Aortic Arch Atheroma Progression and Recurrent Vascular Events in Patients With Stroke or Transient Ischemic Attack

Souvik Sen, MD, MS; Alan Hinderliter, MD; Pranab K. Sen, PhD; Jennifer Simmons, BSW; James Beck, PhD; Steven Offenbacher, DDS, PhD, MMSc; E. Magnus Ohman, MD; Stephen M. Oppenheimer, MD, PhD

Background—It is not known whether progression of aortic arch (AA) atheroma is associated with vascular events in patients with stroke or transient ischemic attack (TIA).

Methods and Results—AA atheroma was detected on baseline transesophageal echocardiogram in 167 consecutive patients who had prevalent stroke or TIA. Of these, 125 consented to a follow-up transesophageal echocardiogram at 12 months. Adequate paired AA images were obtained in 117 (78 with strokes, 39 with TIAs), which allowed detailed measurements of plaques. On admission for their index stroke or TIA, patients were assessed for stroke risk factors, stroke subtypes, baseline AA plaque characteristics, and laboratory parameters. Progression of AA atheroma was observed in 33 patients (28%) on 12-month follow-up transesophageal echocardiogram. It was determined that the progression group had significantly higher adjusted homocysteine levels ($P<0.0001$) and neutrophil counts ($P<0.0001$) than the no-progression group. These patients were followed up for a median of 1.7 years from the index stroke/TIA (range 0.5 to 4.5 years) for vascular events including stroke, TIA, myocardial infarction, and death due to vascular causes. Kaplan-Meier curves showed fewer patients with AA atheroma progression remained free of the composite vascular end point (49% compared with 89% in the no-progression group; $P<0.0001$). AA atheroma progression was associated with composite vascular events (hazard ratio 5.8, 95% confidence interval 2.3 to 14.5, $P=0.0002$) after adjustment for a propensity score based on confounders.

Conclusions—In this preliminary study of stroke/TIA patients with AA atheroma on transesophageal echocardiogram, AA atheroma progression was associated with recurrent vascular events. (Circulation. 2007;116:928-935.)

Key Words: aorta ▪ atherosclerosis ▪ disease progression ▪ echocardiography ▪ stroke

S

ignificant aortic arch (AA) atheroma is the second most prevalent cardioembolic risk factor for stroke after atrial fibrillation and is present in 16% to 20% of all patients with stroke and transient ischemic attack (TIA). It is a risk factor for new and recurrent stroke and has no definitive treatment. Transesophageal echocardiography (TEE) provides an established, validated, cost-effective, and safe method for detection and measurement of AA atheroma. In a retrospective analysis of a prospectively conducted sequential TEE study, we demonstrated that AA atheroma has a high rate of progression; in 29% of stroke/TIA patients, AA atheroma worsened by ≥1 grade in 9 months, whereas fewer than 10% of carotid artery atheromas progressed over 12 months. A limitation of the prior study was that the method used could not ensure that the plaque thickness measurement and gradation scores occurred at precisely the same location on baseline and follow-up images. To overcome this methodological limitation, we designed a prospective study using detailed serial-view, quantitative plaque thickness measurements and sectional area measurements and methods to ensure imaging and gradation in similar locations over a period of 12 months, to better estimate the rate of progression.

Clinical Perspective p 935

Observational studies suggest that carotid plaque progression may be an independent risk factor for coronary artery disease and stroke. Although AA atheroma has been identified as a risk factor for recurrent stroke, it is not known whether progression is associated with ischemic event recurrence. In the present study, we sought to investigate the

Received October 21, 2006; accepted June 15, 2007.
From the University of North Carolina Stroke Program, Departments of Neurology (S.S., J.S.), Cardiology (A.H., E.M.O.), Biostatistics (P.K.S.), Dental Ecology (J.B.), and Periodontology (S.O.), University of North Carolina, Chapel Hill, and Sentinent Medical Services (S.M.O.), Cockeysville, Md. Dr Ohman is now affiliated with Duke University Medical Center, Durham, NC.
Correspondence to Souvik Sen, MD, MS, FAHA, Director of UNC Hospital Stroke Center, Associate Professor of Neurology, 7003A Neuroscience Hospital, CB# 7025, Chapel Hill, NC 27599-7025. E-mail SenS@neurology.unc.edu
© 2007 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.106.671727

928
The relationship between AA atheroma progression and recurrent vascular events, including stroke, TIA, myocardial infarction (MI), and vascular death.

**Methods**

Consecutive stroke/TIA patients (n=307) underwent TEE within 1 month of symptom onset as part of their stroke workup. All patients had computed tomography/MRI of the brain to confirm stroke, had risk factors assessed, and were classified into etiologic stroke subtypes at the time of admission for their index stroke/TIA. All patients had complete blood count, fasting lipid profile, and homocysteine level measurement as part of their stroke risk assessment. Exclusion criteria were age <18 years, intracerebral hemorrhage, subarachnoid hemorrhage, coma, conditions limiting life expectancy to <12 months (for example, end-stage cancer), and no aortic atheroma on baseline TEE. Of these patients, 167 had evidence of aortic atheroma (measurable plaque ≥1 mm in ascending aorta, AA, or descending thoracic aorta), and 125 of these eligible patients consented to a follow-up TEE at 12 months based on a protocol approved by the institutional review board. Of the 42 patients who did not consent, 35 refused and 7 were deceased before their follow-up TEE. Adequate paired aortic images were obtained in 117 of 125 patients (78 with stroke, 39 with TIA), which enabled us to make detailed plaque measurements.

**TEE Assessment of AA Atheroma**

A comprehensive TEE with detailed imaging of the aorta was performed with a Hewlett-Packard 21364A omniplane probe (Hewlett-Packard, Palo Alto, Calif). Imaging and quantification of AA atheroma were conducted with modifications of the previously described methods. Briefly, the proximal and mid ascending aorta were imaged at a probe depth of ~30 cm with a multiplane angle of 100° to 150° to view the vessel in the long axis. The descending thoracic aorta was examined by advancing the probe to the distal esophagus, imaging the aorta in cross section (at 0°), and then slowly withdrawing the probe to image proximal segments. As the transducer reached the AA, the multiplane angle was rotated to between 0° and 90° to acquire sequential short-axis views.

The modifications included the acquisition of digital images of the diseased areas in each segment of the AA with annotation of the distance of the transducer from the incisors. Identical locations in the AA were evaluated on the 1-year examination (Figure 1), with the depth of the transducer, plaque morphology, and surrounding anatomic landmarks used for guidance.

Two observers, masked to clinical data and the order of the TEE, independently quantified atheroma. Plaque thickness was measured as the maximal thickness of the intimal and medial layers and graded as mild (<1 mm), moderate (1 to 3.99 mm), or severe (≥4 mm) with the criteria of Amarenco et al. AA atheroma progression was defined as an increase in maximal thickness of the plaque in the AA by ≥1 grade, and regression was defined as a decrease in maximal thickness by ≥1 grade. Good interobserver reliability existed between the 2 observers in the assessment of aortic plaque progression and regression in the ascending aorta (κ=0.77), AA (κ=0.85), and descending thoracic aorta (κ=0.86). Excellent intraobserver reliability was noted for the first observer (κ=0.93 to 1.00) and the second observer (κ=0.91 to 0.94). Plaques noted on the index TEE were also assessed for morphological features, including heteroechogenicity, mobility, and ulceration, that have been specifically linked to cerebral embolism. Heteroechogeticity of the plaque was defined as focal increase echocardiographic density within the aortic plaque combined with a broad acoustic shadow that indicated the presence of calcifications. Ulcerated plaques were defined as having 1 or more craters ≥2 mm in depth and width. Complex mobile plaques were defined as those that protruded, were ≥4 mm in maximum thickness, and were associated with mobile lesions that were suggestive of “debris” or a free-floating thrombus.

**Clinical Definitions**

Stroke risk factors, stroke, and TIA were defined on the basis of previously described criteria. Stroke risk factors, laboratory assessments, and stroke subtype (described below) were assessed at the time of the initial qualifying event (stroke or TIA). MI was defined according to criteria modified from the 2000 Consensus Conference of the European and American Colleges of Cardiology, on the basis of symptoms and ECG changes, in conjunction with contemporary biochemical markers of myocardial necrosis (troponin or creatine kinase). Vascular death was defined as death ≤30 days due to stroke or MI, death of patients for whom other causes of death had been excluded, or a sudden death due to unexplained cause(s). Antiplatelet therapy included aspirin, aspirin with extended-release dipyridamole, clopidogrel, and ticlopidine. Oral anticoagulation implied warfarin therapy for a known indication (for example, atrial fibrillation), and statin therapy indicated daily statin therapy. The medication history was collected at the time of the protocol-mandated 12-month TEE examination.

**Laboratory Measurements**

A complete blood count, erythrocyte sedimentation rate, and fasting lipid profile were obtained from each patient as part of their admission workup. Patients without renal failure (creatinine ≥2.5 mg/dL) were included for homocysteine assessment (repeated at 12 months to eliminate elevation secondary to acute-phase reaction). None were taking medications (for example, phenytoin) that elevate homocysteine levels. Fasting blood samples were transported on ice, and plasma was separated and stored at 4°C until measurement by high-performance liquid chromatography with fluorescence detection by previously published methods.

![Figure 1. In the AA, sequential cross-sectional images were obtained; probe depth and plaque morphology were used to measure plaque thickness at identical locations.](http://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.117.029390)
Cause of Stroke
Stroke cause was classified with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. A cardioembolic cause was considered in patients with major brain artery or branch cortical artery occlusion who had at least 1 major cardiac source identified in the TOAST criteria. Potential large-artery atherothrombosis was assessed by carotid ultrasound and/or magnetic resonance angiography. All tests performed as part of the initial stroke workup, including transthoracic echocardiography, TEE, ECG, and 24-hour Holter studies, were used to determine cardiac sources of stroke. Small-vessel occlusive disease was considered in patients without evidence of cardioembolism or large-artery atherothrombosis described above. These patients should also have presented with 1 of the lacunar syndromes and should have had a corresponding infarct (<1.5 cm in its largest diameter) on relevant brain stem or subcortical hemispheric location on computed tomography/MRI.

Statistical Analysis
Statistical analysis was performed with SAS version 9.1.3 (SAS Institute, Cary, NC). All continuous variables are reported as mean±SEM. Intergroup difference was assessed by χ² test for categorical variables and t test for continuous variables. Adjusted intergroup difference was assessed by logistic regression analysis for categorical variables and multiple linear regression analysis for continuous variables. Initially, the cumulative event-free rates for the time to composite vascular events (stroke, TIA, MI, and vascular death) were estimated by the Kaplan-Meier product-limit method, and the 2 groups with and without AA progression were compared by the log-rank test. Subsequently, Cox proportional hazards multi-variable analysis was used to identify risk factors for composite vascular events after adjustment for significant confounders by the methods discussed below. The periods of exposure and event measurement were segregated by exclusion of the events that occurred during the 12-month interval between TEEs. Covariates assessed for confounding included stroke risk factors, laboratory parameters known to be associated with stroke risk (LDL cholesterol, HDL cholesterol, leukocyte count, and homocysteine levels), stroke subtype, and plaque characteristics on index TEE. Of these, only the covariates that were noted to change the effect measure (hazard ratio [HR]) by ≥5% were considered to produce confounding and were included in the composite stroke that was subsequently included in the final model. We used propensity scores because the number of confounders was large in relation to the composite vascular outcomes. To generate propensity scores, a logistic regression model was first created in which the confounders were independent variables and AA progression was the dependent variable. Propensity scores were then calculated for each study subject by applying the subject’s values to the logistic model. The propensity score reflects each subject’s conditional probability of being exposed (AA progression) given the confounding variables. The c-statistic for the propensity score model was 0.71, which indicates an acceptable discrimination between the progression of AA and the no-progression group. We used Cox proportional hazards models to examine the association between AA progression and time to composite vascular events, adjusting for propensity score as a continuous variable in lieu of adjusting for the multiple confounders used to generate the propensity score. The assumption of proportional hazards was not violated, and a linear association between

### TABLE 1. Baseline Clinical Characteristics of Stroke/TIA Patients With and Without Progression of AA Atheroma

<table>
<thead>
<tr>
<th>Risk factors, stroke etiology, and medication history</th>
<th>Progression (n=33)</th>
<th>No Progression (n=84)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.4±1.0</td>
<td>28.7±0.7</td>
<td>0.56</td>
</tr>
<tr>
<td>Black race</td>
<td>23</td>
<td>25</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89</td>
<td>76</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35</td>
<td>23</td>
<td>0.18</td>
</tr>
<tr>
<td>Smokers</td>
<td>33</td>
<td>19</td>
<td>0.21</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>18</td>
<td>20</td>
<td>0.86</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>43</td>
<td>27</td>
<td>0.14</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5</td>
<td>12</td>
<td>0.26</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>21</td>
<td>15</td>
<td>0.48</td>
</tr>
<tr>
<td>TIA</td>
<td>31</td>
<td>34</td>
<td>0.75</td>
</tr>
<tr>
<td>TOAST classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherothrombosis</td>
<td>15</td>
<td>5</td>
<td>. .</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>24</td>
<td>14</td>
<td>. .</td>
</tr>
<tr>
<td>Small-vessel occlusive disease</td>
<td>3</td>
<td>22</td>
<td>0.02†</td>
</tr>
<tr>
<td>Others (known, unknown, and ≥2 causes)</td>
<td>28</td>
<td>24</td>
<td>. .</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>78</td>
<td>77</td>
<td>0.89</td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>24</td>
<td>26</td>
<td>0.91</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>58</td>
<td>58</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Body mass index, a continuous value, is depicted as adjusted mean±SEM (adjusted for age and gender with a general linear model). The remaining parameters are reported as proportions (%), adjusted for age and gender with a logistic regression model. Stroke etiology was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. *Bonferroni-adjusted α-level of significance for multiple comparisons: α=0.05/16=0.003. †Two-by-six contingency table χ² test.
propensity score and evaluated outcome was ascertained. The results
were expressed as adjusted HRs and corresponding 95% confidence
intervals (CIs).

Statistical significance was considered to be $P \leq 0.05$, except
where indicated. The Bonferroni-adjusted $\alpha$-level of significance,
adjusted for multiple comparison, was used (Tables 1, 2, and 3). The
$k$-statistic was used to compute interobserver and intraobserver
reliability of assessment of AA atheroma grade.

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

Of 307 consecutive stroke/TIA patients, 167 had AA athero-
sclerosis on baseline TEE and met the selection criteria, of
whom 125 consented to a 12-month follow-up TEE. These
125 patients who had follow-up TEE were significantly older
(65±1.1 versus 60±1.2 years, $P=0.002$) and had higher
prevalences of hypertension (79% versus 64%, $P=0.006$) and
peripheral vascular disease (17% versus 2%, $P<0.001$) than
the 182 patients who did not have follow-up TEE (of whom
140 did not meet the inclusion criteria, 35 refused, and 7
died). Of the 125 patients who had follow-up TEE, 117 had
adequate paired aortic images to assess progression and
follow-up vascular event information. The age- and gender-
adjusted characteristics of the 117 patients who had a
follow-up TEE with adequate paired images of AA showing
progression ($n=33$) and no progression ($n=84$) are described

### TABLE 2. AA Plaque Characteristics on Baseline TEE of Stroke/TIA Patients With
and Without Progression of AA Atheroma Over 12 Months

<table>
<thead>
<tr>
<th>AA Plaque Characteristics</th>
<th>Progression (n=33)</th>
<th>No Progression (n=84)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA plaque grade (AAPT in mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I ($&lt;1.00$ mm)</td>
<td>3</td>
<td>9</td>
<td>…</td>
</tr>
<tr>
<td>Grade II ($1.00–3.99$ mm)</td>
<td>71</td>
<td>56</td>
<td>0.20</td>
</tr>
<tr>
<td>Grade III ($\geq4.00$ mm)</td>
<td>23</td>
<td>37</td>
<td>…</td>
</tr>
<tr>
<td>AA plaque morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heteroechogenicity</td>
<td>26</td>
<td>39</td>
<td>0.20</td>
</tr>
<tr>
<td>Ulceration</td>
<td>13</td>
<td>9</td>
<td>0.56</td>
</tr>
<tr>
<td>Complex mobile plaque</td>
<td>21</td>
<td>5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

All values are percentages, adjusted for age and gender with a logistic regression model. AAPT indicates AA plaque thickness.

AA plaque grade was based on AAPT (in millimeters).

*Bonferroni-adjusted $\alpha$-level of significance for multiple comparisons: $\alpha=0.05/3=0.017$.

### TABLE 3. Baseline Laboratory Characteristics of Stroke/TIA Patients With
and Without Progression of AA Atheroma

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>Progression (n=33)</th>
<th>No Progression (n=84)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.3±0.3</td>
<td>13.6±0.2</td>
<td>0.50</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>38.8±0.8</td>
<td>39.3±0.5</td>
<td>0.60</td>
</tr>
<tr>
<td>Total WBC count, $10^9$/L</td>
<td>7.7±0.3</td>
<td>6.9±0.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Neutrophil count, $10^9$/L†</td>
<td>6.8±0.4</td>
<td>4.8±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lymphocyte count, $10^9$/L</td>
<td>1.7±0.2</td>
<td>2.0±0.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Monocyte count, $10^9$/L</td>
<td>0.4±0.03</td>
<td>0.4±0.02</td>
<td>0.71</td>
</tr>
<tr>
<td>Eosinophil count, $10^9$/L</td>
<td>0.2±0.02</td>
<td>0.2±0.02</td>
<td>0.33</td>
</tr>
<tr>
<td>Basophil count, $10^9$/L</td>
<td>0.03±0.01</td>
<td>0.04±0.006</td>
<td>0.39</td>
</tr>
<tr>
<td>Platelet count, $10^9$/L</td>
<td>274±12.7</td>
<td>248±7.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Baseline AAPT, mm</td>
<td>3.5±0.4</td>
<td>3.6±0.2</td>
<td>0.86</td>
</tr>
<tr>
<td>Sedimentation rate, mm/h</td>
<td>25±4.6</td>
<td>26±3.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>187±7.0</td>
<td>185±4.4</td>
<td>0.79</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>110±7.1</td>
<td>105±4.4</td>
<td>0.55</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50±2.9</td>
<td>54±1.8</td>
<td>0.29</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>158±18.1</td>
<td>149±11.4</td>
<td>0.67</td>
</tr>
<tr>
<td>Homocysteine, $\mu$mol/L†</td>
<td>14.5±0.9</td>
<td>9.7±0.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

All continuous values are depicted as adjusted mean±SEM, adjusted for age and gender with a general linear model.

*Bonferroni-adjusted $\alpha$-level of significance for multiple comparisons: $\alpha=0.05/16=0.003$.

†$P<0.003$. 

---

Sen et al Progression of Aortic Arch Atheroma 931

Downloaded from http://circ.ahajournals.org/ by guest on April 12, 2017
in Table 1. The patients with AA progression were older \((P=0.01)\) and exhibited a trend toward a higher age- and gender-adjusted prevalence of hypertension \((P=0.06)\). The proportions of the stroke subtypes appeared to be different between the progression and no-progression groups \((P=0.02)\). Specifically, patients with small-vessel occlusive disease were less likely \((3\% \text{ versus } 22\%, \ P=0.01)\) to have AA atheroma progression. No difference existed in the proportion of patients undergoing antiplatelet therapy, oral anticoagulation, or statin therapy. At baseline, the largest lesion was mild in 12 patients \((10\%)\), moderate in 66 \((56\%)\), and severe in 39 \((33\%)\). Baseline severity grade did not appear to influence progression (Table 2). Complex mobile plaques were noted in 11 \((9\%)\) of 117 patients on the index TEE. A trend toward a higher age- and gender-adjusted proportion \((21\% \text{ versus } 5\%, \ P=0.04)\) of complex mobile plaque was noted in the progression group compared with those without progression. No significant difference existed in the proportion of patients with heterogeneous echogenicity, which was more frequent in the no-progression group, or ulceration, which was more frequent in the progression group. Of the 117 patients, 33 \((28\%)\) showed progression, and 16 \((14\%)\) had regression of their index lesion at 12 months. Among the 84 patients whose AA atheroma did not progress, no significant differences \((\text{statistical or clinical})\) existed between the subgroups of patients who regressed \((n=16)\) and those who did not \((n=68)\) with regard to vascular events, stroke risk factors, and laboratory parameters. Hence, these 2 subgroups are justifiably combined and compared with the progression group. It may be argued that in patients who died before the follow-up TEE \((n=7)\), AA atheroma progressed rapidly, which led to an earlier vascular death. The inclusion of these patients in the progression group did not influence the results; hence, the analysis is not discussed further.

Plasma homocysteine and neutrophil counts were significantly higher in the AA progression group than in the no-progression group (Table 3). The unadjusted total white blood cell count was higher \((P=0.002)\) in patients with AA atheroma progression \((8.9\pm0.4\times10^9/L)\) than in those without progression \((7.4\pm0.2\times10^9/L)\). However, after adjustment for age and gender, total white blood cell count trended to be higher \((P=0.03)\) in patients with AA atheroma progression \((7.7\pm0.3\times10^9/L)\) than in those without progression \((6.9\pm0.2\times10^9/L)\). Age and gender adjustment did not appear to significantly alter any of the remaining parameters. The age- and gender-adjusted neutrophil count was higher \((P<0.0001)\) in patients with AA atheroma progression \((6.8\pm0.4\times10^9/L)\) than in those without progression \((4.8\pm0.2\times10^9/L)\). The age- and gender-adjusted homocysteine level measured at \(<1\) month from the index event was significantly \((P<0.0001)\) higher in patients with AA atheroma progression \((14.5\pm0.9\ \mu\text{mol/L})\) than in those without progression \((9.7\pm0.6\ \mu\text{mol/L})\). No significant differences existed between the progression and no-progression groups in the remaining laboratory parameters.

Over a median of 1.7 years from the 12-month follow-up TEE \((\text{range } 0.5 \text{ to } 4.5 \text{ years})\), 25 patients exhibited vascular events, which included 8 strokes, 7 TIs, 8 MIs, and 2 vascular deaths. On the basis of the grade of AA plaque severity on the index TEE, 2 \((17\%)\) of 12 with mild lesions, 15 \((23\%)\) of 66 with moderate lesions, and 8 \((21\%)\) of 39 with severe lesions experienced vascular events. In this limited sample, these differences in event rates did not attain statistical significance \((P=0.8)\). Eighteen \((55\%)\) of the 33 who exhibited AA progression had vascular events, including 5 strokes, 4 TIs, 7 MIs, and 2 vascular deaths. Among the 84 patients who did not exhibit progression, 7 \((8\%)\) had vascular events, including 3 strokes, 3 TIs, and 1 MI, over the same period of follow-up. A significant difference existed in cumulative event-free survival between the progression group \((\text{mean survival } 2.3 \text{ years}, \ 95\% \text{ CI } 1.7 \text{ to } 2.9 \text{ years})\) and the no-progression group \((\text{mean survival } 4.1 \text{ years}, \ 95\% \text{ CI } 3.8 \text{ to } 4.5 \text{ years})\). The 2 distributions were significantly different according to log-rank testing \((P<0.0001)\), as depicted in the Kaplan-Meier survival curve (Figure 2). Covariates assessed for confounding included clinical characteristics listed in Table 1, selected laboratory parameters known to be associated with stroke risk \((\text{LDL cholesterol, HDL cholesterol, leukocyte count, and homocysteine levels})\), and AA plaque characteristics on index TEE (Table 2). Of these, hypertension, diabetes mellitus, coronary artery disease, stroke subtype, antiplatelet therapy, and homocysteine level were noted to change the HR by \(\pm 5\%). These covariates were used to generate the propensity score. Multivariable Cox regression showed AA atheroma progression was associated with composite vascular events \((HR \ 5.8, \ 95\% \text{ CI } 2.3 \text{ to } 14.5, \ P=0.0002)\) after adjustment for propensity score based on the abovementioned confounders.

**Discussion**

Our findings indicate that in stroke/TIA patients, AA atheroma progressed in \(28\%)\) and regressed in \(14\%)\) over a
12-month period. To the best of our knowledge, we are the first to report an association between AA progression and composite vascular events including stroke, TIA, MI, and death. The Kaplan-Meier plots (Figure 2) suggest a significant separation of survival curves in the progression and nonprogression group beyond the 12-month follow-up TEE. Observer bias is an unlikely explanation for the association because the echocardiographers grading AA atheroma and progression were masked to the patients’ clinical information, order of the TEE, and outcome. Sudden plaque rupture, thrombus formation, and subsequent incorporation of thrombus into atherosclerotic plaque are known to cause rapid progression of atherosclerosis.23 These activities increase the risk of embolization and clinically important ischemic vascular events.24 It is also possible that AA progression correlates with atheroma progression in other vascular territories, including the brain, leading to a high rate of vascular recurrence, including stroke and TIA. Nonetheless, vascular events such as MI, stroke, TIA, and vascular death may be linked to AA progression by shared vascular risk factors.

The study confirms our earlier finding that AA atheroma is a dynamic process, with progression noted in 29% and regression in 9%, and with AA atheroma progression correlating with hyperhomocysteinemia (≥14.0 μmol/L) and non-lacunar (TOAST) stroke subtypes.8 Montgomery et al25 prospectively reevaluated 30 patients with moderate to severe aortic plaque noted on initial planar/multiplanar TEE (obtained as part of a workup for cardiac or an embolic event). Over a mean of 1 year, progression was reported in 23% and regression in 10%.25 In a small group of 16 patients with familial hypercholesterolemia taking pravastatin, Pistavos et al.26 using monoplanar TEE, noted a rate of progression of 19% and a rate of regression of 38% over 2 years. More recently Geraci and Weinberger,27 using supraclavicular B-mode ultrasonography of the proximal AA in 89 patients evaluated for transient neurological symptoms, noted a progression rate of 19% and a regression rate of 18% over a mean of 7.7 months (range 3 to 18 months). Compared with these studies, we report a similar rate of progression (28% over 12 months). Parenthetically, in the extracranial vasculature, atheroma appears to progress at a lesser rate than AA over a longer follow-up. Thus, in the internal carotid artery, a progression rate of 15% to 19% has been reported over 1.5 to 3.0 years.8–11 Nonetheless, these studies did not report regression of carotid atheroma and did not assess risk factors associated with atheroma progression. The rate of regression of AA atheroma noted on TEE in the present study (14%) is similar to that reported in the initial TEE series (10%)25 but is lower than that reported in patients taking statins.26 Newer imaging modalities, including MRI, multidetector computed tomography, and electron-beam computed tomography, have been shown to be promising approaches to measure AA progression.28–30 Several recent trials testing the effect of statins and lipid-lowering agents have used MRI to image changes in the thoracic aorta.28 Yet, none of these trials have demonstrated an association between AA progression and vascular events. To the best of our knowledge, to date, multidetector computed tomography and electron-beam computed tomography have never been used to measure AA progression or associated vascular events.

The present study has limitations that merit comment. First, its generalizability may be limited by the requirement that individuals with stroke/TIA agree to have an initial and a follow-up TEE. The findings may not be extrapolated to the segment of the population that does not meet these requirements. In a study of community-based participants who were not referred for stroke evaluation, AA atheroma was not predictive of stroke at follow-up.34 Second, because TEE is a seminvasive test, measurements of AA atheroma at intermediate time points were not performed. Third, no significant association existed between traditional risk factors and AA plaque progression. This may have been because the moderate sample size in the present study resulted in the study being underpowered. Detection of such modest associations may have required a larger sample size, which was beyond the scope of the present study. Fourth, analyses of the relationships in the present study, by necessity, involved multiple tests of significance, with the resulting increased opportunity for type 1 error. For example, the results in Table 1 involved 16 tests of significance. Thus, although the significance level used here was α = 0.05, an even higher probability of a significant association could be expected by chance alone. After adjustment of the levels of nominal statistical significance for multiple testing with a family-wise error rate (FWER) of 0.05 (Bonferroni adjusted α-level: FWER/number of tests = 0.05/16 = 0.003), only homocysteine levels (P < 0.0001) and a high neutrophil count (P < 0.0001) were significantly associated with progression. Finally, the association between aortic plaque progression and composite vascular events noted in this preliminary study should be interpreted with caution because of its susceptibility to potential biases, such as those that arise from the selection process and unmeasured confounding. An example of unmeasured confounding could be the lack of data on between-group LDL cholesterol and blood pressure throughout the follow-up. Given the importance of lipid lowering and blood pressure on the progression of atheroma, this limits our ability to fully assess the role of AA plaque progression to predict recurrent vascular events.

Age, stroke subtype, and complex mobile plaque on index TEE, which may have had plausible associations with progression with an unadjusted α-level of 0.05, failed to show an association. Briefly, age may be reflective of duration of exposure to vascular risk factors on plaque formation, whereas the negative association of small-vessel occlusive strokes and AA atheroma progression probably reflects a converse positive association between the non–small-vessel occlusive strokes (cardioembolism and large-artery atherothrombosis) and AA atheroma progression. Prior studies have reported an association of large-artery atherothrombosis32 and cardioembolic sources33 with AA atheroma. Finally, complex mobile plaques are thought to represent mobile “debris” or a free-floating thrombus that might serve as a nidus for plaque activity and progression by thrombus accretion.19

The age- and gender-adjusted homocysteine and neutrophil counts were significantly associated with AA progression. Homocysteine may induce endothelial dysfunction–mediated
atheroma progression. Alternatively, hyperhomocysteinemia may result in thrombus accretion on the atheromatous plaque, or it may be a risk marker of atherosclerosis rather than being a risk factor or being in the causal pathway for vascular events. The association with neutrophil count suggests a potential inflammatory/infectious role in atherogenesis and stroke risk. Nevertheless, after the inclusion of the confounding covariates in the model, AA atheroma progression appeared to be associated with the composite of stroke, TIA, MI, and death. The results suggest that in stroke/TIA patients with AA atheroma, a subgroup can be identified who exhibit progression and associated recurrent vascular events on repeat TEE at 12 months. Further studies are needed to validate these findings and to determine whether treatment strategies may reduce this progression and the associated vascular events.

Sources of Funding
Dr Sen was funded by a clinical investigator development award from the Division of the National Institutes of Health. Funding for the study was provided by National Institutes of Health grants 1K23NS02117 and RR00046.

Disclosures
None.

References
Significant aortic arch atheroma is the second most prevalent cardioembolic risk factor for stroke after atrial fibrillation and is present in 16% to 20% of all patients with stroke and transient ischemic attack. It is a risk factor for new and recurrent stroke and has no definitive treatment. Our findings indicate that in stroke/transient ischemic attack patients, aortic arch atheroma has a high rate of progression (28%) and a regression rate of 14% over a 12-month period. We report an association between aortic arch atheroma progression and composite vascular events including stroke, transient ischemic attack, myocardial infarction, and death. The results suggest that in stroke/transient ischemic attack patients with aortic arch atheroma, a subgroup of patients can be identified who, on repeat transesophageal echocardiography at 12 months, exhibit progression and associated recurrent vascular events. Further studies are needed to validate these findings and to determine whether treatment strategies may reduce this progression and the associated vascular events.
Aortic Arch Atheroma Progression and Recurrent Vascular Events in Patients With Stroke or Transient Ischemic Attack
Souvik Sen, Alan Hinderliter, Pranab K. Sen, Jennifer Simmons, James Beck, Steven Offenbacher, E. Magnus Ohman and Stephen M. Oppenheimer

Circulation. 2007;116:928-935; originally published online August 7, 2007; doi: 10.1161/CIRCULATIONAHA.106.671727
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 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/116/8/928

An erratum has been published regarding this article. Please see the attached page for:
/content/116/11/e349.full.pdf

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

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

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
In the version of the article, “Aortic Arch Atheroma Progression and Recurrent Vascular Events in Patients With Stroke or Transient Ischemic Attack,” by Sen et al that was posted online on August 6, 2007 (DOI: 10.1161/CIRCULATIONAHA.106.671727), an error occurred.

In Table 3, the units for homocysteine should have read “μmol/L” rather than “μmol/dL.”

This error has been corrected in the final print version of the article in the August 21, 2007, issue of the journal (Circulation. 2007;116:928–935) and in the current online version. The publisher regrets this error.

DOI: 10.1161/CIRCULATIONAHA.107.186386