Mitral Annular Calcification, Aortic Valve Sclerosis, and Incident Stroke in Adults Free of Clinical Cardiovascular Disease
The Strong Heart Study

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Background and Purpose—Mitral annular calcification (MAC) and aortic valve (AV) sclerosis have each been linked to cardiovascular disease. Whether MAC and AV sclerosis are risk factors for stroke independent of other echocardiographic or laboratory predictors has not been established. We evaluated the relationship between MAC, AV sclerosis, and first stroke events in a population-based cohort.

Methods—Our study cohort consisted of 2723 American Indians participating in the Strong Heart Study who were free of prevalent cardiovascular disease. Participants underwent standardized clinical, echocardiographic, and laboratory evaluation, and incident stroke was ascertained using validated methods.

Results—During a median follow-up of 7 years, 86 strokes occurred. Age- and sex-adjusted incidence rates of stroke were significantly increased for MAC (rate ratio [RR], 3.12; 95% CI, 1.77 to 5.25) but not for AV sclerosis (RR, 1.15; 95% CI, 0.45 to 2.49). MAC was also associated with a reduced time to first stroke events after adjustment for clinical variables and the inflammatory markers C-reactive protein and fibrinogen (hazard ratio [HR], 2.42; 95% CI, 1.39 to 4.21) or the echocardiographic covariates left ventricular hypertrophy and left atrial enlargement (HR, 1.89; 95% CI, 1.04 to 3.41). Individuals with and without AV sclerosis showed no significant difference in stroke-free survival in unadjusted analyses (P=0.698). Crossing of the survival curves precluded multivariable analysis using Cox models.

Conclusions—In this cohort of American Indians without clinical cardiovascular disease, the presence of MAC, but not AV sclerosis, proved to be a strong risk factor for incident stroke after extensive adjustment for other predictors. Individuals exhibiting MAC may benefit from aggressive risk factor modification, but this will require further investigation. (Stroke. 2005;36:000-000.)

Key Words: calcium ■ echocardiography ■ heart valves ■ stroke

Mitral annular calcification (MAC) is characterized by calcium and lipid deposition in the annular fibosa of the mitral valve, whereas aortic valve (AV) sclerosis results from similar accumulation involving the AV leaflets. Clinical precursors of atherosclerosis are also risk factors for MAC and AV sclerosis, and the 2 conditions often exist concurrently. Each, in turn, has been documented to be an independent predictor of cardiovascular events. Several studies although not all, studies have detailed a similar relationship between MAC and stroke, but an independent association between AV calcification and cerebral infarction has only been demonstrated in the presence of AV stenosis. MAC and AV sclerosis are associated with atherosclerosis risk factors that can promote left ventricular (LV) hypertrophy and left atrial (LA) enlargement, each of which has been reported to predict cerebrovascular events. However, available studies linking valvular calcification with cerebral ischemia have adjusted only partly, if at all, for these concurrent echocardiographic predictors. Whether valvular calcification has prognostic value independently of these
abnormalities in cardiac chamber structure is uncertain. Furthermore, inflammatory markers are also correlated with valvular calcification\textsuperscript{14} and have emerged as risk factors in their own right for the occurrence of stroke.\textsuperscript{15,16} Yet the degree to which MAC and AV sclerosis provide additive information to that afforded by these easily obtained measures of inflammation is unknown. We addressed these questions in a population-based cohort free of clinical cardiovascular disease.

Methods

Participants

The Strong Heart Study is a population-based survey of risk factors for cardiovascular disease in 13 American Indian communities.\textsuperscript{17,18} Tribe members 45 to 74 years of age were recruited for an initial examination (July 1989 to January 1992), which included collection of fasting blood samples.\textsuperscript{19–21} The second examination (July 1993 to December 1995) involved the addition of echocardiography, performed in 97% of 3501 returning individuals. The present analyses are limited to 2723 participants in the second examination free of clinical or echocardiographic cardiovascular disease. Clinical cardiovascular disease included a history of stroke, transient ischemic attack, coronary heart disease (CHD), congestive heart failure (CHF), or atrial fibrillation (AF). AF was also excluded by digitized ECG, available for 100% in the initial examination, but only for 30.2% of the study cohort in the second examination because of a catastrophic disk crash; and by echocardiography, based on the presence of a documented A wave on the transmitral Doppler profile. Echocardiographic disease included $>1+$ mitral or aortic regurgitation or stenosis of any severity, LV ejection fraction $<0.50$, or segmental wall motion abnormalities.

Echocardiographic Methods and Measurements

Cardiac sonography was performed with phased-array echocardiograms following a standardized protocol.\textsuperscript{22} A computerized review station equipped with digitizing tablet and monitor overlay was used for measurement. Assessment of LV internal dimensions and wall thicknesses and of LA dimension has been described.\textsuperscript{25} The LA was traced in M-mode or 2D imaging at the base of the mitral leaflets on M-mode or 2D imaging in parasternal or apical windows. Determination of AV sclerosis relied on visualization of bright echoes on the AV leaflets, irrespective of AV orifice or stenosis of any severity, LV ejection fraction $<0.50$, or segmental wall motion abnormalities.

Calculation of Derived Variables

End-diastolic LV dimensions were used to calculate LV mass as described previously.\textsuperscript{23} LV hypertrophy was defined by previously derived partition values of LV mass indexed by height.\textsuperscript{23} Previously determined cut points were used to define the upper limits of normal LA diameter.\textsuperscript{23} LV ejection fraction was derived by Teichholz's method.\textsuperscript{26}

Clinical End Points

Procedures for cardiovascular end point ascertainment have been described.\textsuperscript{26} Adjudication of stroke events was based on the International Diagnostic Criteria.\textsuperscript{27} Definite nonfatal stroke required: (1) a history of rapid-onset, localizing neurologic deficit or change in state of consciousness; (2) documentation of localizing neurologic deficit by a physician or of cerebral infarction or intracranial hemorrhage by imaging within 6 weeks of onset, with $\geq 24$ hours duration of objective physician findings; and (3) no other disease process or event that could cause a localizing neurologic deficit or coma according to medical records. Possible nonfatal stroke required items 1 and 3 above, but in lieu of item 2, relied on an International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM) discharge diagnosis consistent with stroke. For fatal stroke events, a suitable autopsy diagnosis or ICD-9-CM code for imme-

diate or underlying cause on a death certificate could additionally be used for a "definite" or "possible" classification, respectively.

Strokes were categorized as ischemic or hemorrhagic, and the former was classified according to a previously reported scheme:\textsuperscript{28} cardioembolic in the presence of supportive cardiac history or findings; atherothrombotic in the setting of a $\geq 50\%$ stenosis of an ipsilateral cervicobrachial artery; lacunar when characterized by a clinical lacunar syndrome and either negative brain imaging or a corresponding deep lesion $\geq 1.5$ cm in diameter; or other, unknown infarction defying classification into any 1 of the foregoing categories.

Statistical Analysis

Adjusted comparisons used logistic regression and analysis of covariance as appropriate. MAC and AV sclerosis were analyzed as binary variables. Incidence rates were adjusted for age and sex using direct standardization to the entire study cohort. The log-rank test and Cox models were used to assess unadjusted and adjusted differences in time to stroke events, respectively. Eight clinical variables were considered potential confounders, including continuous age, body mass index, total/high-density lipoprotein cholesterol, and logarithmically transformed serum creatinine, and binary sex, hypertension, diabetes, and current smoking. Also considered were the categorical echocardiographic variables LA enlargement and LV hypertrophy and the continuous inflammatory markers CRP (logarithmically transformed) and fibrinogen. Covariates exhibiting univariable relationships to stroke-free survival in Cox models at a significance of $P<0.20$ were included in multivariable analyses. Fulfillment of proportional hazards assumption was tested by use of log–log plots.

Results

The characteristics of the study cohort are presented in Table 1, with generally greater prevalences or values for cardiovascular risk factors among individuals with MAC or AV sclerosis.

During a median follow-up of 7 years, there were 86 strokes, 55 (64%) of which were definite and 10 (11.6%) were fatal. Available information prevented classification of stroke in 16 cases. Sixty-eight patients had documented computed tomography or MRI of the brain. Neurovascular imaging was documented in 46 cases. Sixty-two strokes were ischemic, comprising 7 (11.3%) cardioembolic, 6 (9.7%) atherothrombotic, 19 (30.6%) lacunar, and 30 (48.4%) other, unknown infarctions. Eight events were intraparenchymal hemorrhages.

There were 19 incident strokes in individuals with MAC and 7 in participants with AV sclerosis. Age- and sex-adjusted incidence rates for individuals with and without MAC were 12.6 and 4.1 per 1000 person years (incidence rate ratio [IRR], 3.12; 95% CI, 1.77 to 5.25), and for participants with and without AV sclerosis, 5.4 and 4.7 per 1000 person years (IRR, 1.15; 95% CI, 0.45 to 2.49).

Kaplan–Meier curves (Figure) illustrate a significantly shorter stroke-free time for individuals with MAC but not with AV sclerosis. For MAC, the corresponding unadjusted hazard ratio (HR) for stroke is shown in Table 2. This increased risk was diminished after adjustment for clinical risk factors, indicative of confounding. Further confounding was uncovered after adjustment for echocardiographic predictors, chiefly LA enlargement. This attenuated the association further, but the latter remained statistically significant (HR, 1.89; 95% CI, 1.04 to 3.41). Separate adjustment for...
inflammatory markers did not meaningfully alter the association observed after controlling for clinical predictors. The relationship was virtually unchanged after exclusion of interim cases of myocardial infarction, CHF, or AF.

In contrast to MAC, for which the proportional hazards assumption was satisfied, the hazards associated with AV sclerosis were not proportional. This precluded use of multivariable Cox models to assess the relationship between AV sclerosis and incident stroke. It also prevented adjustment for this variable in models assessing the relationship between MAC and stroke. Nevertheless, when evaluation was limited to the subset of participants without AV sclerosis, the relationship between MAC and stroke did not change appreciably.

Discussion
This study shows MAC, but not AV sclerosis, to be an independent predictor of stroke events in American Indians without clinical cardiovascular disease. To our knowledge, this is the first time that MAC has been determined to confer prognostic information after comprehensive adjustment for clinical confounders and echocardiographic or inflammatory covariates.

Previous studies have reported conflicting findings with respect to MAC and stroke. A prospective evaluation of older adults documented a significant relationship after adjustment for selected clinical and echocardiographic covariates, but this was not confirmed by another prospective study of older subjects. Like these studies, the strengths of the present investigation lie in its population-based design and its systematic ascertainment of baseline risk factors and incident events. However, the focus of our study is on a younger, ethnically distinct cohort with a high prevalence of atherosclerosis risk factors. Although there are no data regarding different ethnic predispositions to MAC, the consistent association of the latter with atherosclerosis risk factors across populations makes an ethnic susceptibility independent of these factors unlikely. Regardless, our results in this ethnically distinct population after extensive adjustment for

### Table 1: Baseline Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort</th>
<th>MAC+ (n=252)</th>
<th>MAC− (n=2471)</th>
<th>AV Sclerosis+ (n=204)</th>
<th>AV Sclerosis− (n=2519)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>59.2±7.7</td>
<td>62.9±8.2</td>
<td>58.8±7.5</td>
<td>&lt;0.001</td>
<td>64.5±7.9</td>
<td>58.8±7.5</td>
</tr>
<tr>
<td>Women, %</td>
<td>64.9</td>
<td>76.2</td>
<td>63.7</td>
<td>&lt;0.001</td>
<td>53.9</td>
<td>65.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>43.9</td>
<td>60.7</td>
<td>42.3</td>
<td>&lt;0.001</td>
<td>57.4</td>
<td>42.9</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>46.9</td>
<td>57.2</td>
<td>45.9</td>
<td>0.001</td>
<td>52.7</td>
<td>46.4</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>31.2</td>
<td>23.2</td>
<td>32.1</td>
<td>0.210</td>
<td>27.4</td>
<td>31.5</td>
</tr>
<tr>
<td>Total/high-density lipoprotein cholesterol†</td>
<td>5.0±1.9</td>
<td>5.1±2.1</td>
<td>5.0±1.8</td>
<td>0.082</td>
<td>5.3±2.6</td>
<td>5.0±1.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²†</td>
<td>31.5±6.3</td>
<td>32.4±6.4</td>
<td>31.3±6.3</td>
<td>0.005</td>
<td>30.5±5.8</td>
<td>31.5±6.3</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL†</td>
<td>0.9±1.4</td>
<td>0.9±1.5</td>
<td>0.9±1.4</td>
<td>0.557</td>
<td>0.9±1.5</td>
<td>0.9±1.4</td>
</tr>
<tr>
<td>LA enlargement, %</td>
<td>16.3</td>
<td>31.5</td>
<td>14.7</td>
<td>&lt;0.001</td>
<td>22.0</td>
<td>15.8</td>
</tr>
<tr>
<td>LV hypertrophy, %</td>
<td>18.9</td>
<td>31.5</td>
<td>17.6</td>
<td>0.001</td>
<td>25.3</td>
<td>18.4</td>
</tr>
<tr>
<td>AV sclerosis, %</td>
<td>7.5</td>
<td>17.9</td>
<td>6.4</td>
<td>&lt;0.001</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>MAC, %</td>
<td>9.3</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>22.1</td>
<td>8.2</td>
</tr>
<tr>
<td>C-reactive protein, g/L†</td>
<td>3.9±2.7</td>
<td>4.1±2.8</td>
<td>3.9±2.7</td>
<td>0.761</td>
<td>3.6±3.0</td>
<td>3.9±2.6</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL†</td>
<td>359±81</td>
<td>374±93</td>
<td>358±80</td>
<td>0.083</td>
<td>375±94</td>
<td>358±80</td>
</tr>
</tbody>
</table>

*Age- and sex-adjusted; †Mean±SD.

a, MAC and incident stroke. b, AV sclerosis and incident stroke.
potential confounders not only buttress but also widen the scope of previous observations detailing a MAC–stroke relationship.

Furthermore, unlike previous investigations of MAC and cerebrovascular events, the present study also assessed the predictive value of AV sclerosis, with which MAC shares common risk factors and histopathologic features. Our analyses failed to demonstrate a univariable or age- and sex-adjusted association between AV sclerosis and stroke outcomes. Absence of proportional hazards precluded multivariable adjustment of the AV sclerosis–stroke relationship by Cox models, but such adjustment for covariates that bear a relationship to the exposure of interest and are themselves predictors of the outcome would have been expected, if feasible, to result in a weakening of the unadjusted association.

Several explanations may account for the predictive ability of MAC for incident stroke detailed herein. Because MAC is determined by the same clinical risk factors that lead to subclinical and then to clinical atherosclerosis, it may reflect the strength and duration of exposure to these risk factors better than cross-sectional assessments of the same. Moreover, MAC may also signal a susceptibility to the development of atherosclerosis in response to the same risk factor profile. Thus, MAC may serve as an accurate time-averaged marker of subclinical atherosclerotic disease and, hence, of cerebrovascular risk. Support for this notion is provided by reports of associations between MAC and aortic atheroma, carotid atherosclerosis, and CHD, all of which are direct or indirect determinants of stroke risk.

However, MAC may not be a marker of stroke risk exclusively but may also play a causative role in thromboembolism. Various reports attest to this possibility by documenting mobile calcific or thrombotic debris, often in the setting of frank ulceration of annular calcium, in patients with cerebral embolism, and even demonstrating calcific or bland emboli in the infarct-related artery at autopsy. In addition, MAC may predispose to infective endocarditis and embolization of vegetative material. MAC has also been reported to be a risk factor for incident AF, although the present analyses accounted in large measure for this risk.

The absence of a relationship between AV sclerosis and stroke is unexpected. It is no less well documented that AV calcification is related to atherosclerosis risk factors, aortic and carotid atheroma, and CHD than it is for MAC. But the failure to detect an AV sclerosis–stroke relationship in this study could be attributable not to a difference in kind, but of degree. By eliminating all but the least severe cases, the exclusion of patients with AV stenosis from analysis may have left a population with such mild AV calcification as to dampen its potential predictive power. This is suggested by the fact that the only study to date to demonstrate a predictive role for AV calcification for incident stroke has done so in the setting of established AV stenosis. Because the degree of AV calcification (or MAC) was not assessed, even on a semiquantitative scale, this possibility cannot be addressed directly in the present study. Irrespectively, our findings suggest that in patients without AV stenosis, which imposes a hemodynamic stimulus to LV hypertrophy and LA enlargement, MAC may be a stronger biomarker for stroke risk than nonstenotic AV calcification.

This study has several limitations. Classification of stroke events was based on the documented diagnostic evaluations conducted in medical facilities serving these communities. Consequently, a proportion of strokes could not be categorized, and the number of ischemic stroke subtypes was too small to permit meaningful analysis of MAC-related stroke mechanisms. Furthermore, the loss of digitized ECGs from the second examination allowed only partial use of this modality to exclude baseline AF in our cohort. Nevertheless, our findings persisted in separate analyses of the subgroup for which such data were available. Together with the use of complete ECG data from the initial examination, and of clinical history and transmitral Doppler echocardiography to exclude prevalent AF, this makes it unlikely that our results would be attributable to unrecognized AF among individuals with MAC.

In conclusion, these findings show that MAC, but not AV sclerosis, is a powerful independent predictor of incident stroke in American Indians free of clinical cardiovascular disease. These results build on early autopsy observations, echocardiographic case reports, and previous longitudinal studies by confirming the prognostic value of MAC and, more importantly, by showing independence of the latter from an extensive set of covariates in a distinct population. The detection of MAC by transthoracic echocardiography in similar patients may warrant more aggressive risk factor modification, but the efficacy of specific approaches requires further investigation.

Acknowledgments

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References

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