Gender Differences in the Risk of Ischemic Stroke Associated With Aortic Atheromas

Marco R. Di Tullio, MD; Ralph L. Sacco, MD; Maria Teresa Savoia, MD; Robert R. Sciacca, EngScD; Shunichi Homma, MD

Background and Purpose—Atherosclerotic plaque of the proximal portion of the aorta is associated with an increased risk of ischemic stroke in the elderly. Different cutoffs of plaque thickness have been used in the literature for risk stratification and have been applied to both men and women. However, the assumption that the relationship between plaque thickness and stroke risk is the same in the 2 genders has not been proven. The aim of this study was to evaluate whether the prevalence of different degrees of aortic plaque thickness differed in men and women with ischemic stroke.

Methods—We performed transesophageal echocardiography in 152 patients aged >59 years with acute ischemic stroke (76 men and 76 women) and in 152 control subjects of similar age (70 men and 82 women). Odds ratios (ORs) for ischemic stroke with 95% CIs for different plaque thickness definitions were calculated for the overall group and separately for men and women by logistic regression analysis after adjusting for age, arterial hypertension, and hypercholesterolemia.

Results—Aortic plaques ≥4 mm were significantly more frequent in men than in women (31.5% versus 20.3%, respectively; \( P=0.025 \)) and were associated with ischemic stroke in both men (adjusted OR 6.0, CI 2.1 to 16.8) and women (adjusted OR 3.2, CI 1.2 to 8.8). However, plaques 3 to 3.9 mm in thickness had a significant association with stroke in women (adjusted OR 4.8, CI 1.7 to 15.0) but not in men (adjusted OR 0.8, CI 0.2 to 3.0). Plaques <3 mm were not associated with a significantly increased stroke risk for either sex.

Conclusions—Smaller aortic plaques are significantly associated with ischemic stroke in women but not in men. If the increased prevalence of smaller plaques in women is confirmed to be associated with increased risk for embolic stroke, different cutoff points may have to be adopted in men and women for risk stratification and for decisions regarding medical intervention. (Stroke. 2000;31:2623-2627.)

Key Words: aortic arch ■ cerebrovascular disorders ■ echocardiography, transesophageal ■ stroke, ischemic

The presence of atherosclerotic plaques in the proximal portion of the aorta has been shown to be associated with an increased risk of ischemic stroke in the elderly. Stroke risk has been shown to increase progressively with increasing plaque thickness, but cutoff points of steeper increase in risk have also been identified. A cutoff point of 4 mm has been widely used for risk stratification on the basis of the results of the largest studies on this topic, but a value of 5 mm has also been used in other studies. Regardless of the value chosen, these cutoff points have been considered to apply to both men and women, under the assumption that the stroke risk associated with an atherosclerotic plaque should not be affected by the gender of the patient. However, the role of aortic plaque as a risk factor for stroke has not been evaluated independently in men and women to test this assumption. The aim of the present study was to assess the stroke risk associated with proximal aortic plaque separately in men and women and to identify gender-specific cutoff points to be used for stroke risk stratification.

Subjects and Methods

A case-control study was conducted between 1992 and 1995 on 152 patients aged >59 years with acute ischemic stroke (76 men and 76 women) and 152 control subjects of similar age (70 men and 82 women). Methods for patient recruitment have been published previously. Briefly, eligible stroke patients were any patients of appropriate age in the acute stage of an ischemic stroke consecutively referred to the echocardiography laboratory for transesophageal echocardiography (TEE) as a part of their diagnostic workup. Controls were stroke-free subjects undergoing TEE over the same period of time for reasons unrelated to cerebrovascular or systemic embolism. The present study was approved by the institutional review board. All patients provided their informed consent to participate in the study.

Results of the analysis of the association between aortic atheroma and ischemic stroke in the same population have been published previously. The present article reports on a subset analysis by gender and with the application of various atheroma thickness cutoffs.

Diagnostic Evaluation

The presence of cardiovascular risk factors was ascertained by means of interview and review of medical records. Arterial hypertension...
was defined as blood pressure $>$ 160/90 mm Hg during the admission, a positive history, or the presence of antihypertensive treatment. Diabetes mellitus was defined on the basis of positive history or appropriate medical treatment. Hypercholesterolemia was defined as a total serum cholesterol $>$ 200 mg/dL at admission or the presence of appropriate medical treatment.

Neuroimaging studies in stroke patients consisted of head CT or MRI, carotid duplex Doppler examination, transcranial Doppler ultrasound examination of the anterior and middle cerebral arteries and basilar arteries, and cerebral angiography when clinically indicated.

Cardiac evaluation included 12-lead ECG, transthoracic echocardiography, and biplane or multiplane TEE with use of a 5-MHz transducer.

Based on the diagnostic evaluation described above, stroke diagnostic subtypes were defined by a neurologist aware of the results of imaging studies. Among stroke patients, the stroke mechanism was considered to be atherosclerotic in 22%, cardioembolic in 28%, and lacunar in 12%; the remaining 38% were considered to have a cryptogenic stroke.

Detection of Aortic Plaques
The aorta was imaged in both transverse and longitudinal views. The proximal aorta was defined as the portion of the vessel between the aortic valve and the takeoff of the left subclavian artery. Plaques were defined as discrete protrusions of the intimal surface with different appearance and echogenicity from the adjacent intact portion. The thickness of the plaque was measured perpendicular to the lumen of the vessel by means of appropriate computer software. In the case of multiple plaques, the thickest was considered for stroke-risk analysis. The presence of ulcerations or mobile components was recorded. The interpretation of the studies was performed by a single experienced observer, blinded to case-control status. A reproducibility analysis at our laboratory for plaque thickness measurement showed a mean variability of 0.21 mm. An example of plaque measurement is provided in the Figure.

Statistical Analysis
Differences between mean values were assessed by Student $t$ test for unpaired data, and differences between proportions were assessed by $\chi^2$ test, replaced by Fisher exact test in the case of an expected cell count < 5. Unadjusted odds ratios for stroke of different plaque thicknesses (2 to 2.9 mm, 3 to 3.9 mm, and $\geq$ 4 mm) were calculated by means of logistic regression analysis (SAS statistical package, version 6.12) for the overall group and separately for each gender. Adjusted odds ratios for different plaque thicknesses were then calculated by multivariate logistic regression analysis, including variables identified as associated with stroke by univariate analysis (arterial hypertension and hypercholesterolemia) and age (biologically relevant variable) as independent variables. The adjustment for hypertension and hypercholesterolemia as dichotomous (present versus absent) or continuous (blood pressure values and serum cholesterol levels) variables did not significantly affect the risk estimates. Odds ratios obtained with dichotomous variable definitions will be presented in Results.

Results

Study Population
Table 1 summarizes the distribution of traditional stroke risk factors among cases and controls in the overall study population (ie, regardless of the gender of the patient) and in each gender subgroup. Hypercholesterolemia was found to be significantly associated with ischemic stroke in the overall group and in both genders. Arterial hypertension was significantly associated with stroke in men but not in women. Cigarette smoking and diabetes mellitus were not found to be significantly associated with stroke in either sex. The proportion of patients with previous stroke or carotid stenosis $>$ 60% was not significantly different between men and women.

Among stroke patients, the stroke mechanism was considered to be atherosclerotic in 22%, cardioembolic in 28%, and lacunar in 12%; the remaining 38% were considered to have a cryptogenic stroke.

A patent foramen ovale was found in 37 stroke patients (24.5%), without significant differences between women (18 patients [24%]) and men (19 patients [25%]).

In the 70 stroke patients in the present study who had serum fibrinogen levels tested, abnormal levels were found in a significantly higher proportion of women (28 [80%] of 35 patients) than men (17 [49%] of 35 patients, $P = 0.006$).

<table>
<thead>
<tr>
<th>TABLE 1. Stroke Risk Factor Distribution in Overall Group and by Sex</th>
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<tbody>
<tr>
<td>Overall Group</td>
</tr>
<tr>
<td>Cases, %</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
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<tr>
<td><strong>High cholesterol</strong></td>
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<tr>
<td><strong>Cigarette smoking</strong></td>
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<tr>
<td><strong>Carotid stenosis $&gt;$ 60%</strong></td>
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<td><strong>Prior stroke</strong></td>
</tr>
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</table>
Frequency of Aortic Plaques
Aortic plaques of any size were found in >70% of the study population (224 of 304 subjects), without significant differences between men (108 [74%] of 146 subjects) and women (113 [72%] of 158 subjects). Plaques ≥4 mm in thickness were significantly more frequent in men than in women (31.5% versus 20.3%, respectively; P=0.001) and in women (17.1% versus 3.7%, respectively; P=0.001). The present study documented an increased risk have been proposed 5–8 and represent the best option when trying to assess stroke risk in individual patients. This approach is usually applied to all patients regardless of gender, under the assumption that (all other conditions being equal) stroke risk is similar in men and women for any given aortic plaque thickness. This reasoning is based on data from some of the main studies on the topic, 5–8 in which results have been adjusted for gender as one of the potential confounding variables of the association between aortic plaque and stroke in multivariate analyses. However, the separate gender analysis in the present study suggests that the same cutoff points may not be equally suited for risk stratification in men and women. Smaller plaques are significantly associated with an increased stroke risk in women but not in men. This observation adds to the body of knowledge on the role of aortic plaques as stroke risk factors in the elderly. In the literature, stroke risk has been shown to increase with increasing plaque thickness.5 Cutoff points of sharply increased risk have been proposed5–8 and represent the best option when trying to assess stroke risk in individual patients. Why smaller plaques are significantly associated with ischemic stroke in women but not in men is not immediately clear. It should be noted that the present study documented an epidemiological association between smaller plaques and stroke in women but did not seek to establish a causative link between these plaques and the stroke mechanism in individ-

### Table 2. Association Between Aortic Arch Atheroma Thickness and Ischemic Stroke in Overall Group and by Sex

<table>
<thead>
<tr>
<th>Atheroma Thickness</th>
<th>Stroke Patients (N=152)</th>
<th>Control Subjects (N=152)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–2.9 mm</td>
<td>n=26, %17.1</td>
<td>n=41, %27.0</td>
<td>1.25 (0.64–2.43)</td>
<td>1.46 (0.70–3.05)</td>
</tr>
<tr>
<td>Overall group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>n=13, %8.9</td>
<td>n=18, %25.7</td>
<td>1.11 (0.42–2.91)</td>
<td>1.29 (0.43–3.82)</td>
</tr>
<tr>
<td>Women</td>
<td>n=13, %17.1</td>
<td>n=23, %28.1</td>
<td>1.39 (0.55–3.55)</td>
<td>1.55 (0.55–4.41)</td>
</tr>
<tr>
<td>3–3.9 mm</td>
<td>n=30, %19.7</td>
<td>n=27, %17.8</td>
<td>2.18 (1.09–4.36)</td>
<td>2.59 (1.18–5.69)</td>
</tr>
<tr>
<td>Overall group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>n=10, %13.2</td>
<td>n=14, %20.0</td>
<td>1.10 (0.39–3.10)</td>
<td>0.84 (0.23–3.00)</td>
</tr>
<tr>
<td>Women</td>
<td>n=20, %26.3</td>
<td>n=13, %15.9</td>
<td>3.79 (1.46–9.80)</td>
<td>4.98 (1.65–15.0)</td>
</tr>
<tr>
<td>≥4 mm</td>
<td>n=68, %44.7</td>
<td>n=29, %19.1</td>
<td>4.61 (2.46–8.64)</td>
<td>4.51 (2.25–9.05)</td>
</tr>
<tr>
<td>Overall group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>n=38, %50.0</td>
<td>n=15, %21.4</td>
<td>3.88 (1.61–9.40)</td>
<td>5.97 (2.13–16.8)</td>
</tr>
<tr>
<td>Women</td>
<td>n=30, %39.5</td>
<td>n=14, %17.1</td>
<td>5.28 (2.14–13.0)</td>
<td>3.21 (1.17–8.80)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
*Adjusted for age, arterial hypertension, and hypercholesterolemia.

Association Between Aortic Plaques and Ischemic Stroke
The association between aortic plaque thickness and stroke for the overall group (ie, regardless of the gender of the patient) and for each gender subgroup is reported in Table 2. Plaques ≥4 mm in thickness were strongly associated with stroke in both the overall group and in each gender subgroup. The significant association persisted after adjustment for other stroke risk factors. Plaques 3 to 3.9 mm in thickness were also significantly associated with ischemic stroke in the overall group, but breakdown of the data by gender revealed that the association was present only in women. This remained true after adjustment for other stroke risk factors. Plaques of <3 mm in thickness were not found to be associated with ischemic stroke in either sex. Ulcerated or mobile plaques were significantly more frequent in stroke patients than in control subjects in the overall group (22.4% versus 2.6%, respectively; P=0.001) and in both men (27.6% versus 1.4%, respectively; P=0.001) and women (17.1% versus 3.7%, respectively; P=0.001). The small number of subjects with ulcerated or mobile lesions in the control group prevented the performance of a multivariate analysis.

Discussion
The present study demonstrates that the thickness of atherosclerotic plaques in the proximal portion of the aorta has a different association with the risk of ischemic stroke in men and women. Smaller plaques are significantly associated with an increased stroke risk in women but not in men. This observation adds to the body of knowledge on the role of aortic plaques as stroke risk factors in the elderly. In the literature, stroke risk has been shown to increase with increasing plaque thickness.5 Cutoff points of sharply increased risk have been proposed5–8 and represent the best option when trying to assess stroke risk in individual patients. This approach is usually applied to all patients regardless of gender, under the assumption that (all other conditions being equal) stroke risk is similar in men and women for any given plaque thickness. This reasoning is based on data from some of the main studies on the topic, 5–8 in which results have been adjusted for gender as one of the potential confounding variables of the association between aortic plaque and stroke in multivariate analyses. However, the separate gender analysis in the present study suggests that the same cutoff points may not be equally suited for risk stratification in men and women and that lower cutoff points may have to be used for women.
ual patients. Therefore, the actual role of these smaller plaques as a source for embolic stroke is not determined in the present study. Plaque thickness may be a marker of other underlying processes (such as extensive small-vessel atherosclerosis) that may play different roles in the 2 genders. It has been suggested that the greater stroke risk associated with larger plaques may be due to the more frequent presence on them of thrombotic material, which could be responsible for both the greater plaque thickness and its increased embolic potential. Larger plaques have in fact been shown to be highly dynamic lesions, in which thrombus formation and resolution continuously occur. Our findings are not incompatible with this hypothesis, because all of the ulcerated or mobile plaque components, suggestive of previous or current thrombus presence, were observed in the present study in plaques ≥4 mm thick. These complex lesions were strongly associated with stroke in both men and women in the present study as well as in previous studies. As we have recently reported for the same population, large complex plaques appear as a possible culprit for stroke, whereas equally large but noncomplex lesions are associated with only a modest increase in stroke risk. This combined information seems to suggest that although complex morphological features of the plaque may be directly involved in the stroke mechanism, plaque thickness in itself may primarily be a marker of increased risk, the underlying reasons for which may somewhat differ between men and women. Cofactors may exist (such as hypercoagulable states or lipid abnormalities) that may be differently distributed between men and women. In a subgroup of 70 stroke patients in the present study who had serum fibrinogen levels tested, abnormal levels were found in a significantly higher proportion of women (28 [80%] of 35 patients) than men (17 [49%] of 35 patients, P = 0.006). Elevated fibrinogen levels have been shown to be a risk factor for cardiovascular disease and stroke and to be associated with the degree of carotid stenosis, especially in the elderly. Atherogenic effects of fibrinogen have been described, possibly as the result of its interactions with some lipoproteins, such as lipoprotein(a) and HDL. Finally, fibrinogen levels have been shown to be associated with the severity of aortic atherosclerosis detected by TEE, as in the present study. The study of hemostatic markers and lipoprotein profiles as potential cofactors might allow further insight into the mechanism of the association between aortic plaques and stroke and might possibly explain some of the gender differences we observed.

The therapeutic options in patients with ischemic stroke and proximal aortic plaques remain to be determined. Anticoagulation appears indicated in the case of complex lesions, because there is evidence that it may reduce the stroke recurrence rate. Preliminary evidence has also been reported of a beneficial effect of anticoagulation in patients with large noncomplex plaques, but more data are needed to confirm this indication. Aortic arch endarterectomy in patients with high-risk lesions has been shown to be associated with considerable morbidity and mortality and should be reserved for selected cases. The present study suggests that differences in risk between men and women should also be kept in mind and that further investigation is needed, along with data on possible cofactors of increased risk and potential alternative treatments (eg, antiplatelet agents and lipid-lowering drugs). Estrogen replacement therapy could also be considered in postmenopausal women, because it has been shown to reduce both fibrinogen and LDL cholesterol levels.

The present study has some limitations. Doppler examination of the carotid arteries was not performed in control subjects; therefore, its effect on the risk of stroke in men and women could not be factored into the analysis. However, among stroke patients, no significant difference was observed in the frequency of carotid stenosis between men and women, making the possibility of a significant effect of carotid disease as a confounding factor of the association between aortic plaque and stroke unlikely. Control subjects were patient controls rather than normal volunteers. However, clinical indications for TEE did not differ between men and women; therefore, the patients’ underlying clinical conditions should not have affected the intergender analyses performed.

In conclusion, the present study demonstrated that differences exist between men and women in the relationship between aortic plaque thickness and risk of ischemic stroke. This observation and the possible need for different cutoff points of increased risk should be kept in mind when assessing stroke risk in individual patients. The significance of these differences and their explanation require further investigation.

Acknowledgments

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