Aortic Arch Plaques and Risk of Recurrent Stroke and Death

Marco R. Di Tullio, MD; Cesare Russo, MD; Zhezhen Jin, PhD; Ralph L. Sacco, MD, MS; J.P. Mohr, MD; Shunichi Homma, MD; for the Patent Foramen Ovale in Cryptogenic Stroke Study Investigators

Background—Aortic arch plaques are a risk factor for ischemic stroke. Although the stroke mechanism is conceivably thromboembolic, no randomized studies have evaluated the efficacy of antithrombotic therapies in preventing recurrent events.

Methods and Results—The relationship between arch plaques and recurrent events was studied in 516 patients with ischemic stroke 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 transthoracic 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

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 studies4 and subsequently confirmed by in vivo studies that used transthoracic echocardiography (TEE) to identify the plaques and to evaluate the associated risk of stroke with a case-control2–4 or a prospective5–9 design. Large plaques (≥4 mm) have been proven to confer a sharply increased stroke risk.5,6 Complex morphological features of the plaque, such as ulcerations or superimposed thrombi, also have been shown to contribute to the increased risk,7,10,11 whereas the presence of calcification appears to decrease it.12 However, the optimal medical treatment to decrease the risk of recurrent embolic events in patients with large aortic plaques has not yet been established. Because the stroke mechanism in patients with large plaques has often been considered to be thromboembolic in nature, systemic anticoagulation and antiplatelet agents have been proposed as possible preventive options. The actual role of these treatments and their efficacy in patients with different types of plaques have not yet been established. Anticoagulation has been advocated occasionally in plaques with superimposed mobile components suggestive of thrombus.13 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).

Clinical Perspective on p 2382

Methods

Patient Recruitment
PICSS relied on WARSS for patient recruitment and follow-up. WARSS was a 48-center double-blind study that randomized 2206...
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 a stroke related to a procedure 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 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 84 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 least HR of 1.35 per 1-mm increase in plaque thickness, the present study had 80% power to detect a minimum hazard ratio (HR) of 1.18 per 1-mm increase in plaque thickness.
The risk associated with various plaque characteristics.

A value of \( P < 0.05 \) was considered significant for all analyses.

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 (\( \geq 4 \) 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%; \( P = 0.27 \)).
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.

Table 2. Rates of Recurrent Stroke/Death by Aortic Arch Plaque Status in the Entire Study Group and in Stroke Diagnostic Subtypes

<table>
<thead>
<tr>
<th></th>
<th>Events/Total (%)</th>
<th>Strokes of Known Cause, Events/Total (%)</th>
<th>Cryptogenic Strokes, Events/Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>84/516 (16.3)</td>
<td>57/302 (18.9)</td>
<td>27/214 (12.6)</td>
</tr>
<tr>
<td>No plaques</td>
<td>18/179 (10.1)</td>
<td>14/94 (14.9)</td>
<td>4/85 (4.7)</td>
</tr>
<tr>
<td>Small plaques (&lt;4 mm)</td>
<td>39/236 (16.5)</td>
<td>25/144 (17.4)</td>
<td>14/92 (15.2)</td>
</tr>
<tr>
<td>Large plaques (≥4 mm)</td>
<td>27/101 (26.7)</td>
<td>18/64 (28.1)</td>
<td>9/37 (24.3)</td>
</tr>
<tr>
<td>Complex plaques</td>
<td>12/44 (27.3)</td>
<td>8/29 (27.6)</td>
<td>4/15 (26.7)</td>
</tr>
<tr>
<td>Noncomplex plaques</td>
<td>15/57 (26.3)</td>
<td>10/35 (28.6)</td>
<td>5/22 (22.7)</td>
</tr>
</tbody>
</table>

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.

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. In the warfarin group, the effect of the average INR achieved during follow-up on the risk of recurrent stroke and death was evaluated. In a model including the various definitions of arch plaques and significant stroke risk factors, a significant protective effect was observed for INR ≥1.5 in both the entire study group (adjusted HR, 0.37; 95% CI, 0.18 to 0.77) and the cryptogenic subgroup (adjusted HR, 0.14; 95% CI, 0.03 to 0.60).

**Hemorrhagic Events**

The incidence of major hemorrhagic events was low and similar between the warfarin and aspirin groups (0.88 versus 2.16 per 100 patient-years; \(P=0.13\)). Minor hemorrhagic events were more frequent in the warfarin group (26.76 versus 10.0 per 100 patient-years; \(P<0.001\)).

**Discussion**

Our study is the first to report on the incidence of recurrent stroke and death in stroke patients with aortic arch plaques randomized to warfarin or aspirin treatment. The presence of large plaques in the proximal segment of the aorta is an established risk factor for ischemic stroke, linked to a 2.5-fold to 9-fold increase in stroke risk in case-control studies, with an even greater risk in cases of complex plaque morphology, and with a ≥4-fold increase in stroke risk in prospective studies. In patients with prior stroke, the risk of recurrent stroke associated with large or complex aortic plaques has been quite consistent among different studies, with HRs ranging from 2.48 to 3.8. Large aortic arch plaques have a definite embolic potential, demonstrated by the frequent microembolic signals observed by transcranial Doppler. The stroke mechanism in patients with large or complex aortic plaques is believed to be predominantly thromboembolic. The frequency of thromboembolic events in patients with severe arch plaques has been reported to be as high as 33% at 1 year compared with only 0.7% for atheroembolism. Superimposed thrombus was found in 17 of 120 plaques (14%) in an autopsy study. Because of this thromboembolic propensity, anticoagulation or antiplatelet treatment appears to be a reasonable preventive treatment for reducing the risk of embolic events. However, the available data on the effect of oral anticoagulation or antiplatelet therapy are sparse and inconclusive, and the information has been derived from observational studies not designed to test treatment efficacy. The type of treatment was often left to the discretion of the treating physician, making the results difficult to interpret. Most studies included subjects with cardioembolic stroke mechanism who required anticoagulation. In the present study, patients with aortic plaques were double-blindly randomized to treatment with warfarin or aspirin. Patients with cardioembolic stroke were excluded, as were those with high-degree carotid stenosis, whose inclusion also might have affected the interpretability of the results. Over a follow-up of 2 years, we observed that large plaques (≥4 mm) remained associated with a doubling of the risk of recurrent stroke and death in the overall study cohort despite medical therapy and after adjustment for other pertinent covariates. The risk was seen exclusively in cryptogenic stroke patients, suggesting that aortic plaques may indeed have played an important role in the stroke mechanism when no other cause was present. Moreover, the highest risk estimates were obtained in the presence of complex plaque morphology in both the overall study group (HR, 2.55) and the cryptogenic stroke patients (HR, 9.50), further suggesting a possible direct role of the plaque in the embolic mechanism. This possibility was corroborated by the earlier occurrence of outcome events observed for complex plaques (Figure 2). In cryptogenic stroke patients, the 2-year event rate on medical treatment was relatively low (4.7%; Table 2), but the presence of aortic plaques increased it to the same level seen in patients with other causes of stroke. This observation suggests that aortic plaques are a strong risk factor for recurrent events in cryptogenic stroke patients. Plaque thickness ≥4 mm was a useful criterion for risk stratification, as previously reported. The presence of ulcerations or mobile components added to the prediction of risk; in particular, our data suggest that ulcerations of the plaque surface should be actively sought because of the associated increase in risk and their relatively frequent detection on large plaques (8.9% in our study versus only 0.6% for mobile forms). It should be noted that, given the small numbers of events within individual classes and the consequently wide 95% CIs of the estimated HRs, the plaque size–complexity analyses in our study should be regarded as exploratory, especially in the cryptogenic subgroup.

Medical treatment with warfarin or aspirin did not affect the statistical significance of the association between severe aortic plaques and the risk of stroke and death. In fact, the HRs that we observed were only slightly lower than those previously reported in the literature from studies in which the treatment was not randomized or even not prescribed to some of the study patients.

The level of anticoagulation achieved in the warfarin group in our study was determined by the protocol requirements of the parent study (WARSS), 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.
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 promises 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 randomization. Statin treatment is recommended as a general recommendation to be applied to all patients with evidence of atherosclerosis than as a specific recommendation in patients with aortic plaques. Although the level of anticoagulation achieved in the warfarin and aspirin treatment on the risk of stroke and death was assessed without the confounding effect of statin treatment randomization, but more as a general recommendation to be applied to all patients with evidence of atherosclerosis.

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.

Sources of Funding

This study was supported by the National Institutes of Health–National Institutes of Neurological Disorders and Stroke R01-NS-32525 (Dr Homma) and R01-NS-28371 (Dr Mohr).

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, $\geq 4$ 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.

Go to http://cme.ahajournals.org to take the CME quiz for this article.
Aortic Arch Plaques and Risk of Recurrent Stroke and Death
Marco R. Di Tullio, Cesare Russo, Zhezhen Jin, Ralph L. Sacco, J.P. Mohr and Shunichi Homma
for the Patent Foramen Ovale in Cryptogenic Stroke Study Investigators

_Circulation_. 2009;119:2376-2382; originally published online April 20, 2009;
doi: 10.1161/CIRCULATIONAHA.108.811935
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/119/17/2376

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2009/04/17/CIRCULATIONAHA.108.811935.DC1