Gender Differences in Outcomes Among Patients With Symptomatic Intracranial Arterial Stenosis

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Background and Purpose—There are limited and conflicting data on gender differences in clinical outcomes among patients with symptomatic intracranial arterial stenosis. This study examined gender differences in patients enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study.

Methods—Participants were 569 men and women with symptomatic intracranial arterial stenosis. They were followed-up for the occurrence of ischemic stroke and the combined end point of stroke or vascular death from February 1999 through July 2003 (mean follow-up, 1.8 years).

Results—Two-year rates of the primary end point were 28.4% and 16.6% for women and men, respectively. Cumulative probabilities of the outcomes over time were estimated by the Kaplan-Meier product-limit method and were compared between men and women with the use of the log-rank test. Cox proportional hazards regression analyses were used to estimate the hazard ratio of gender (women to men) for ischemic stroke and for the primary end point. The probabilities of ischemic stroke ($P=0.005$) and of the combined end point of stroke or vascular death ($P=0.017$) over time were significantly higher in women than men. Women had a greater multivariate-adjusted risk for ischemic stroke (HR, 1.85; 95% CI, 1.14 to 3.01; $P=0.013$) and for the combined end point of stroke or vascular death (HR, 1.58; 95% CI, 1.01 to 2.48; $P=0.045$).

Conclusions—Women with symptomatic intracranial arterial stenosis are at significantly greater risk for ischemic stroke and for the combined end point of stroke or vascular death. These findings suggest the need for vigorous screening of risk factors and for aggressive management of risk factors and stroke in women. They also suggest the need to ensure adequate numbers of women in clinical trials designed to explore new and promising therapies for intracranial arterial stenosis. (Stroke. 2007;38:2055-2062.)

Key Words: cerebrovascular disease ■ gender ■ intracranial arterial disease ■ risk factors

Intracranial arterial stenosis is a significant risk factor for vascular events, having been implicated as a causal factor in 8% to 10% of all ischemic strokes, and as a major factor in recurrent stroke and vascular mortality. The burden of intracranial stenosis is not equally distributed across demographic strata. The disease has been reported as more common in blacks, Hispanics, and Asians than in whites and as more severe in blacks and Asians. The risk of intracranial stenosis increases with advancing age. There are also reports of gender differences in the prevalence and severity of intracranial stenosis, but those studies are few in number and provide conflicting results. In a review of early clinical studies, a female preponderance of intracranial stenosis and a male preponderance of extracranial disease were reported. However, more recent clinical evidence has indicated a male preponderance of intracranial stenosis. Moreover, data from early autopsy series indicated that cerebral atherosclerosis (both intracranial and extracranial) was more prevalent and more severe in men, particularly between the ages of 40 and 60. An additional autopsy study showed that the degree of endothelial surface involvement by raised intracranial atherosclerotic lesions was greater in men at nearly every age.

Compounding the limited data on gender differences in the prevalence and severity of intracranial stenosis is the paucity of data on gender differences in clinical outcomes among patients with this disease. To address this issue, the current analysis examined gender differences in the risk for outcome events among patients enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study. In view of a male preponderance of intracranial atherosclerosis in most previous studies and population-based evidence of a higher incidence of stroke and higher rates of stroke recurrence in men than in women, we hypothesized that men would have a greater risk for ischemic stroke and for the combined outcome of stroke or vascular death in WASID.
Materials and Methods

Study Population
Participants were 569 men and women who were enrolled in the WASID Study. WASID was a randomized multi-site clinical trial performed in 59 medical centers in North America (58 United States, 1 Canada) from February 1999 through July 2003. This trial compared the efficacy of warfarin versus aspirin for preventing stroke or vascular death in patients with symptomatic stenosis of a major intracranial artery. Details of the WASID study design and results of the comparison of warfarin and aspirin have been previously published. Patients were eligible to participate in WASID if they met the following eligibility criteria: 40 years of age or older; a transient ischemic attack or nondisabling stroke that occurred within 90 days before being randomized into the study; angiographically confirmed stenosis (50% to 99%) of a major intracranial artery (carotid siphon, middle cerebral, vertebral, or basilar); and a modified Rankin score of ≤ 3. Patients were excluded if they had 50% to 99% stenosis of the extracranial carotid artery tandem to an intracranial carotid or middle cerebral artery stenosis; nonatherosclerotic stenosis of an intracranial artery; an embolism of cardiac origin; a contraindication for aspirin or warfarin therapy; a requirement for heparin therapy on study entry; or a comorbid condition that predicted short-term survival (eg, ≤ 5 years). Each site’s Institutional Review Board approved the study protocol and all patients gave written informed consent to participate.

Assessment of Baseline Characteristics
All baseline data were obtained on entry into the trial. Age, race/ethnicity, educational level, marital status, employment status, living arrangement, insurance status and type, physical activity levels, alcohol use, smoking status, and medical history were self-reported. The racial/ethnic designations were as follows: American Indian, Asian, black, Hispanic, white, and other. Race/ethnicity was assessed because of the well-known racial/ethnic disparities in the occurrence of stroke. A history of coronary artery disease was defined as having a history of myocardial infarction, history of angina, coronary angioplasty, or coronary artery bypass surgery. Values for lipid levels were obtained from the medical record if they had been measured within 90 days before enrollment in the trial. If this condition had not been met, these measurements had to be taken within 48 hours of the qualifying event or between 6 weeks and 4 months after the qualifying event because cholesterol levels may decline after acute stroke. Blood pressures were obtained from the right arm while the patient was in a seated position. Hypertension was defined as the average of 2 blood pressure readings taken 5 minutes apart with systolic blood pressure > 160 mm Hg, or diastolic blood pressure > 95 mm Hg, or use of antihypertensive medication. Diabetes was defined as at least 2 fasting venous serum glucose levels > 125 mg/dL, or oral hypoglycemic medication use, or insulin therapy.

Assessment of End Points
Patients were followed-up for a mean of 1.8 years (maximum, 4.5 years). Endpoints were ascertained through monthly telephone contacts with patients or family members and 4-month clinical examinations by a neurologist who was blinded to the patients’ study group assignment. All patients suspected of having a stroke underwent brain MRI or CT. The 2 main outcomes considered in the current analysis were ischemic stroke and the combined end point of stroke events or death from vascular causes other than stroke. The latter was the primary end point in the therapeutic trial. The diagnostic criterion for ischemic stroke was a new focal neurologic deficit of sudden onset lasting at least 24 hours, unrelated to a hemorrhage on brain CT scanning or MRI. Death from vascular causes other than stroke included sudden death or death within 30 days after a myocardial infarction, pulmonary embolism, rupture of an aortic aneurysm, acute ischemia of a limb or internal organ, subdural or subarachnoid hemorrhage, or major systemic hemorrhage. Independent panels of neurologists and cardiologists who were blind to the participants’ study group assignments adjudicated all study end points.

Statistical Analysis
Because there were no differences in the outcome of patients treated with warfarin versus aspirin in the WASID trial, all patients were included in this analysis. Baseline sociodemographic and lifestyle characteristics, comorbid conditions, family history of vascular disease, angiographic findings, and characteristics of the qualifying event were examined for differences between women and men. The χ² test (or Fisher exact test, when appropriate) was used to test differences in proportions for categorical variables. An independent sample test was used to test differences in means for the continuous variables. Cumulative probabilities of the outcomes over time were estimated by the Kaplan-Meier product-limit method and were compared between men and women with the use of the log-rank test. Cox proportional hazards regression analyses were used to estimate the hazard ratio of gender (women to men) for ischemic stroke and for the primary end point adjusted for other factors. Four consecutively nested hierarchical regression models were fit for each analysis. Model 1 included gender only. Model 2 was adjusted for the standard stroke risk factors of age, race/ethnicity, history of hypertension, history of diabetes, cigarette smoking, and history of lipid disorders. Model 3 included model 2 factors along with the factors that were unbalanced between men and women in univariate analysis, which were marital status, alcohol drinking, physical activity, diastolic blood pressure, history of coronary artery disease, anterior versus posterior circulation, and qualifying event (TIA or stroke), body mass index. Model 4 included model 3 factors along with factors related to the primary end point (severe stenosis and time from qualifying event to enrollment) and stroke severity (NIH Stroke Scale). Statistical significance was set at α level of 0.05. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

Results
Three-hundred fifty men and 219 women were included in this analysis. The mean ages were 63.8 (SD, 11.5) and 63.2 (SD, 11.4) for men and women, respectively. Descriptive analysis of baseline sociodemographic characteristics indicated that women, compared with men, were proportionally higher black, unmarried, widowed, separated/divorced, unemployed, or living alone (Table 1). Women were more sedentary but less likely to consume alcohol or to have ever smoked cigarettes (Table 2). Regarding comorbidity, women had higher body mass indexes, and higher total and high-density lipoprotein cholesterol levels. In addition, women were more likely to be free of coronary artery disease, and were more likely to have a family history of stroke and stenosis involving the anterior cerebral circulation, most likely attributable to increased stenosis of the middle cerebral artery (Table 3). There were no significant differences between men and women in the proportions with severe (70% to 99%) stenosis. During the follow-up period, 59 combined end points (nonfatal/fatal strokes or nonstroke-related vascular deaths) were documented in women and 66 in men: the 2-year rates were 28.4% and 16.6% for women and men, respectively. Of the combined end points, 106 (8 fatal) were recurrent ischemic stroke events (53 in men and 53 in women), 3 hemorrhagic strokes (2 in men and 1 in women), and 16 nonstroke-related vascular deaths (11 in men and 5 in women). The cumulative probability of ischemic stroke (log-rank test, P = 0.005; Figure 1) and of the combined end point of stroke or vascular death (log-rank test, P = 0.02; Figure 2) were higher in women than men, indicating that women had significantly shorter vascular-event free survival. In propor-
Results from this analysis show that compared with their male counterparts enrolled in the WASID trial, women have a higher risk for recurrent ischemic stroke and for the combined end point of stroke or vascular death. In multivariate analyses, adjusting for sociodemographic features, lifestyle, vascular risk factors, angiographic findings, and features of the qualifying event, gender was independently associated with both outcomes, suggesting that these factors could not account for women’s increased risk.

An explanation for our findings is complex and not easily disentangled. Female gender may be a proxy for other factors that are associated with a poor outcome. One such factor is social isolation. Women in this analysis were more likely to be unmarried, widowed, separated/divorced, or living alone. These attributes are markers for social isolation. Social isolation adversely affects health, being positively associated with an increased risk for the onset of a first myocardial infarction, cardiac and all-cause mortality, stroke recurrence, and death after stroke. It is hypothesized that social ties buffer people from the deleterious effects of hardships, traumas, and trials. Social connectedness may also be associated with better compliance with medication, adoption of more positive health behaviors, and greater access to needed resources.

Female gender may also be a proxy for low socioeconomic status. Seventy-five percent of the women in our study had an educational attainment that was at or below high school. Sixty percent were unmarried, 30% widowed, 24% separated/divorced, and 31% were living alone. A low educational attainment level and the state of being unmarried, widowed, separated/divorced, or living alone are highly correlated with a low socioeconomic status. Together, these sociodemographic attributes may be indicative of a group of women who occupy the lower socioeconomic status strata. Such an observation is important because a socioeconomic status gradient has been observed in the risk for stroke, stroke management, and poststroke mortality. Mechanisms for the well-known inverse association between socioeconomic status and health are not fully understood, but are thought to include reduced consumption of health information and lower levels of health literacy, more deleterious health behaviors, reduced access to resources, and greater exposure to psychosocial stress and depression.

It is important to note that women had a greater clustering of risk factors that were indicative of metabolic abnormalities (e.g., high body mass indexes, hypertension, and diabetes) and those that portend increased risk based on sociodemographic features, lifestyle, and family history of stroke. Therefore, the results might have been due to a confluence of adverse baseline factors through which recurrent stroke and vascular death was the final common pathway.

Another potential explanation for the higher risk for stroke in women in this study is vessel size. Women may have smaller intracranial arteries than men, which could pose a greater risk for stroke in the territory of a stenotic intracranial artery. Recent WASID analyses showed that women compared with men had a greater, although marginally statisti-
cally significant, risk for ischemic stroke in the territory of the symptomatic intracranial artery. 25

Recent evidence of a gender-based survival bias among acute myocardial infarction patients may also help to explain the shorter vascular event-free survival among women. The findings have been conflicting at times, but studies have reported higher short-term mortality rates among women with acute myocardial infarction compared with men.26,27 The reasons for decreased short-term survival in women are not well understood. The greater incidence of diabetes in women and its adverse cardio-

TABLE 2. Lifestyle Characteristics, Comorbid Conditions, and Family History of Vascular Disease by Gender

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men, N=350</th>
<th>Women, N=219</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol drinking, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>170 (48.6)</td>
<td>60 (27.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>180 (51.4)</td>
<td>159 (72.6)</td>
<td></td>
</tr>
<tr>
<td>Physical activity level, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedentary</td>
<td>71 (20.3)</td>
<td>76 (34.7)</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>183 (52.3)</td>
<td>98 (44.8)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>76 (21.7)</td>
<td>42 (19.2)</td>
<td></td>
</tr>
<tr>
<td>Vigorous</td>
<td>20 (5.7)</td>
<td>3 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current</td>
<td>77 (22.0)</td>
<td>44 (20.1)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>182 (52.0)</td>
<td>64 (29.2)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>91 (26.0)</td>
<td>111 (50.7)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>28.3 (4.9)</td>
<td>29.3 (5.7)</td>
<td>0.030</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, mean (SD)</td>
<td>139.0 (16.4)</td>
<td>141.1 (18.0)</td>
<td>0.162</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg, mean (SD)</td>
<td>77.9 (9.9)</td>
<td>75.2 (10.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Plasma HDL cholesterol, mg/dL, mean (SD)</td>
<td>41.5 (11.3)</td>
<td>49.0 (15.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma LDL cholesterol, mg/dL, mean (SD)</td>
<td>121.3 (36.2)</td>
<td>126.8 (41.4)</td>
<td>0.131</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL, mean (SD)</td>
<td>193.8 (40.2)</td>
<td>211.5 (47.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, mean (SD)</td>
<td>162.8 (111.0)</td>
<td>178.0 (109.7)</td>
<td>0.136</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td></td>
<td></td>
<td>0.067</td>
</tr>
<tr>
<td>Yes</td>
<td>285 (81.9)</td>
<td>192 (87.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>63 (18.1)</td>
<td>27 (12.3)</td>
<td></td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td></td>
<td></td>
<td>0.057</td>
</tr>
<tr>
<td>Yes</td>
<td>122 (35.0)</td>
<td>94 (42.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>227 (65.0)</td>
<td>125 (57.1)</td>
<td></td>
</tr>
<tr>
<td>History of coronary artery disease, n (%)</td>
<td>105 (30.4)</td>
<td>46 (21.7)</td>
<td>0.024</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>240 (69.6)</td>
<td>166 (78.3)</td>
<td></td>
</tr>
<tr>
<td>History of lipid disorders, n (%)</td>
<td></td>
<td></td>
<td>0.337</td>
</tr>
<tr>
<td>Yes</td>
<td>233 (69.4)</td>
<td>158 (73.2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>103 (30.6)</td>
<td>58 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Family history of stroke, n (%)</td>
<td></td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>Yes</td>
<td>127 (38.8)</td>
<td>104 (50.2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>200 (61.2)</td>
<td>103 (49.8)</td>
<td></td>
</tr>
<tr>
<td>Family history of MI, n (%)</td>
<td></td>
<td></td>
<td>0.465</td>
</tr>
<tr>
<td>Yes</td>
<td>143 (44.6)</td>
<td>98 (47.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>178 (55.4)</td>
<td>107 (52.2)</td>
<td></td>
</tr>
</tbody>
</table>

*χ² test of association or t test for comparison of means.
HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction.

vascular effects has been implicated. This hypothesis has been confirmed in some studies,28,29 but not in others.30,31

It is important to discuss the limitations and strengths of this analysis. A potential weakness is that data concerning lifestyle and medical and familial histories were self-reported and therefore are subject to the inherent biases of this method of data collection, ie, social desirability and inaccuracies resulting from poor recall. A strength of this analysis is the prospective data collection in the WASID study—a design that permits strong evidence of the relationship between
gender and the outcomes. However, the generalizability of these findings may be limited since patients were mostly drawn from university medical centers and recruited according to strict eligibility criteria of a clinical trial. For this reason, replication in population-based studies is needed. Other strengths include the use of conventional angiography to assess intracranial stenosis and the use of objective criteria to determine the end points.

Compared with men, women with symptomatic intracranial arterial stenosis are at significantly greater risk for recurrent ischemic stroke and for the combined end point of stroke or vascular death. These findings are contrary to expectation and emphasize the need to shift our perception of gender disparities in cerebrovascular disease. Equally important, they call for action to reduce the stroke burden among women and to improve their chances for survival. Disability, dementia, and death are common stroke sequelae. Findings from our analysis suggest that the stroke burden in women might be particularly high.

There are other implications of our findings. They suggest the need to ensure adequate numbers of women in clinical trials designed to explore new and promising therapies for intracranial arterial stenosis. Clinically, they suggest the need for vigorous screening of risk factors and for aggressive management of risk factors and stroke in women. From a public health perspective, they suggest the need for more effective broad-based interventions directed at the primary prevention of risk factors. In the context of a generally poor prognosis for intracranial arterial stenosis and the current climate of uncertainty regarding optimal therapy, primary prevention of the risk factors is urgently needed.
Appendix

Administrative Structure and Participants

Operations Committee
M. Chimowitz, M. Lynn, H. Howlett-Smith, B. Stern, V. Hertzberg, G. Cotsonis. Emory University, Atlanta, Ga

Clinical Coordinating Center (CCC)
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B. Tilley

Anticoagulation Consultant
J. Ansell

Internal Safety Monitor
K. Smith

Internal Clinical Event Monitor
J. Khan

NIH/NINDS Liaison
B. Radziszewska, J. Marler

Performance and Safety Monitoring Committee (PSMC)
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Cleveland Clinic Foundation

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University of Miami
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MetroHealth Medical Center, Cleveland
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University of California, San Francisco/San Francisco General Hospital
C. Hemphill, W. Smith, M. Farrant, L. Hewlett, S. Fields. Supported in part by NIH grant M01 RR0083-42 from the General Clinical Research Center at San Francisco General Hospital

TABLE 4. HRs for the Association between Gender and Outcomes (n=510)

<table>
<thead>
<tr>
<th>Regression Models</th>
<th>Ischemic Stroke</th>
<th>Combined End Point of Stroke or Vascular Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (unadjusted)</td>
<td>1.56 (1.04, 2.35)</td>
<td>1.37 (0.94, 2.00)</td>
</tr>
<tr>
<td>Model 2 (age, race/ethnicity, history of hypertension, history of diabetes, cigarette smoking, history of lipid disorders)</td>
<td>1.40 (0.91, 2.16)</td>
<td>1.24 (0.83, 1.84)</td>
</tr>
<tr>
<td>Model 3 (model 2 with marital status, drinking, physical activity, BMI, diastolic blood pressure, history of coronary artery disease, anterior vs posterior circulation, qualifying event (TIA or stroke))</td>
<td>1.76 (1.09, 2.84)</td>
<td>1.50 (0.96, 3.32)</td>
</tr>
<tr>
<td>Model 4 (model 3 with severe stenosis, time from qualifying event, NIH Stroke Scale)</td>
<td>1.85 (1.14, 3.01)</td>
<td>1.58 (1.01, 2.48)</td>
</tr>
</tbody>
</table>

*The HR for women to men.
Vancouver General Hospital
A. Woolfenden, P. Teal, C. Johnston, D. Synnot, J. Busser

Johns Hopkins Medical Center
R. Wityk, E. Aldrich, R. Llinas, K. Lane, T. Trail, L. White, T. Traill. Supported in part by NIH grant M01 RR00052 from the General Clinical Research Center at The Johns Hopkins University School of Medicine

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Oregon Stroke Center

Rush-Presbyterian, St. Luke’s Medical Center
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Marshfield Clinic
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Ochsner Foundation Clinic & Hospital
R. Felberg, A. Cole, K. Fitzpatrick, K. Mckinley, S. Deitelzweig, C. Frisard

Beth Israel Deaconess Medical Center
C. Chaves, I. Linfante, C. Horkan, L. Barron, P. Ryan, D. Tarsey

University of Michigan
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