The presence of atherosclerotic plaques in the aortic arch is a risk factor for ischemic stroke. The association between atherosclerosis in the aortic arch and stroke risk was initially established in autopsy studies and subsequently confirmed by in vivo studies that used transesophageal echocardiography (TEE) to identify the plaques and to evaluate the associated risk of stroke with a case-control or a prospective design. Large complexes of plaques have not yet been established. Anticoagulation has been advocated occasionally in plaques with superimposed mobile components suggestive of thrombus. However, the role of anticoagulation in the far larger subset of patients with large but nonmobile plaques, as well as the role of the more frequently used antiplatelet treatment, has not been elucidated in randomized clinical studies to date. In the present study, we sought to define the adverse event rate in stroke patients with large aortic plaques who were double-blindly randomly assigned to warfarin or aspirin treatment as part of the National Institute of Neurological Disorders and Stroke (NINDS)–funded Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), based on the study population of the Warfarin-Aspirin Recurrent Stroke Study (WARSS; NIH R01-NS-28371; J.P.M., principal investigator).

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Methods

Patient Recruitment

PICSS relied on WARSS for patient recruitment and follow-up. WARSS was a 48-center double-blind study that randomized 2206 patients with large arch plaques (>4 mm) who were double-blindly randomized to treatment with warfarin or aspirin as part of the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), based on the Warfarin-Aspirin Recurrent Stroke Study (WARSS). Plaque thickness and morphology were evaluated by transesophageal echocardiography. End points were recurrent ischemic stroke or death over a 2-year follow-up. Large plaques (>4 mm) were present in 19.6% of patients; large complex plaques (those with ulcerations or mobile components) were seen in 8.5%. During follow-up, large plaques were associated with a significantly increased risk of events (adjusted hazard ratio [HR], 2.12; 95% confidence interval [CI], 1.04 to 4.32), especially those with complex morphology (HR, 2.55; 95%CI, 1.10 to 5.89). The risk was highest among cryptogenic stroke patients, both for large plaques (HR, 6.42; 95% CI, 1.62 to 25.46) and large complex plaques (HR, 9.50; 95% CI, 1.92 to 47.10). Event rates were similar in the warfarin and aspirin groups in the overall study population (16.4% versus 15.8%; P=0.43).

Conclusions

In patients with stroke, especially cryptogenic stroke, large aortic plaques remain associated with an increased risk of recurrent stroke and death at 2 years despite treatment with warfarin or aspirin. Complex plaque morphology confers a slight additional increase in risk. (Circulation. 2009;119:2376-2382.)

Key Words: aorta ■ atherosclerosis ■ echocardiography ■ stroke
stroke patients to either warfarin or aspirin and followed them up for stroke recurrence or death over a 24-month period. A complete list of participating centers and investigators can be found in the online-only Data Supplement. Patient recruitment started in June 1993, and follow-up was completed in June 2000. At each center, cryptogenic stroke patients in WARSS were solicited to undergo TEE for the purposes of PICSS. PICSS also included all WARSS patients who underwent TEE for clinical purposes. Details of the PICSS protocol have been published previously. All protocols for WARSS and PICSS were approved by the Institutional Review Board at each participating center, and informed consent was obtained from each participant.

**Eligibility**
Patients 30 to 85 years of age deemed safe to undergo warfarin therapy were eligible. Eligible patients were those who experienced ischemic stroke within the previous 30 days and rated ≥3 (no or moderate residual disability) on the Glasgow Outcome Scale. Patients were ineligible if they had a baseline international normalized ratio (INR) above the normal range (≥1.4), had had a stroke related to a procedure or attributable to a cardioembolic source, or were scheduled to undergo surgery for high-grade carotid stenosis. Patients with contraindications to TEE also were excluded.

**Stroke Subtyping**
All baseline strokes were subtyped by a local neurology principal investigator on the basis of predefined criteria modeled after the NINDS Stroke Data Bank and Trial of Organon in Acute Stroke Therapy (TOAST). Cryptogenic strokes typically had no definite source despite a thorough diagnostic evaluation.

**Medications and Blinding**
Medications used were aspirin in 325-mg tablets taken once daily and warfarin in 2-mg scored tablets taken daily, adjusted to achieve and maintain an INR of 1.4 to 2.8. Patients were randomized to active aspirin or warfarin and an identical placebo. All patients followed the same schedule of clinic contacts for blood draws for INR, medication monitoring, and warfarin (or warfarin dummy) dose adjustment. All participants other than the principal investigator statistician were blinded.

**Follow-Up**
All patients were followed up for 2 years, operationalized as 24±1 month (maximum, 761 days). Follow-up was done on a monthly basis by telephone or in person to assess compliance and to regulate INRs. Quarterly and annual in-person follow-ups for detailed examination also were made.

**TEE Protocol**
All patients underwent TEE guided by a predefined PICSS protocol using either a biplane or multiplane probe; the videotapes were sent to the core laboratory at Columbia for central analysis. The TEE protocol emphasized delineation of embolic sources, including identification and characterization of aortic arch plaques.

**Analysis of Tapes**
For the purpose of the present report, all videotapes were reviewed by a single experienced echocardiographer (M.R.D.T.) blinded to patient clinical characteristics and treatment status. Aortic plaques were defined as previously published. The aortic arch was defined as the portion of aorta between the curve at the end of the ascending portion and the takeoff of the left subclavian artery. A plaque was defined as a discrete protrusion of the intimal surface of the vessel at least 2 mm in thickness, different in appearance and echogenicity from the adjacent intact intimal surface. The presence and location of any plaque were recorded. In cases of multiple plaques, the most advanced lesion was considered. Plaque thickness was measured as a continuous variable. Plaques were then classified into small (<4 mm) or large (≥4 mm; Figure 1A). The presence of ulcerations or mobile components (Figure 1B) also was recorded. An ulceration was defined as a discrete indentation of the luminal surface of the plaque with base width and maximum depth of at least 2 mm each. Plaques with ulceration and/or mobile components were defined as complex plaques according to a previously published definition.

**Assessment of End Points**
The primary end point was recurrent ischemic stroke or death resulting from any cause. Clinical evidence of a recurrent ischemic stroke was a new lesion on computed tomography or magnetic resonance imaging or, when new lesions were absent, clinical syndrome consistent with stroke of ≥24 hours’ duration. All clinical and radiological events were adjudicated independently by 5 treatment-blinded neurologist-adjudicators. Data from all hemorrhages were submitted to a treatment-blinded adjudicator who classified them as major or minor. Major hemorrhages were defined as intracranial, intraspinal, intracerebral, subarachnoid, subdural, or epidural hemorrhage or any other bleeding requiring transfusion. All other hemorrhagic events were considered minor.

**Statistical Analysis**
The statistical power of the study was calculated with the PASS software (version 2002, NCSS Statistical Software, Kaysville, Utah) with procedure for Cox proportional-hazards model. With the observed events in 516 patients, the overall event rate is assumed to be 16.3%. For continuous measurement of plaque thickness, the observed SD was 1.893, and the ratio of the observed events to the expected events was 16.3%. The statistical power of the study was calculated with the PASS software (version 2002, NCSS Statistical Software, Kaysville, Utah) with procedure for Cox proportional-hazards model. With the observed events in 516 patients, the overall event rate is assumed to be 16.3%. For continuous measurement of plaque thickness, the observed SD was 1.893, and the ratio of the observed events to the expected events was 16.3%.
Table 2. Sociodemographic Variables, Stroke Characteristics, and Risk Factors by Arch Plaque Presence/Thickness

<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th>Entire Group (n=516)</th>
<th>No Plaque (n=179)</th>
<th>Small Plaque (n=236)</th>
<th>Large Plaque (n=101)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.5±12.1</td>
<td>51.7±12</td>
<td>62.7±10</td>
<td>66.1±9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>225/516 (43.8)</td>
<td>78/179 (43.6)</td>
<td>99/236 (42.0)</td>
<td>48/101 (47.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>228/516 (44.2)</td>
<td>77/179 (43.0)</td>
<td>101/236 (42.8)</td>
<td>50/101 (49.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>282/515 (54.8)</td>
<td>94/179 (52.5)</td>
<td>131/235 (55.7)</td>
<td>57/101 (56.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>College educated, n (%)</td>
<td>143/509 (28.1)</td>
<td>58/177 (32.8)</td>
<td>64/233 (27.5)</td>
<td>21/99 (21.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>On Medicaid, n (%)</td>
<td>151/511 (29.6)</td>
<td>60/178 (33.7)</td>
<td>64/234 (27.4)</td>
<td>27/99 (27.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Stroke characteristics, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>214/516 (41.5)</td>
<td>85/179 (47.5)</td>
<td>92/236 (39.0)</td>
<td>37/101 (36.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Glasgow score &lt;5*</td>
<td>176/516 (34.1)</td>
<td>49/179 (27.4)</td>
<td>84/236 (35.6)</td>
<td>43/101 (42.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Barthel score &lt;95†</td>
<td>141/516 (27.3)</td>
<td>33/179 (18.4)</td>
<td>72/236 (30.5)</td>
<td>36/101 (35.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>324/509 (63.7)</td>
<td>104/176 (59.1)</td>
<td>141/233 (60.5)</td>
<td>79/100 (79.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>154/515 (29.9)</td>
<td>39/179 (21.8)</td>
<td>68/235 (28.9)</td>
<td>47/101 (46.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sedentary lifestyle, n (%)</td>
<td>172/511 (33.7)</td>
<td>45/177 (25.4)</td>
<td>77/234 (32.9)</td>
<td>50/100 (50.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Heart disease, n (%)‡</td>
<td>100/516 (19.4)</td>
<td>27/179 (15.1)</td>
<td>42/236 (17.8)</td>
<td>31/101 (30.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>72/478 (15.1)</td>
<td>15/162 (9.3)</td>
<td>40/222 (18.0)</td>
<td>17/94 (18.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Current smoker, n (%)‡</td>
<td>147/513 (28.7)</td>
<td>55/178 (30.9)</td>
<td>65/235 (27.7)</td>
<td>27/100 (27.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)§</td>
<td>264/515 (51.3)</td>
<td>103/179 (57.5)</td>
<td>118/236 (50.0)</td>
<td>43/100 (43.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>High cholesterol, n (%)</td>
<td>209/515 (40.6)</td>
<td>79/178 (44.4)</td>
<td>96/236 (40.7)</td>
<td>34/101 (33.7)</td>
<td>0.25</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>256/512 (50.0)</td>
<td>103/178 (57.9)</td>
<td>107/233 (45.9)</td>
<td>46/101 (45.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.3±5.5</td>
<td>29.5±6.3</td>
<td>27.9±5.1</td>
<td>27.3±4.6</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Denominators in the table may differ from the column totals because of missing values in the data collection.

*Glasgow outcome score <5 indicates any degree of residual disability, either at work or in social life, because of physical or mental deficit.
†Barthel score <95 indicates less than complete independence in performing activities of daily life.
‡History of myocardial infarction or angina, valvular heart disease, congestive heart failure, atrial fibrillation, or other cardiac arrhythmias.
§Consumption of at least 1 alcoholic beverage per week.

with a sample size of 214, 12.6% event rates observed, an SD of 1.893, and an R² value with other covariates of 0.09, using 2-sided 0.05 significance level.

Differences between proportions were assessed by the χ² test; differences between mean values were assessed by unpaired Student t test. Unadjusted HRs for the association between the various definitions of plaque (small, large, complex, or noncomplex) and recurrent ischemic stroke and death were calculated.

Cox proportional-hazards models were used to assess the risk of stroke/death associated with aortic arch plaques. HRs and 95% confidence intervals [CIs] for aortic plaques and stroke/death were calculated. Adjusted HRs were obtained using stepwise models including the variables listed in Table 1, with the entry and removal threshold set at P=0.2. Multigroup comparisons were used to assess the risk associated with various plaque characteristics.

Two-year event rates (stroke and death) were calculated in patients with no or small plaques or with large plaques and with different plaque complexity. Kaplan–Meier event-free curves were constructed in patients with different plaque definitions. The difference between groups was evaluated by means of the log-rank test.

In the warfarin group, a subanalysis was performed to evaluate the effect of the level of INR achieved on the risk of recurrent stroke/death. The average level of INR during follow-up was used for this analysis.

The SAS statistical package (version 9.1.3, SAS Institute Inc, Cary, NC) was used in the analyses, all performed by 1 investigator (Z.J.). A 2-tailed value of P=0.05 was considered significant for all analyses.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline TEE Findings
Of 630 patients, TEE studies were available for analysis for 627. Adequate visualization of the aortic arch was obtained in 516 of them (82%); they constitute the study population for the present report. Compared with the study population of WARSS, patients included in the present study were younger (by an average 3.5 years), were less often white (44.2% versus 56.8%), and because of the requirement of the PICSS protocol, more often had cryptogenic strokes (41.5% versus 26.1%). Gender distribution, educational level, prevalence of cardiovascular risk factors, index stroke severity, and residual disability were similar between the 2 study groups.

Aortic arch plaques were present in 337 of 516 patients (65.3%); large plaques (≥4 mm) were seen in 101 (19.6%). Complex plaque features (ulcerations, mobile components) were present in 46 patients (8.9%). Plaques both large and complex were present in 44 patients (8.5%). Patient characteristics by aortic plaque presence and thickness are shown in Table 1. The frequency of large plaques was not significantly different between patients with cryptogenic stroke (37 of 214, 17.3%) and patients with stroke of known cause (64 of 302, 21.2%; P=0.27).

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Laboratory Tests

The mean INR in patients treated with warfarin was 1.95 ± 0.46 (median, 1.96). Mean time interval between blood draws was 28.1 ± 13.4 days.

End Points

Of the 516 patients, 10 (1.9%) withdrew consent or were lost to follow-up at a mean of 13.2 ± 10.5 months after randomization. A total of 84 end points (16.3%) occurred during follow-up, including 61 strokes and 23 deaths.

Primary Events in Relation to Aortic Arch Plaque Status

Two-year incidence of recurrent stroke or death progressively increased with arch plaque size, from 10.1% in patients with no plaque to 16.5% in patients with small plaque to 26.7% in those with large plaque (Table 2). The same trend was observed in cryptogenic stroke patients, with incidence rates of 4.7%, 15.2%, and 24.3%, respectively. In the entire group, a significant difference was found in the time to recurrent stroke or death between patients with no arch plaque, small plaque, large complex plaque, or large noncomplex plaque ($P=0.003$). Kaplan–Meier curves are shown in Figure 2.

Large complex plaques had a 2-year event rate similar to that for large noncomplex plaques, but most of the events occurred at an earlier time. It should be noted that patients with large or large complex plaques had a worse risk profile than patients with small or no plaque (Table 1).

In multivariate analysis adjusted for race-ethnicity, Glasgow score, prior stroke, diabetes, heart disease, and sedentary lifestyle, each 1-mm increase in plaque thickness was associated with a significant increase in risk of events in the overall study group (HR, 1.13; 95% CI, 1.01 to 1.28) and even more in cryptogenic stroke patients (HR, 1.38; 95% CI, 1.12 to 1.68). Despite this association, the covariate-adjusted multigroup comparison model for plaque size (no versus small versus large plaque) was not statistically significant ($P=0.11$); neither was the comparison model for plaque size/complexity (no versus small versus large noncomplex versus large complex plaque; $P=0.17$). Significant findings were observed, however, in multivariate comparisons between specific plaque types. Compared with no plaque, large plaques were associated with an increased risk of recurrent stroke and death in the overall group (adjusted HR, 2.12; 95% CI, 1.04 to 4.32), especially those with complex morphology (adjusted HR, 2.55; 95% CI, 1.10 to 5.89). The risk was particularly high in patients with cryptogenic stroke (adjusted HR, 6.42; 95% CI, 1.62 to 25.46 for large plaques; adjusted HR, 9.50; 95% CI, 1.92 to 47.10 for large complex plaques). No significant increase in risk was observed for any type of aortic plaque in patients with stroke of known cause.

Treatment With Warfarin or Aspirin

No significant differences between the 2 treatment arms were observed with regard to demographics, clinical characteristics, and cardiovascular risk factors. Frequencies of small, large, and large complex plaques also were not significantly different between the treatment groups. In patients treated with warfarin, the mean INR was not significantly different among those with no, small, or large arch plaques (1.95 ± 0.45, 1.92 ± 0.47, and 2.03 ± 0.45, respectively; $P=0.34$).

Two-year incidence of recurrent stroke/death was similar between the warfarin-treated (43 of 256, 16.4%) and aspirin-
Over a follow-up of 2 years, we observed that large plaques also might have affected the interpretability of the results. Were those with high-degree carotid stenosis, whose inclusion as aspirin. Patients with cardioembolic stroke were excluded, as double-blindly randomized to treatment with warfarin or anticoagulation. The frequency of thromboembolic events in patients with large or complex aortic plaques is believed to be predominantly thromboembolic. The level of anticoagulation achieved in the warfarin group in our study was determined by the protocol requirements of the parent study (WARSS),14 with a lower target INR range (1.4 to 2.8) than usually recommended for cardioembolic sources of stroke (INR, 2 to 3). However, the mean INR achieved in our study was 1.95, and a protective effect of warfarin on the risk of stroke and death was observed starting at an INR of 1.5, as was the case in the parent study. Therefore, the level of anticoagulation achieved in our patients appears adequate. Our study has preventive implications, suggesting that treatment with warfarin or aspirin is not sufficient to significantly affect the risk associated with large aortic plaques. For warfarin treatment, it is possible that further selection of suitable patients, beyond the assessment of plaque thickness, may be needed. We recently reported that patients presenting with acute ischemic stroke and large aortic plaques show an activation of coagulation parameters that is not observed in matching control subjects and that the coexistence of large aortic plaques and hypercoagulability at presentation is associated with an increased risk of recurrent stroke and death.22
The assessment of coagulation parameters may identify a subgroup of patients with large arch plaques who may benefit the most from treatment with warfarin.

Statin treatment holds promise in patients with large plaques, although the only study to date that reported a favorable effect of statins while showing no benefit from aspirin or warfarin treatment was retrospective with no treatment randomization. Statin treatment is recommended in the current American Heart Association/American Stroke Association guidelines for the prevention of recurrent stroke, but more as a general recommendation to be applied to all patients with evidence of atherosclerosis than as a specific recommendation in patients with aortic plaques. High-dose statin treatment decreased the risk of recurrent stroke in the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study, but no separate data were available for patients with aortic atherosclerosis. More research is necessary to clarify the role of statins in reducing the risk of embolic events in stroke patients with large aortic plaques.

Our study has some limitations. Because enrollment was performed at a time when statins were not routinely prescribed after stroke, the effect of statin treatment on our results cannot be evaluated. On the other hand, the effect of warfarin and aspirin treatment on the risk of stroke and death was assessed without the confounding effect of statin treatment. Although the level of anticoagulation achieved in the warfarin group appears adequate, the possibility that a higher level of anticoagulation might have significantly affected the results cannot be excluded.

Conclusions
Our study shows that, among patients with ischemic stroke treated with warfarin or aspirin, large aortic plaques, especially those with complex morphology, remain associated with a significant increase in risk of recurrent stroke and death, which is observed exclusively in patients with an initial cryptogenic stroke. Further studies are needed to evaluate whether patient selection or different treatment strategies may be associated with more effective prevention of recurrent events.

Acknowledgments
We wish to thank J.L.P. Thompson, PhD, and Bruce Levin, PhD, for their expert statistical suggestions.

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Disclosures
None.

References
Large aortic arch plaques are associated with increased risk of ischemic stroke. The efficacy of antithrombotic therapies in reducing this risk has not been established. This study examined the risk of recurrent stroke and death associated with the presence of aortic plaques in 516 patients with acute ischemic stroke randomized to warfarin or aspirin treatment. The prevalence of large plaques (ie, ≥4 mm thick) in this study group was 19.6%; that of large complex plaques (ie, large plaques with ulcerations or mobile components) was 8.5%. After 2 years of follow-up, the presence of large aortic plaques was associated with a 2-fold increase in risk of stroke and death after adjustment for other risk factors; the risk was especially high (2.5-fold increase) when complex plaque morphology was present. Patients whose index stroke had no clear explanation (ie, cryptogenic stroke) had a much greater risk of recurrent events when large arch plaques were present, especially when complex plaque features existed. Therefore, in patients with cryptogenic stroke, the aortic arch should be examined for the presence of plaque, and plaque thickness and morphology should be recorded for risk stratification. In this study, the risk of recurrent stroke and death associated with large aortic plaques remained significant despite prophylactic treatment with warfarin or aspirin, suggesting that different treatment strategies or better selection of patients for antithrombotic strategies may be necessary.
Aortic Arch Plaques and Risk of Recurrent Stroke and Death
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for the Patent Foramen Ovale in Cryptogenic Stroke Study Investigators

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