Risk Factors for Progression of Aortic Atheroma in Stroke and Transient Ischemic Attack Patients

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**Background and Purpose**—Aortic atheroma is an independent risk factor for stroke and undergoes temporal progression. Clinical and risk factor associations of such progression are unknown. Hyperhomocysteinemia has been linked with atherosclerosis, including that in the cerebral vasculature. This study investigated associations between elevated homocysteine levels and other stroke vascular risk factors and the risk of aortic atheroma progression in patients with cerebrovascular disease.

**Methods**—Fifty-seven stroke and 21 transient ischemic attack patients underwent multiplanar transesophageal echocardiograms within 1 month of symptom onset and again at 9 months. Aortic atheroma was graded and stratified by use of existing criteria. Stroke risk factors; use of anticoagulant, antiplatelet, and hypolipidemic drugs; and clinical and etiological subtypes of stroke were recorded and compared in patients stratified for the presence or absence of aortic atheroma progression.

**Results**—Of the 78, 29 (37%) progressed, 32 (41%) remained unchanged, and 17 (22%) regressed. Progression was most marked at the aortic arch (P≤0.005), followed by the ascending segment (P≤0.04). In nearly two thirds of the patients in whom aortic atheroma remained unchanged over 9 months, no atheroma was evident on baseline transesophageal echocardiogram. Only homocysteine levels ≥14.0 μmol/L (P≤0.02), total anterior cerebral infarct (P≤0.02), and large-artery atherosclerosis (P≤0.005) significantly correlated with progression.

**Conclusions**—Among vascular risk factors, elevated homocysteine levels are associated with aortic atheroma progression. Stroke and transient ischemic attack patients with aortic atheroma should undergo assessment of homocysteine levels, which, if elevated, may be treated with vitamins in an effort to arrest aortic atheroma progression. *(Stroke. 2002;33:930-935.)*

**Key Words:** atherosclerosis ■ echocardiography, transesophageal ■ hyperhomocysteinemia ■ ischemic attack, transient ■ risk factors ■ stroke

Aortic atheroma ≥4 mm is an independent risk factor for new and recurrent stroke1,2 for which there is no definitive treatment. Anticoagulation and antiplatelet agents are frequently used to treat stroke patients with aortic atheroma without any definitive evidence of beneficial effect in prevention of distal embolization.3 The lack of therapeutic options is partly attributable to the relatively few studies that have identified the natural history of aortic atheroma in stroke patients.4,5 These studies demonstrate a dynamic natural history with evidence of regression and progression, the former suggesting that aortic atheroma may be treatable. Prevention of progression to a more severe grade of aortic atheroma (≥4-mm thickness) could appreciably reduce stroke risk. Recent case series have cited the role of lipid-lowering agents in the treatment of aortic atheroma in patients with hyperlipidemia and conceivably may induce plaque regression.6,8 Recently, we reported segmental variation in risk factors promoting aortic atheroma in stroke and transient ischemic attack (TIA) patients.9 That study, along with previous studies in nonstroke patients, has shown a distal-proximal gradation with the greatest severity in the descending aorta and the least severity in the ascending aorta.10 Patients with distal aortic atheroma may therefore be candidates for strategies to arrest progression to the ascending segments, which may serve as a source of embolization to the cerebral vasculature. The present study investigated sequential changes in aortic atherosclerosis in each of the 3 thoracic aortic segments (ascending, arch, and descending). The role of stroke risk factors in promoting the progression of aortic atheroma over 9 months was analyzed. In addition, because hyperhomocysteinemia is an independent risk factor for cerebrovascular disease,11,12 coronary artery disease,13,14 peripheral vascular disease,15,16 carotid atherosclerosis,17,18 and...
aortic atheroma.\textsuperscript{19,20} A further objective of this study was to investigate whether hyperhomocysteinemia ($\geq 14.0$ $\mu$mol/L) was associated with aortic atheroma progression.

Methods

One hundred eighty-one consecutive patients admitted to Johns Hopkins hospital with stroke or TIA between 1995 and 1999 underwent first transesophageal echocardiographic (TEE) assessment within 1 month of symptom onset. Exclusion criteria were age $<18$ years, stroke of indeterminate onset, previous symptomatic stroke, subarachnoid hemorrhage, coma, and serious medical conditions limiting life expectancy. Of these patients, 115 returned for a 9-month visit, and 84 agreed to a second TEE. Of these 84 patients, 4 were excluded from analysis because of intracerebral hemorrhage and 2 because the aortic arch could not be adequately visualized. Seventy-eight patients were thus included in the analysis. All patients underwent a brain CT and/or MRI to confirm the diagnosis and assessment of risk factors and were classified into one of the 3 groups of patients with and without progression of aortic atheroma. Most of these patients (44 of 54, 81\%) had a fasting homocysteine level assessment between the first and third months after stroke onset (mean, 47 days).

TEE Assessment of Aortic Atheroma

Patients were assessed with omniplanar TEE. Details of the procedure and gradation of aortic atheroma have previously been described.\textsuperscript{9} Briefly, with a Hewlett-Packard Sonos 1000 system and a 5.0-MHz transducer of a Hewlett-Packard 21364A transesophageal probe, the ascending, arch, and descending segments of the thoracic aorta were visualized. Aortic atheroma was graded as mild ($<1$ mm), moderate (1 to 3.9 mm), or severe ($\geq 4$ mm) by use of the criteria of Amarenco et al.\textsuperscript{1} Two cardiologists blinded to clinical status and previous TEE data reviewed each TEE videotape independently. Aortic atheroma progression was defined as an increase in maximal plaque thickness in each segment by $\geq 1$ grades. Similarly, regression was defined as a decrease in maximal thickness of atheromatous plaque by $\geq 1$ grades. To compare the frequency of change in each aortic segment, changes in severity were ranked as $+2$ if worsening occurred by 2 grades, $+1$ in cases of worsening by 1 grade, 0 in cases of no change, $-1$ if improvement occurred by 1 grade, and $-2$ if there was improvement by 2 grades.

Demographics and Risk Factors

Simple definitions of cerebrovascular risk factors paralleled the routine clinical setting as follows: hypertension, previously diagnosed with patient already taking antihypertensive medication; diabetes, previously diagnosed with or without treatment with an antidiabetic agent; hypercholesterolemia, previously diagnosed with or without treatment with cholesterol-lowering medications; cigarette smoker, smoking $\geq 1$ cigarette daily; alcohol user, alcoholic beverages consumed daily; peripheral vascular disease, symptoms of intermittent claudication or peripheral vascular disease with confirmation by ultrasonographic vascular study or previous peripheral vascular bypass surgery; atrial fibrillation, history of atrial fibrillation or atrial fibrillation on admission ECG and/or 24-hour Holter examination; coronary artery disease, confirmed history of myocardial infarction, angina, or ischemic cardiac failure; and TIA, neurological symptoms of sudden onset (nonconvulsive) of presumed vascular origin lasting $<24$ hours without evidence of structural damage on CT/MRI. Patients suspected of complicated migraine or seizures or those presenting with vague neurological symptoms were excluded. Stroke was defined as persistent neurological deficit of sudden onset (nonconvulsive) lasting $>24$ hours with CT/MRI confirmation.

Homocysteine Measurement

Patients without renal failure (creatinine $\geq 2.5$ mg/dL) were included in the assessment of fasting plasma homocysteine level. None were taking medications (eg, Dilantin) known to elevate homocysteine levels. Fasting blood samples were transported on ice, and plasma was separated and stored at 4$^\circ$C until measurement of total homocysteine with high-performance liquid chromatography with fluorescence detection.

Stroke Classification and Etiology

Strokes were classified according to the Oxfordshire Community Stroke Project (OCSF) criteria.\textsuperscript{21} In brief, lacunar infarcts were diagnosed if patients presented clinically with pure motor, sensory, or ataxic hemiparetic findings confirmed with an appropriate CT/MRI lesion. Total anterior circulation infarcts (TACIs) were diagnosed if patients presented with a cortical disorder (eg, dysphasia, dyscalculia) and/or homonymous hemianopsia and/or ipsilateral sensory or motor findings involving at least 2 regions with CT/MRI confirmation. Posterior circulation infarcts were diagnosed in the presence of cranial nerve palsies and contralateral motor or sensory deficits, bilateral motor or sensory findings, or disorders of eye movement or cerebellar dysfunction. Partial anterior circulation infarcts were diagnosed if patients presented with only 2 of the 3 components of the TACI syndrome and CT/MRI confirmation of an appropriate lesion.

Stroke origin was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.\textsuperscript{22} Cardioembolic cause was considered in patients with major brain artery or branch cortical artery occlusion who had at least 1 cardiac source identified according to the TOAST criteria. Potential large-artery atherosclerotic source of thrombosis or embolism was assessed by carotid ultrasound and/or MR angiography. Only transthoracic echocardiography (not TEE), ECG, and 24-hour Holter data were used to determine cardiac source listed in the TOAST classification.

Statistical Analysis

The Wilcoxon signed-rank test was used to determine whether progression of severity grade of aortic atheroma was significant in each of the 3 segments of the thoracic aorta. Any association of stroke subtype with progression of aortic atheroma was explored with the $\chi^2$ test. Two-tailed $t$ tests compared mean ages and mean levels of serum cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and homocysteine of the 2 groups of patients with and without progression of aortic atheroma. Univariate analysis with the $\chi^2$ test investigated the association between each stroke risk factor except age and progression of aortic atheroma. Finally, multiple logistic regression explored the association between aortic atheroma progression and all stroke risk factors. This technique allows assessment of whether stroke risk factors independently increased the chance of detecting progression of aortic atheroma by TEE. The $k$ index assessed interobserver reliability between the 2 cardiologists assessing TEE evidence of aortic atheroma. Statistical analysis was performed with SPSS for Windows, version 10.0.

Results

Seventy-eight patients underwent TEE within 1 month of stroke or TIA and again at 9 months. Of these, 51\% were female, 74\% were black, 23\% were white, and 1.5\% (each) were Asian and Hispanic. Fifty-seven (73\%) suffered an ischemic stroke, and 21 (27\%) had a TIA as the qualifying cerebrovascular event. The first TEE was performed at 9.5 to 14 days and the second at 9.6 $\pm$ 1 months. The $k$ indexes for interobserver reliability between the 2 blinded cardiologists grading the aortic plaque by TEE were 0.76, 0.72, and 0.79 for the ascending, arch, and descending segments, respectively. In 37\% patients, aortic atheroma progressed by $\geq 1$ grade. Of the remaining 63\% patients, 22\% exhibited regres-
sion by \( \geq 1 \) grade, and 41\% showed no change. Patients who exhibited regression of aortic atheroma were identical to those who revealed no change in terms of demographics, frequency of risk factors, and stroke subtypes and therefore were grouped together for analysis.

Changes in Thoracic Aortic Atheroma According to Segment
These changes are depicted schematically for the ascending (Figure 1), arch (Figure 2), and descending (Figure 3) segments of thoracic aorta. In all segments, most plaques remained unchanged (54 of 78, 69\%, in the ascending; 48 of 78, 61\%, in the arch; 51 of 78, 65\%, in the descending segment). Of these, most showed no or minimal atheroma (<1 mm) at baseline (grade 1: 44 of 54, 81\%, in the ascending; 35 of 48, 73\%, in the arch; 27 of 51, 53\%, in the descending segment). Progression predominantly occurred from grade 1 to 2 (15 of 18, 83\%, in the ascending; 17 of 23, 74\%, in the arch; 8 of 15, 53\%, in the descending segment). Regression occurred in a small proportion of patients (6 of 78, 8\%, in the ascending segment; 7 of 78, 9\%, in the arch; 12 of 78, 15\%, in the descending segment). Aortic atheroma progression occurred more frequently in the arch (\( P=0.005 \)) and the ascending segment (\( P=0.036 \)); there was no significant difference in progression rate identified in the descending segment compared with other segments (\( P=0.635 \)).

Vascular Risk Factors and Medications
On univariate testing, no significant differences were detected in the prevalence of more common vascular risk factors in patients with or without progression of thoracic aortic atherosclerosis (Table 1). However, hyperhomocysteinemia (\( \geq 14.0 \) \( \mu \)mol/L) was significantly associated with progression of aortic atheroma (\( P=0.02 \)). Similarly, on multivariate analysis, hyperhomocysteinemia was again significantly associated with progression of aortic atheroma (\( P=0.02 \)) and was the only vascular risk factor to show this association. Although the mean homocysteine level was higher in patients with (12.0 \( \mu \)mol/L) than in those without (9.8 \( \mu \)mol/L) progression, the difference just escaped statistical significance (\( P=0.06 \)).

Of the 78 patients, 2 were taking warfarin at the time of the sentinel event, and 25 were subsequently placed on this treatment after investigation into the cause of stroke or TIA. Five patients were taking aspirin or antiplatelets at the time of their stroke or TIA, and 37 subsequently began this treatment. Of those patients with hypercholesterolemia, 19 were taking statins at the time of initial presentation. The remaining 11 were not receiving medications for this condition but were treated with diet and/or dietary supplements. There was no significant difference in lipid profile (mean levels of total cholesterol, LDL, HDL, and triglycerides) between the progression and nonprogression groups (Table 1).

There was equal exposure to treatment with antiplatelet agents (aspirin, ticlopidine, or clopidogrel), oral anticoagulants (warfarin), or hypolipidemic agents (statins) in patients with and without aortic atheroma progression (Table 2). In addition, no association was found between medication exposure and regression of aortic atheroma.
TABLE 1. Prevalence of Risk Factors in Patients With or Without Progression of Atherosclerosis

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Progression (N=29)</th>
<th>No Progression (N=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61±12</td>
<td>59±12</td>
<td>0.4*</td>
</tr>
<tr>
<td>Black race, n (%)</td>
<td>19 (65)</td>
<td>39 (80)</td>
<td>0.2</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>14 (48)</td>
<td>24 (49)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>23 (79)</td>
<td>32 (65)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>10 (34)</td>
<td>18 (37)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>12 (41)</td>
<td>18 (37)</td>
<td>0.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>201±50</td>
<td>193±43</td>
<td>0.5*</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>127±47</td>
<td>112±37</td>
<td>0.1*</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>47±12</td>
<td>48±15</td>
<td>0.8*</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>141±70</td>
<td>148±72</td>
<td>0.7*</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>21 (72)</td>
<td>35 (71)</td>
<td>0.9</td>
</tr>
<tr>
<td>Alcohol use, n (%)</td>
<td>12 (41)</td>
<td>21 (43)</td>
<td>0.9</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>7 (24)</td>
<td>12 (24)</td>
<td>1.0</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>1 (3)</td>
<td>2 (4)</td>
<td>0.9</td>
</tr>
<tr>
<td>PVD, n (%)</td>
<td>4 (14)</td>
<td>5 (10)</td>
<td>0.6</td>
</tr>
<tr>
<td>Hyperhomocysteinemia, n (%)</td>
<td>6/17 (35)</td>
<td>2/27 (7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Homocysteine level, μmol/L</td>
<td>12.0±3.8</td>
<td>9.8±3.5</td>
<td>0.06*</td>
</tr>
</tbody>
</table>

*P test (equality of variance assumed). All others used χ² test for equality of proportions.

CAD indicates coronary artery disease; PVD, peripheral vascular disease. Values are mean±SD when appropriate.

TABLE 2. Effect of Medication on Progression of Atherosclerosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Progression (n=29), n (%)</th>
<th>No Progression (n=49), n (%)</th>
<th>P (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet agent</td>
<td>19 (65)</td>
<td>23 (47)</td>
<td>0.1</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>7 (24)</td>
<td>20 (41)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypolipidemic agent</td>
<td>8 (28)</td>
<td>11 (22)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

TABLE 3. Stroke Subtypes According to TOAST Criteria

<table>
<thead>
<tr>
<th>OCSP Subtype</th>
<th>Progression (n=29), n (%)</th>
<th>No Progression (n=49), n (%)</th>
<th>P (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACI</td>
<td>3 (10)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>PACI</td>
<td>6 (21)</td>
<td>13 (26)</td>
<td>0.6</td>
</tr>
<tr>
<td>LACI</td>
<td>8 (28)</td>
<td>19 (39)</td>
<td>0.3</td>
</tr>
<tr>
<td>POCI</td>
<td>4 (14)</td>
<td>4 (8)</td>
<td>0.4</td>
</tr>
<tr>
<td>TIA</td>
<td>8 (28)</td>
<td>13 (26)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

PACI indicates partial anterior circulation infarct; LACI, lacunar infarcts; and POCI, posterior circulation infarcts.

TABLE 4. Stroke Subtypes According to TOAST Criteria

<table>
<thead>
<tr>
<th>TOAST Subtype</th>
<th>Progression (n=29), n (%)</th>
<th>No Progression (n=49), n (%)</th>
<th>P (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolic</td>
<td>0</td>
<td>5 (10)</td>
<td>0.08</td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>6 (21)</td>
<td>1 (2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Small-artery occlusion</td>
<td>11 (38)</td>
<td>19 (39)</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>4 (14)</td>
<td>11 (22)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Stroke Classification

TACI (Table 3) and large-artery atherosclerosis stroke as the cause of stroke (Table 4) were significantly associated with an increase in aortic plaque thickness. TEE data were not used to ascertain the TOAST classification.

Discussion

This study indicates that aortic atheroma is a dynamic process: 37% of stroke/TIA patients showed plaque progression over 9 months, and 22% showed regression over a similar period. Traditional vascular stroke risk factors did not appear to influence these changes. Progression of aortic atheroma correlated with hyperhomocysteinemia (≥14.0 μmol/L), TACI (OCSP), and large artery atherosclerosis (TOAST) subtypes of stroke.

Montgomery et al prospectively reevaluated 30 patients with moderate to severe aortic plaque noted on initial biplanar or multiplanar TEE (obtained as part of a workup for cardiac disease or an embolic event). Over a mean period of 1 year, progression was reported in 23% and regression in 10%. In a small group of 16 patients with familial hypercholesterolemia taking pravastatin, Pistavos et al using monoplanar TEE, noted a progression rate of 19% and a regression rate of 38% over 2 years. More recently, Geraci and Weinberger, using supravclavicular B-mode ultrasonography of the proximal aortic arch in 89 patients evaluated for transient neurological symptom or nonspecific dizziness, noted a progression rate of 19% and a progression rate of 18% over a mean of 7.7 months (range, 3 to 18 months). Compared with these studies, we report a higher rate of progression (37%). The discrepancy may reflect the selection in the present study of symptomatic patients with well-defined cerebrovascular events who could possibly be at higher risk of progression. Symptomatic patients may have a greater degree of plaque instability and therefore, conceivably, a greater likelihood of developing intraplaque hemorrhage, leading to an increase in thickness. In addition, multiplanar TEE was used in the present study, a technique that is possibly more sensitive than monoplanar or biplanar TEE in accurately grading aortic atheroma. A further point for consideration relates to the high incidence of smokers (72%) in this study compared with other studies. Although this might combine with other as-yet-unidentified factors to increase the incidence of atheroma progression, the percentages of smokers in the progression and nonprogression groups were similar (Table 1). Finally, in previous studies, repeated investigations were distributed over a wide range of time periods, which might skew data. Parenthetically, in the extracranial vasculature, atheroma appears to progress at a slower rate over longer follow-up. Thus, in the internal carotid artery, a progression rate of 15% to 19% has been reported over 1.5 to 3 years. Compared with these studies, we report a higher rate of progression (37%).
ing to a thickness of 7 or 8 mm may be graded as severe (grade 3) in both instances and hence may be regarded falsely as not having progressed. Second, use of thickness as the only variable does not consider the effect of aortic remodeling that is associated with atherosclerosis. Age-related loss of elasticity frequently results in distension and unfolding of the aortic arch and accompanies aortic atherosclerosis.\(^2\)\(^6\) Hence, use of plaque area and plaque burden may be a better way to quantify aortic atheroma. Third, we did not investigate the development of new plaques or qualitative changes such as plaque mobility, protrusion, ulceration, and hypoechochogenicity, variables that have been implicated in increasing embolic risk.\(^2\)\(^7\) Fourth, because TEE is a semi-invasive test, it is difficult to have a complete measurement of aortic atheroma beyond the 2 time points. This limits the examination of plaque changes that may occur between the 2 studies or beyond the second study at 9 months. Finally, the lack of association between traditional risk factors and change in plaque thickness may indicate a lack of sufficient power to detect such relationships once the cohort is broken into smaller subgroups for comparison.

Of the 181 sequential stroke and TIA patients undergoing TEE examination during the study period, only 43% were included in the analysis. The representative nature of this sample could be questioned. Comparison of these 78 patients with the 103 patients excluded from the study indicates no significant differences in demographic factors (age, race, sex, and traditional risk factors for stroke); 18% of the included patients and 17% of those excluded fulfilled the criteria for hyperhomocysteinemia. There were no differences in medication profile, clinical stroke distributions (OCSP), or TOAST stroke subtype. We therefore suggest that these data are probably representative of the larger group of patients from whom this study group was drawn.

Previously, we reported that atheroma most severely affects the descending segment, followed by the arch and ascending aorta. A differential contribution of risk factors associated with aortic atheroma formation in these 3 segments was detected.\(^9\) We therefore speculated that the atheroma process originates in the descending segment and progresses to the arch and ascending segments. These findings are in agreement with the observation of the present study that the incidence of progression of atheroma was greatest in the aortic arch, followed by the ascending aorta. It is possible that the descending segment, by virtue of its more severe plaque thickness, is subjected to the ceiling effect described earlier and hence is less likely to show progression in plaque severity with the use of current criteria.

We report that elevated homocysteine levels (≥14.0 μmol/L) significantly correlated with progression of aortic atheroma. It is possible that homocysteine may mediate endothelial dysfunction, resulting in plaque progression.\(^2\)\(^8\) Alternatively, hyperhomocysteinemia may produce a hypercoagulable state that may result in thrombus deposition on the atheromatous plaque.\(^2\)\(^9\) Because hyperhomocysteinemia specifically can be treated with vitamin therapy (folic acid, B6, B12), it can be speculated that such treatment may prevent the progression of aortic atheroma. Indeed, a recent study has indicated that progression of carotid atherosclerosis may be arrested and regression could be promoted by treating hyperhomocysteinemia with folic acid 2.5 mg/d, pyridoxine 25 mg/d, and cyanocobalamin 250 μg/d.\(^3\)\(^0\) although it should be noted that the natural history of carotid atherosclerosis may differ from that in the aortic arch.

TACI is commonly attributed to large-artery atherosclerosis that results in occlusion of or cardioembolism in the anterior cerebral arteries (middle cerebral or internal carotid artery). Because large-artery atherosclerosis, a major cause of TACI, and aortic atheroma share risk factors, it is not surprising that large-artery atherosclerosis on TOAST and TACI in the OCSP stroke classification correlated significantly with progression of aortic atheroma. It is conceivable that measures used to prevent progression of aortic atheroma may similarly affect other large cerebral arteries and result in a reduction of overall stroke risk. Previously, we have described a link between proximal segmental (ascending aorta and aortic arch) atheroma and coronary artery disease.\(^9\) This suggests that plaque progression to these segments may be associated with cardiac ischemia, intracardiac thrombus, and hence cardioembolic stroke. Thus, the relationship between TACI and progression does not exclude the possibility that aortic atheroma plaque progression may be associated with coronary artery disease and may contribute to intracardiac thrombus formation and hence cardioembolic stroke.\(^3\)\(^1\) In fact, the relationship between cardioembolic stroke origin and aortic plaque progression bordered on significance (\(P=0.08\)).

The lack of demonstrated beneficial effect of stroke prevention medications in this study may have several possible causes. First, power issues may interfere with the ability to demonstrate anything other than substantial efficacy. In this regard, there are at least 2 possible causes of plaque progression, each with therapeutic implications. If this is a result of accretion of atherothrombotic material, antithrombotic agents may be beneficial. Alternatively, if it results from plaque instability and associated intraplaque hemorrhage, plaque stabilization with statins may be more appropriate. Although we are constrained in studying the effect of these medications on plaque progression by sample size, it is possible that the lack of efficacy of antiplatelet agents and anticoagulants may be related to a greater atheromatous component than thrombus in the plaque. A second issue relates to the time of exposure. Many patients started treatment after the sentinel event, and it may well be that this was insufficient to demonstrate an effect on progression prevention or regression. Further studies are therefore needed to investigate stratified treatment approaches that are based on the specifics of plaque composition, as well as duration of potential therapies.

Conclusions

Aortic atheroma is a dynamic disease in stroke and TIA patients, progressing in 37% and regressing in 22%. The most significant progression occurred in the aortic arch, followed by the ascending segment. There is a possible distal-proximal distribution of aortic involvement with atheromatous plaque; hence, arresting progression to involvement of proximal segments, as well as to a severe grade (≥4 mm), may reduce the risk of embolization to the cerebral vasculature.
Progression of aortic atheroma independently correlates with elevated homocysteine levels (≥14 μmol/L). Homocysteine may serve as a mediator of aortic plaque progression; therefore, levels should be ascertained in stroke and TIA patients with aortic atheroma. If elevated, this may be amenable to vitamin therapy. Progression also correlated with TACI (OCSP) and large-artery atherosclerosis (TOAST).

Existing therapy used in stroke prevention (antiplatelet agents, anticoagulants, statins) may not influence the progression of aortic atheroma, and investigation of new treatment approaches may be indicated.

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References


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