The Metabolic Syndrome Is Associated With a Higher Resistance to Intravenous Thrombolysis for Acute Ischemic Stroke in Women Than in Men

Juan F. Arenillas, MD, PhD; Patricio Sandoval, MD; Natalia Pérez de la Ossa, MD; Mónica Millán, MD; Cristina Guerrero, MD; Domingo Escudero, MD, PhD; Laura Dorado, MD; Elena López-Cancio, MD; José Castillo, MD, PhD; Antoni Dávalos, MD, PhD

Background and Purpose—The metabolic syndrome (MetS) might confer a higher resistance to intravenous thrombolysis in acute middle cerebral artery (MCA) ischemic stroke. MetS increases the risk of stroke in women to a greater extent than in men. We aimed to investigate whether there might be sex differences in the impact of MetS on the response to intravenous thrombolysis for acute MCA ischemic stroke.

Methods—We prospectively studied consecutive ischemic stroke patients, treated with intravenous tissue-type plasminogen activator according to SITS-MOST criteria, with an MCA occlusion on prebolus transcranial Doppler examination. Resistance to thrombolysis was defined as the absence of complete MCA recanalization 24 hours after tissue-type plasminogen activator infusion by transcranial Doppler criteria. MetS was diagnosed according to the criteria established by the American Heart Association/National Heart, Lung, and Blood Institute 2005 statement.

Results—A total of 125 patients (75 men, 50 women; mean age, 67.6 ± 11 years) were included. MetS was diagnosed in 76 (61%) patients. Resistance to clot lysis at 24 hours was observed in 53 (42%) patients. Two multivariate-adjusted, logistic-regression models identified that MetS was associated with a higher resistance to tissue-type plasminogen activator, independently of other significant baseline variables (odds ratio = 9.8; 95% CI, 3.5 to 27.8; $P = 0.0001$) and of the individual components of the MetS. The MetS was associated with a significantly higher odds of resistance to thrombolysis in women (odds ratio = 17.5; 95% CI, 1.9 to 163.1) than in men (odds ratio = 5.1; 95% CI, 1.6 to 15.6; $P$ for interaction = 0.0004).

Conclusions—The effect of MetS on the resistance to intravenous thrombolysis for acute MCA ischemic stroke appears to be more pronounced in women than in men.

Key Words: acute stroke ■ thrombolysis ■ outcome ■ metabolic syndrome ■ sex differences

The metabolic syndrome (MetS) is a cluster of vascular risk factors that share insulin resistance as a common underlying pathophysiologic mechanism. Its components are central obesity, high blood pressure (BP), hyperglycemia, and atherogenic dyslipidemia.1 The MetS has been shown to be associated with an increased risk for cardiovascular disease and ischemic stroke.2,3 Recent epidemiologic studies have highlighted its increasing prevalence worldwide, which is as high as 40% in people age > 20 years,4 with > 47 million people affected in the United States alone.5

MetS is characterized by defective endogenous fibrinolysis with an enhancement of fibrinolysis inhibitors like plasminogen activator inhibitor-1,6,7 which may contribute to the increased risk of thromboembolic events, including ischemic stroke, in MetS patients. In addition, as suggested by our previous studies,8 this impairment in endogenous fibrinolysis might worsen the response to thrombolytic therapy in acute ischemic stroke and lead to a higher resistance to clot lysis after tissue-type plasminogen activator (t-PA) administration.

The impact of MetS on global cardiovascular risk, ischemic stroke risk, development of carotid atheromatosis, and other vascular effects seems to be higher in women than in men.9 A recent population-based, prospective study has confirmed this observation.3 However, whether the effect of MetS on the effectiveness of thrombolytic therapy for acute ischemic stroke is influenced by sex remains unknown. Therefore, we conducted a prospective study to investigate...
whether the impact of MetS on the resistance to thrombolysis for acute ischemic stroke varies between men and women.

**Patients and Methods**

**Patient Selection**

We studied consecutive patients with an acute ischemic stroke affecting the middle cerebral artery (MCA) territory who were treated with intravenous t-PA according to SITS-MOST criteria at a standard 0.9 mg/kg dose within the first 3 hours from stroke onset. All t-PA–treated patients were prospectively recorded in a database that contained all of the variables that were used in this study. Of a total of 184 consecutive stroke patients admitted to our Stroke Unit and treated with intravenous t-PA between August 2003 and June 2007, 129 showed MCA occlusion on prebolus transcranial Doppler (TCD) examination. Complete data for MetS diagnosis could be determined in the 125 patients who were finally included in this study. Besides t-PA, 8 patients received NXY-059 or placebo within the SAINT I and SAINT II clinical trials, and 15 were treated with citicoline versus placebo within the ICTUS trial. No other investigational drugs were used. The study protocol was approved by the local ethics committee, and informed consent was obtained from all patients or their relatives.

**Clinical Assessment**

All patients were admitted to a Stroke Unit. Baseline examinations included a medical history, physical examination, routine blood biochemistry and blood count, ECG, chest x-ray, urgent cervical ultrasound and TCD examinations, and noncontrast brain computed tomography (CT). Carotid ultrasound imaging was obtained with a General Electric Vivid 7 Pro (GE Vingmed Ultrasound) device, equipped with multifrequency transducers. Prebolus systolic and diastolic BP values, temperature, and glycemia were determined on admission. Neurosonographic examinations were performed on admission, every 15 minutes during t-PA infusion, and at 2, 6, and 24 hours after stroke onset.

Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS). Cerebral CT scans were performed immediately before t-PA bolus and repeated after 24 to 36 hours, or earlier when neurologic deterioration occurred. Early CT signs of infarction were evaluated on the admission CT by neuroradiologists with extensive expertise in acute stroke imaging who were blinded to the clinical and TCD data.

A detailed history on vascular risk factors (age, sex, cigarette smoking, hypertension, diabetes, and hypercholesterolemia), diagnosed coronary heart disease, and intermittent claudication was obtained from each patient. To identify stroke etiology, additional diagnostic procedures such as special coagulation tests, immunologic study, echocardiography, and ECG-Holter were performed when indicated. Patients were classified according to modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria into different stroke subtypes.13 Clinical long-term outcome was evaluated 3 months after stroke onset by the modified Rankin Scale (mRS). An mRS score >2 was considered indicative of poor outcome.

**Diagnosis of MetS**

The MetS was diagnosed according to the criteria established by the American Heart Association and National Heart, Lung, and Blood Institute in 2005. As a modification of the original diagnostic criteria, central obesity was defined as a body mass index (BMI) >25 kg/m². Patients were considered to have the MetS when 3 or more criteria were met. Fasting blood levels of glucose, HDL cholesterol, and triglycerides were measured with standardized methods in blood samples obtained 48 to 72 hours after admission, once adequate nutrition for the patients had been started.

**TCD Assessment of Resistance to Clot Lysis**

A standard TCD examination was performed in the Stroke Unit immediately before t-PA administration to detect the presence of an MCA occlusion. We used portable TCD units (Four View, Rimed and Doppler Box, DWL) equipped with 2-MHz pulsed-wave diagnostic transducers. All TCD examinations were performed by neurologists with expertise in acute stroke TCD monitoring who were involved in this study. The MCA was explored through the temporal acoustic window at an insonation depth between 40 and 65 mm. MCA occlusions were defined according to the Thrombolysis in Brain Ischemia (TIBI) grading system. The presence of flow signals corresponding to TIBI grades 0 (absent), 1 (minimal), 2 (blunted), or 3 (dampened) was considered indicative of arterial occlusion. A control TCD examination was performed by the same neurosonologist 24 hours after t-PA bolus to assess the evolution of vessel status. A single bolus of echotransmitting agent (Sonovue) was administered at each time point if the patient had an inadequate acoustic window. Complete arterial recanalization was diagnosed when the end-diastolic flow velocity improved to normal or elevated values were obtained (TIBI grade 4 or 5). Resistance to clot lysis was defined by the absence of complete arterial recanalization at 24 hours.

**Statistical Analysis**

Statistical analyses were performed with the SPSS statistical package (version 12.0; SPSS Inc, Chicago, Ill). Statistical significance for intergroup differences was assessed by the χ² test for categorical variables and the Student t test and Mann-Whitney U test for continuous variables. All continuous variables except NIHSS score and glycemia were normally distributed. Resistance to clot lysis was considered the primary outcome variable, whereas long-term clinical outcome was considered a secondary end point. Multivariable-adjusted logistic-regression models were applied to study the relation between MetS, resistance to thrombolysis, and poor clinical outcome. To evaluate whether the effect of MetS on the primary outcome variable differed between men and women, the interaction term MetS∗sex was included in the regression analysis. For all regression models, adjustment was done by age and all variables with a P<0.05 on the respective bivariate analyses. Results of regression analyses are expressed as odds ratios (ORs) and their corresponding CIs. A probability value <0.05 was considered significant.

**Results**

**Descriptive Analysis**

We studied 125 consecutive acute ischemic stroke patients with a documented MCA occlusion treated with intravenous t-PA. Of these, 75 were men and 50 were women. Among women, 48 (96%) were postmenopausal. MetS was diagnosed in 76 (61%) patients. Table 1 shows the distribution of baseline variables across the 2 sexes. Compared with women, men were younger, were more frequently smokers, and had lower BMI and HDL cholesterol values. With respect to stroke etiology, there was a predominance of cardioembolic strokes among women. No significant differences were observed in other relevant baseline variables, such as initial stroke severity, time from onset to treatment, admission glycemia, presence of early infarct CT signs, or MetS severity as defined by the number of criteria that were met.

**Predictors of Resistance to Thrombolysis: Sex Interaction**

Resistance to clot lysis was observed in 53 (42%) patients. The following variables were found to be associated with resistance to thrombolysis in bivariate analysis, as shown in Table 2: diabetes, MetS, atherothrombotic origin, higher admission diastolic BP, and higher admission glycemia. A multivariable logistic-regression model identified MetS as independently associated with resistance to thrombolysis.
This study demonstrates the existence of sex differences in the impact of MetS on the resistance to systemic thrombolysis for acute MCA ischemic stroke. Confirming the results of a
previous study by our group, we found that the MetS was independently associated with a higher resistance to clot lysis after t-PA therapy, this time in a substantially larger series of patients. This finding could be explained by a derangement of the endogenous fibrinolytic system related to insulin resistance, a key feature of MetS, as suggested by previous work in this field. Nevertheless, the main novelty of the present study is that the effect of MetS in hampering the arterial recanalization process appeared to be more pronounced in women than in men. Moreover, MetS emerged as an independent predictor of poor long-term outcome in patients with acute MCA stroke treated with intravenous t-PA. Future research should clarify whether this association between MetS and poor outcome is explained only by

Table 2. Variables Associated With Resistance to Thrombolysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arterial Recanalization (n=72)</th>
<th>Resistance to Lysis (n=53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y 67.2±12.1</td>
<td>67.9±9.5</td>
<td>0.731</td>
<td></td>
</tr>
<tr>
<td>Sex, male 43 (59.7)</td>
<td>32 (60.4)</td>
<td>0.941</td>
<td></td>
</tr>
<tr>
<td>Smoking 31 (43.1)</td>
<td>24 (45.3)</td>
<td>0.804</td>
<td></td>
</tr>
<tr>
<td>Hypertension 44 (61.1)</td>
<td>34 (64.2)</td>
<td>0.729</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (type 2) 11 (15.3)</td>
<td>19 (35.8)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia 37 (51.4)</td>
<td>28 (52.8)</td>
<td>0.937</td>
<td></td>
</tr>
<tr>
<td>MetS 29 (40.3)</td>
<td>47 (88.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Central obesity 43 (59.7)</td>
<td>44 (83)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>High BP 44 (61.1)</td>
<td>35 (66)</td>
<td>0.572</td>
<td></td>
</tr>
<tr>
<td>High fasting glucose (&gt;100 mg/dL) 35 (48.6)</td>
<td>45 (84.9)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>High triglycerides (&gt;150 mg/dL) 8 (11.1)</td>
<td>15 (28.3)</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Low HDL cholesterol 39 (54.2)</td>
<td>26 (49.1)</td>
<td>0.547</td>
<td></td>
</tr>
</tbody>
</table>

Stroke characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arterial Recanalization (n=72)</th>
<th>Resistance to Lysis (n=53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset to start of t-PA, min 141.9±34.6</td>
<td>136.4±34.2</td>
<td>0.383</td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS score 15 (9–19)</td>
<td>17 (11–20)</td>
<td>0.229</td>
<td></td>
</tr>
<tr>
<td>Proximal vs distal MCA occlusion 40 (55.6)/32 (44.4)</td>
<td>32 (64)/21 (39.6)</td>
<td>0.590</td>
<td></td>
</tr>
<tr>
<td>Early CT signs 25 (34.7)</td>
<td>20 (38.5)</td>
<td>0.785</td>
<td></td>
</tr>
<tr>
<td>TOAST category (AT/CE) 14 (19.4)/43 (59.7)</td>
<td>20 (38.5)/20 (38.5)</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Admission temperature, °C 36.1±0.6</td>
<td>36.1±0.4</td>
<td>0.640</td>
<td></td>
</tr>
<tr>
<td>Admission systolic BP, mm Hg 148.9±22</td>
<td>154±20</td>
<td>0.191</td>
<td></td>
</tr>
<tr>
<td>Admission diastolic BP, mm Hg 77.3±14</td>
<td>82.9±15</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>Prebolus glycemia, mg/dL 107.5 (95–121)</td>
<td>127 (107–174)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>On statin treatment 15 (20.8)</td>
<td>5 (9.4)</td>
<td>0.359</td>
<td></td>
</tr>
<tr>
<td>On antiplatelet therapy 25 (34.7)</td>
<td>16 (32)</td>
<td>0.928</td>
<td></td>
</tr>
<tr>
<td>With neuroprotectants 16 (22.2)</td>
<td>7 (13.2)</td>
<td>0.387</td>
<td></td>
</tr>
</tbody>
</table>

Results are mean±SD, No. (%), or median (interquartile range), as appropriate.
MetS-related resistance to lysis or whether there are other factors involved, such as early stroke recurrence or reocclusion.

Several studies have provided evidence that women have worse outcomes than men after ischemic stroke.14,15 Whether women have a different clinical response to intravenous t-PA than men remains a controversial issue. A meta-analysis of 3 thrombolytic trials showed that women may benefit more from thrombolysis for acute stroke than men.16 In contrast, a secondary analysis of the Glycine Antagonist in Neuroprotection (GAIN) clinical trial found that men were 3 times as likely to achieve functional independence as women.17 Regarding the likelihood of arterial recanalization, there is insufficient evidence of a differential response to thrombolysis by sex. Although some studies suggested that arterial occlusions may recanalize more frequently in women after intravenous t-PA,18 there is no published evidence of differential early recanalization by sex in clinical trials of intra-arterial thrombolysis.19 In our study, neither stroke outcome nor recanalization rate differed between men and women. In this context, our main results may provide an additional explanation for the well-documented sex differences in stroke outcome and for the suggested lack of therapeutic benefit of t-PA in women. The MetS, which is highly prevalent among acute stroke patients, appears to have a more profound effect on the resistance to thrombolysis, once the protection provided by estrogens is lost.21

The reasons for this sex difference in the impact of MetS on the response to t-PA therapy remain speculative. First, insulin resistance, the underlying pathophysiologic mechanism of MetS, might be more pronounced in postmenopausal women than in men. In this setting, pediatric studies have shown that girls are intrinsically more insulin resistant than boys, and this difference may reappear later in life, once the protection provided by estrogens is lost.21 Second, insulin resistance might lead to a more intense impairment of the fibrinolytic system in women than in men. It has been shown that women with type 2 diabetes mellitus have higher plasma level of plasminogen activator inhibitor-1 and coagulation factor VII than their male counterparts,22 and similar findings have been observed in subjects with coronary artery disease.23 In addition, a greater degree of fibrinolytic derangement has been described in prediabetic women compared with men.24 Finally, both mechanisms might interact synergistically. Clarification of the basic pathways responsible for this sex difference seems essential to improve the therapeutic efficacy of t-PA in both sexes. Future clinical and basic research should investigate the role of insulin resistance and defective fibrinolysis in determining a differential response to t-PA in women.

Our results are in agreement with a growing body of evidence demonstrating that the effect of MetS on vascular disease is more pronounced in women than in men.2,3,5 The prognostic impact of MetS in terms of the associated risk of incident coronary events or ischemic stroke was almost invariably found to be greater in females.25 Moreover, the MetS appeared to be a stronger risk factor for early carotid atherosclerosis in women than in men.26 The origin of this sex difference has not been sufficiently explained. There is limited evidence supporting the presence of a genetic basis for this difference. The GENNID study, a genome-wide search for type 2 diabetes susceptibility genes, has identified several chromosomal regions linked to diabetes and impaired glucose tolerance, 1 of which was located on the X chromosome.26 In addition, an influence of sex on several of the components of the MetS was reported from investigations among male and female twins.27 This notion of a sex difference in the impact of the subcomponents of the MetS is also consistent with our results. In women, obesity showed the strongest impact on the resistance to thrombolysis, whereas blood glucose ranked first in men.

This study has several limitations. First, the sample size was small. Second, obesity was measured by BMI as an index of total body fat, rather than by waist circumference, which is a better indicator of abdominal fat. Third, 23 of our patients were enrolled in acute stroke clinical trials with neuroprotective drugs, although they were equally distributed among the study groups. Fourth, the definition of MetS used in the study included poststroke measurement of blood glucose, cholesterol, and triglycerides 72 to 96 hours after admission. Stress hyperglycemia occurs in a high proportion of acute stroke patients, and the effect of stroke on cholesterol is poorly investigated, so it is possible that the concentrations used for defining MetS in this study do not accurately reflect prestroke metabolic status. Moreover, whether the defined thresholds for MetS still hold after an acute event are unclear. Fifth, regarding predictive models, many variables were tested in bivariate analyses despite a fairly small number of end points, although adjustment by all potential confounders was adequately performed in the logistic-regression models. Finally,

### Table 3. Impact of MetS Subcomponents on the Resistance to Thrombolysis in Men and Women

<table>
<thead>
<tr>
<th>Subcomponent</th>
<th>Men</th>
<th>Women</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.6 (0.9–7.3)</td>
<td>9.7 (1.1–82.1)</td>
<td>3.5 (1.4–8.4)</td>
</tr>
<tr>
<td>High BP</td>
<td>0.9 (0.3–2.4)</td>
<td>1.9 (0.5–6.8)</td>
<td>1.2 (0.6–2.6)</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>10.1 (2.7–38.3)</td>
<td>3.4 (1.0–11.9)</td>
<td>5.9 (2.5–14.4)</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>3.8 (1.0–13.8)</td>
<td>2.5 (0.6–10.3)</td>
<td>3.1 (1.2–8.1)</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>0.6 (0.2–1.7)</td>
<td>1.1 (0.4–3.4)</td>
<td>0.8 (0.4–1.7)</td>
</tr>
</tbody>
</table>

Results of logistic-regression analyses as ORs and (95% CIs). For each subcomponent, 3 different unadjusted logistic-regression analyses were performed: the first in men (left column), the second in women (middle column), and the third for the whole sample (right column).
environmental factors, such as socioeconomic background, degree of education, or quality of premorbid risk factor control, were not assessed in our study. Therefore, our results should be cautiously interpreted and replicated in a larger series of patients.

In conclusion, the MetS is associated with a higher resistance to intravenous t-PA for acute MCA ischemic stroke in women than in men. Sex differences in the MetS effect on cerebrovascular disease cannot be sufficiently explained by available data, thus warranting further research on this topic.

Source of Funding
This study was funded by grants from the Spanish research network RETICS-RD06/0026 (RENEVAS).

None.

References
The Metabolic Syndrome Is Associated With a Higher Resistance to Intravenous Thrombolysis for Acute Ischemic Stroke in Women Than in Men
Juan F. Arenillas, Patricio Sandoval, Natalia Pérez de la Ossa, Mónica Millán, Cristina Guerrero, Domingo Escudero, Laura Dorado, Elena López-Cancio, José Castillo and Antoni Dávalos

Stroke. published online December 24, 2008;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2008/12/24/STROKEAHA.108.531079.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/