tr>
<td>rtPA-independent complications</td>
<td>36 (32.4)</td>
<td>38 (30.2)</td>
<td>1.08</td>
<td>0.74–1.57</td>
<td>0.71</td>
</tr>
<tr>
<td>Death until follow-up irrespective of cause*</td>
<td>15 (13.5)</td>
<td>12 (9.5)</td>
<td>1.42</td>
<td>0.69–2.90</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Female n=91, Male n=105.

ne independent complications as well as death in the first 3 months after onset (see Table 2). Outcome according to mRS could be achieved in 196 (82.7%) patients and was statistically indistinguishable between both groups (see Table 2). The number of patients discharged to a rehabilitation center (58.7% versus 53.2%, RR 0.91, 95% CI 0.72 to 1.14, P=0.4) as well as the number of patients with clinical favorable outcome did not differ significantly (37.4% versus 46.7%, RR 0.80, 95% CI 0.57 to 1.12, P=0.19).

In the logistic regression model only initial NIHSS score and arterial hypertension were predictors of clinical outcome. Neither stroke pattern nor the interaction term for stroke pattern and gender were predictive for clinical outcome.

Discussion

In this large single-center study we compare probable stroke etiology and stroke patterns on CT or MRI in women and men with AIS treated with rtPA within 3 hours after onset of symptoms in addition to analysis of common cerebrovascular risk factors, complications, and clinical outcome.

The most intriguing result is the difference in stroke etiology between women and men with significantly higher percentages of cardioembolic and lower rates of thromboem-bolic as well as lacunar stroke in women, which are also reflected in different frequencies of stroke patterns on CT or MRI scan with higher rates of territorial and lower rates of borderzone and lacunar infarctions in women. With regard to stroke etiology, women showed a significantly higher rate of AF in accordance with earlier studies demonstrating that women have a significantly higher risk for AF related AIS.19,20 This might explain the higher number of territorial strokes in our female study population. Another CT-based study in patients with probable cardioembolic stroke could demonstrate a high rate of lobar and subcortical territorial infarctions.20 In contrast to these findings the number of male patients with symptomatic ICA disease was significantly higher, which is not surprising with regard to the higher prevalence of risk factors such as hyperlipidemia and history of smoking in men. Correspondingly, male patients had more often asymptomatic or symptomatic high grade or subtotal ICA stenosis or occlusion as compared to women. This might, on the other hand, be responsible for the higher frequency of borderzone and lacunar strokes in males.

However, it is not surprising that there is only a trend and no statistically significant difference in stroke patterns between women and men, keeping in mind that territorial as well as embolic infarction pattern may occur in cardioembo-
lism as well as thromboembolism in large vessel disease, whereas borderzone and lacunar infarction are linked to a distinct pathomechanism. Furthermore, early recanalization facilitated by acute therapy with rtPA may also generate rather smaller embolic lesions than large territorial infarctions.

Clinical outcome as measured by the NIHSS and mRS as well as the number of patients with a favorable clinical outcome 3 months after AIS did not differ significantly between women and men. This confirms earlier results of a pooled data analysis of 5 randomized clinical trials11 with intravenous rtPA therapy, a posthoc analysis of a randomized clinical trial with intraarterial rtPA, and a posthoc analysis of gender effects in the Canadian Alteplase for Stroke Effectiveness Study (CASES, 1999 to 2001)21 but differs from the results of a posthoc analysis of the GAIN trial, which excluded patients with rapid clinical improvement within one hour after thrombolysis.14 Comparison of thrombolysis-related and inde-
pendent complications and mortality did not reveal significant differences between both groups.

The frequency of persistent vessel occlusion was signifi-
cantly higher in men compared to women. These findings confirm the results of an earlier smaller study showing a higher recanalization rate in women.13 Given the fact that women with AIS not treated with rtPA have less likely favorable clinical outcomes,3–5,12 these findings underscore the probable higher efficiency of rtPA treatment in women and lead to the question for what reason thrombolysis might be more effective. An appealing explanation might be the better recanalization of a fibrin-rich embolic occlusion asso-
ciated with cardioembolism compared to a platelet-rich oc-
cclusion associated with thromboembolism and preexisting atherosclerosis.22,23 Another explanation might be differences in the endogenous fibrinolytic activity in women compared to men.12 Further investigation is required exploring the under-
lying biochemical interactions.
Disclosures

None.

References


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Stroke. 2009;40:2428-2432; originally published online May 21, 2009;
doi: 10.1161/STROKEAHA.109.548750
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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