Mitral Annular Calcification Predicts Cardiovascular Morbidity and Mortality

The Framingham Heart Study

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Background—Mitral annular calcification (MAC) has been associated with stroke in longitudinal, community-based cohorts and cardiovascular disease (CVD) outcomes in many small retrospective studies. Prospective data are limited on the relation of MAC with CVD morbidity and mortality.

Methods and Results—We examined the association between MAC assessed by M-mode echocardiography and the incidence of CVD, CVD death, and all-cause death over 16 years of follow-up in the Framingham Heart Study subjects who attended a routine examination between 1979 and 1981. Cox proportional hazards models were used to estimate hazard ratios (HRs) associated with the presence of MAC for each outcome. Of 1197 (445 male, 752 female) subjects who had adequate echocardiographic assessment, 14% had MAC. There were 307 incident CVD events and 621 deaths. In multivariable adjusted analyses, MAC was associated with an increased risk of incident CVD (HR, 1.5; 95% CI, 1.1, 2.0), CVD death (HR, 1.6; 95% CI, 1.1, 2.3), and all-cause death (HR, 1.3; 95% CI, 1.04, 1.6). For each 1-mm increase in MAC, the risk of incident CVD, CVD death, and all-cause death increased by ∼10%.

Conclusions—The independent association of MAC with incident CVD and CVD death underscores that cardiac calcification is a marker of increased CVD risk. (Circulation. 2003;107:1492-1496.)

Key Words: calcium ■ echocardiography ■ cardiovascular diseases ■ mortality

Mitral annular calcification (MAC) is a fibrous, degenerative calcification of the mitral valve support ring.1, 2 It was first described in 1908 by Bonninger3 in its association with complete heart block. Since then, it has been associated with endocarditis,4 coronary artery disease,5–9 and congestive heart failure10–12 in several studies, which mostly have been small and retrospective in design. In a prior prospective investigation from the Framingham Heart Study, MAC was independently associated with stroke.13

Subclinical cardiovascular disease (CVD) measurements have been demonstrated to have the same risk factors as clinically overt CVD14 and to be predictive of incident CVD events.15–18 Other valvular calcification measurements, including aortic sclerosis and aortic stenosis, have been shown to be manifestations of subclinical CVD by virtue of their association with CVD risk factors19 and with an increased risk of CVD events, including coronary artery disease,8 stroke,20 and CVD death.21

Because risk factors for MAC are similar to risk factors for CVD, including age, hypertension, hyperlipidemia, diabetes, and obesity,22–25 we hypothesized that MAC also may be a manifestation of subclinical atherosclerotic CVD. Thus, we sought to examine the association of MAC with incident CVD events in the community-based Framingham Heart Study sample. We hypothesized that the risk of incident CVD events would be higher in subjects with MAC.

Methods

Subjects in the original cohort of the Framingham Heart Study were eligible for the present investigation. The Framingham Heart Study began in 1948 with the enrollment of 5209 men and women, 28 to 62 years of age, with subjects undergoing examinations every 2 years.26, 27 M-mode echocardiograms were obtained in the 2291 members of the cohort undergoing a routine examination performed between 1979 to 1981, which served as the index examination for this investigation. Subjects were excluded for mitral stenosis or mitral prosthesis (n = 23). Because of the stringent criteria for measurability, the advanced age of the subjects, and the reliance on the M-mode technique, 49% (n = 1131) of the subjects were excluded for suboptimal M-mode tracings with regard to the interpretation of MAC. Furthermore, we excluded subjects with prevalent myocardial infarction (n = 72), congestive heart failure (n = 35), and CVD at baseline (n = 146) for analyses with these end points as outcomes.

Echocardiography was performed with 2-dimensional guidance through a parasternal window. M-mode recordings were made with
a Hoffrel 201 ultrasound machine with an Aerotech 2.25-MHz transducer and a Jason thermographic printer. Echocardiographers interpreted M-mode echocardiograms, blinded to all clinical information about the subjects, to determine the presence and severity of MAC as defined previously. Briefly, the disorder was considered present if an echodense band was visualized throughout systole and diastole, was distinguishable from the posterior mitral valve leaflet, and was located anterior and parallel to the posterior left ventricular wall. MAC was measured in millimeters by a cardiologist from the leading anterior to the trailing posterior edge at its greatest width during the cycle on at least 3 cardiac cycles.

Risk factors were characterized at the index Framingham Heart Study clinic examination. Details about the methods of risk factor measurement and laboratory analysis have been described. Diabetes was defined as a fasting glucose level \( \geq 140 \text{ mg/dL} \), a random nonfasting glucose level \( \geq 200 \text{ mg/dL} \), or use of insulin or oral hypoglycemic agents. Because only M-mode echocardiography was available at the index examination, baseline valvular disease was defined as any diastolic murmur, or a systolic murmur \( \geq 2/6 \) on the physical examination performed by the Heart Study physician. Covariates were obtained at the index examination except for smoking, HDL cholesterol, and serum creatinine, which were ascertained at the prior examination.

Subjects were followed for up to 16 years for CVD events. A panel of 3 experienced investigators reviewed all CVD events, blinded to MAC status. Incident CVD events included myocardial infarction, coronary insufficiency, congestive heart failure, and nonhemorrhagic stroke; fatal CVD additionally included sudden cardiac death defined by previously reported criteria.

Statistical Analyses

For principal analyses, MAC was dichotomized (present/absent); in secondary analyses, MAC was examined as a continuous variable. Differences in baseline risk factors in subjects with and without MAC were tested by ANOVA or logistic regression after adjustment for age and sex. All incidence rates were age and sex adjusted and presented as events per 10,000 person-years of follow-up. Cox proportional hazards regression models were used to estimate the association of MAC with the risks of myocardial infarction, congestive heart failure, incident CVD events, CVD death, and all-cause death. Because the interaction between MAC and sex was not significant, all analyses were performed for pooled sexes, with adjustment for sex. All multivariable models were adjusted for age, sex, systolic blood pressure, hypertension treatment, diabetes, total/HDL cholesterol, body mass index (BMI), and ECG left ventricular hypertrophy with strain. Additional covariates were outcome specific and were ascertained at the prior examination.

Subjects with MAC were older; more likely to be female; and more likely to have higher systolic blood pressure, higher BMI, diabetes, ECG left ventricular hypertrophy, and clinical valve disease (Table 1). Subjects with MAC were also more likely to have prevalent atrial fibrillation, CVD, and congestive heart failure.

Overall, there were 307 cases of incident CVD, with an age- and sex-adjusted incidence rate of 554 per 10,000 person-years in subjects with MAC compared with 268 in 10,000 in subjects without MAC (Table 2). The Figure shows the age- and sex-adjusted cumulative incidence of CVD; the corresponding hazard ratio (HR) was 1.7 (Table 3). After multivariable adjustment, subjects with MAC were 50% more likely to have CVD in follow-up (HR, 1.5; 95% CI, 1.1, 2.0).

Overall, there were 621 deaths; 213 were attributed to CVD. The CVD mortality rate was 428 per 10,000 compared with 162 in 10,000 in subjects with and without MAC, respectively. The cumulative incidence of CVD death is displayed in the Figure. The age- and sex-adjusted HR for CVD death was 2.0, which remained significant after multivariable adjustment for baseline risk factors (HR, 1.6) and further adjustment for interim myocardial infarction and congestive heart failure (HR, 1.5; 95% CI, 1.1, 2.2).

The all-cause mortality rate among subjects with MAC was 847 per 10,000 person-years, compared with 443 per 10,000 person-years in subjects without MAC; the Cox proportional hazards data are presented in the Figure. In age- and sex-adjusted analyses, the HR was 1.5. After multivariable

### Table 1. Baseline Characteristics of Participants With and Without MAC

<table>
<thead>
<tr>
<th></th>
<th>No MAC</th>
<th>MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69±6.5</td>
<td>73±7.3§</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>61</td>
<td>72†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>139±20</td>
<td>146±22†</td>
</tr>
<tr>
<td>Hypertension treatment, %</td>
<td>25</td>
<td>43§</td>
</tr>
<tr>
<td>Total cholesterol/HDL ratio</td>
<td>4.9±1.6</td>
<td>5.3±1.9‡</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>98±28</td>
<td>99±23</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9±4.0</td>
<td>27.0±4.4§</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>8</td>
<td>15†</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>EGG left ventricular hypertrophy, %</td>
<td>2</td>
<td>9§</td>
</tr>
<tr>
<td>Valve disease, %</td>
<td>5</td>
<td>15§</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>5</td>
<td>12‡</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>2</td>
<td>8‡</td>
</tr>
<tr>
<td>Prevalent CVD, %</td>
<td>11</td>
<td>18†</td>
</tr>
</tbody>
</table>

Values are mean±SD for continuous variables.

*P value for baseline characteristics other than age and sex in subjects with and without MAC obtained from ANOVA or logistic regression after adjustment for age and sex.

†P<0.05; ‡P<0.01; §P<0.001.

### Table 2. Incidence Rates per 10,000 Person-Years (Number of Events) Over 16 Years of Follow-Up in Participants With and Without MAC, Age- and Sex-Adjusted

<table>
<thead>
<tr>
<th></th>
<th>No MAC</th>
<th>MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=1028)</td>
<td>(n=169)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>113 (112)</td>
<td>225 (26)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>153 (150)</td>
<td>383 (41)</td>
</tr>
<tr>
<td>Incident CVD</td>
<td>268 (248)</td>
<td>554 (59)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>162 (162)</td>
<td>428 (51)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>443 (495)</td>
<td>847 (126)</td>
</tr>
</tbody>
</table>
adjustment, the increased risk of all-cause death remained statistically significant (HR, 1.3). In an exploratory analysis adjusting for interim myocardial infarction or congestive heart failure, these results were essentially unchanged (HR, 1.3; 95% CI, 1.03, 1.6; Table 3).

In secondary analyses, MAC was analyzed as a continuous variable. For each 1-mm increase in MAC, the risk of incident CVD, CVD death, and all-cause death adjusted for relevant baseline risk factors increased by 9% (P<0.007), 12% (P<0.004) and 9% (P<0.001), respectively.

There were 138 cases of myocardial infarction and 191 cases of congestive heart failure in follow-up. In age- and sex-adjusted models, MAC was significantly related to incident myocardial infarction (HR, 1.7; P<0.01) and heart failure (HR, 1.9; P<0.001). After further adjustment for baseline covariates, MAC was not an independent risk factor for myocardial infarction (HR, 1.4; 95% CI, 0.8, 2.2) or heart failure (HR, 1.3; 95% CI, 0.9, 1.8). Given the small number of cases for these outcomes, we only had power of 30% and 12%, respectively, to detect HRs of 1.4 and 1.3 at an α level of 0.05 in fully adjusted dichotomous models. Of interest, when we analyzed MAC as a continuous variable in fully adjusted models, MAC was not associated with myocardial infarction but was associated with a significantly increased risk of heart failure. For each 1-mm increase in MAC, the HR for heart failure was 1.1 (95% CI, 1.03, 1.12; P<0.01). Thus, our lack of significant association between the presence or absence of MAC and myocardial infarction and congestive heart failure should be interpreted with caution.

**Discussion**

In summary, the presence of mitral annular calcification predicts incident CVD events, CVD death, and all-cause death. We have shown that this increase in risk occurs in a dose-responsive manner. We believe that the association between MAC and incident CVD and death is consistent with the hypothesis that MAC is a marker of subclinical CVD.

**Possible Mechanisms**

Increasingly, it is recognized that vascular calcification, assessed by multiple modalities, including electron beam CT, 29,30 echocardiography, 21,25 and aortic arch calcification, 32 is associated with CVD risk factors. Recent data also suggest an association between vascular calcification and incident

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**Cumulative Incidence Based on Cox Proportional Hazard Age- and Sex-Adjusted Models of (A) Incident CVD; (B) CVD Death; and (C) All-Cause Death in Up to 15 Years of Follow-Up. Vertical Scale Is from 0 to 0.6. Number of Subjects at Risk for the Event by Presence or Absence of MAC Is Shown Below Figures.**

**TABLE 3.** Association of MAC With Incidence of Disease End Points

<table>
<thead>
<tr>
<th>End Points</th>
<th>HR (95% CI)*</th>
</tr>
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<tbody>
<tr>
<td>Incident CVD</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.7 (1.3, 2.3)§</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.5 (1.1, 2.0)†</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>2.0 (1.4, 2.7)§</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.6 (1.1, 2.3)†</td>
</tr>
<tr>
<td>Adjusted for interim myocardial infarction/congestive heart failure</td>
<td>1.5 (1.1, 2.2)†</td>
</tr>
<tr>
<td>All-cause death</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.5 (1.2, 1.8)§</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.3 (1.04, 1.6)†</td>
</tr>
<tr>
<td>Adjusted for interim myocardial infarction/congestive heart failure</td>
<td>1.3 (1.03, 1.6)†</td>
</tr>
</tbody>
</table>

*No MAC is the referent group. See text for risk factors included in multivariable models.
†P<0.05; ‡P<0.01; §P<0.001.
CVD events.32–34 The pathophysiology of cardiac calcification
is not known but may stem from metabolic causes. For
example, it is known that coronary artery calcification is
common in patients with end-stage kidney disease under-
going dialysis,35 and it has also been observed that MAC is
common in patients with end-stage kidney disease.36 Thus,
derangements in calcium-phosphorus metabolism may con-
tribute to MAC.

The association between vascular calcification, specifically
MAC, and increased cardiovascular risk may also be due to
the burden of shared risk factors, including age, hyperten-
sion, hyperlipidemia, diabetes, and obesity.22–25 Furthermore,
MAC may function as a bioassay for longitudinal exposure to
risk factors. For example, MAC may more accurately “mea-
sure” the impact of longitudinal blood pressure elevation than
a blood pressure reading at one examination. MAC may also
be a marker for atherosclerotic disease burden; the associa-
tion between MAC and aortic plaque37,38 and coronary calcification6 has been previously noted. It is also possible to
speculate that other unmeasured factors such as metabolic,
inflammatory, and hemostatic risk factors might be associated
and may account for relations of MAC with CVD end points.

Study Limitations and Strengths

Some limitations of our study warrant attention. The Fra-
mingham Heart Study sample is neither ethnically diverse nor
nationally representative. However, the coronary heart dis-
 ease risk factor relations from Framingham have recently
been validated in 6 ethnically and geographically diverse
cohorts and were found to be applicable in other popula-
tions.39 Second, our sample was elderly, and our findings may
not be generalizable to younger individuals. In addition, to
have sufficient numbers of events longitudinally to provide
adequate statistical power for analyses, we relied on the
echocardiographic technology available at the baseline ex-
amination, M-mode, which is less sensitive for the detection
of MAC. Finally, as noted above, our study lacked sufficient
power to adequately examine the relation of MAC to many
clinically important CVD outcomes such as endocarditis and
heart failure.

There are several strengths of our study. Many prior studies
of cardiovascular outcomes with MAC have been limited by
sample sizes as small as 38 subjects,7,10–12 retrospective12 or
cross-sectional designs,5,7,25 nonuniform ascertainment of
echocardiography,5,7,40,41 lack of recruitment of an appropri-
ate control group,10–12 and lack of routine ascertainment of
covariate data and multivariable analyses8,25,40

The present study is among the first large-scale
community-based cohort studies to examine the prospective
association between MAC and incident cardiovascular events
and death. Our study is the first to show a graded relation
between MAC severity and clinical outcome. To our knowl-
edge, the only prior longitudinal cohort study to examine the
relation of MAC to CVD outcomes was the Cardiovascular
Health Study,9 which examined multiple echocardiographic
variables including left ventricular mass, dimensions, and
wall thickness and left atrial dimensions, in addition to MAC
(dichotomously analyzed). The investigators observed that
the presence of MAC was associated with an unadjusted
increased hazard for incident stroke, heart failure, coronary
heart disease, and all-cause death. However, after adjustment
for CVD risk factors, MAC only remained predictive of
incident coronary heart disease. Possible reasons for the
disparate findings between the two studies may include the
older mean age (73 years), the shorter duration of follow-up
(7 years), and the utilization of 2-dimensional MAC assess-
ment in the Cardiovascular Health Study. Conceivably, our
reliance on the less-sensitive M-mode technology may have
led to the detection of more severe degrees of MAC, with a
greater risk of incident events.

Implications

In conclusion, MAC was independently associated with
incident CVD, cardiovascular death, and all-cause death after
adjusting for traditional CVD risk factors, suggesting that
MAC is a marker of increased cardiovascular risk. We have
shown that this increased risk occurs in a graded fashion by
MAC severity. The mechanisms of increased risk are un-
doubtedly multifactorial and include mechanical characteris-
tics of MAC, shared risk factors between MAC and cardio-
vascular outcomes, and valvular calcification as an overall
marker of atherosclerotic burden. The association of calcifi-
cation of the mitral annulus with increased CVD risk parallels
the previously reported elevated cardiovascular risk observed
with the presence of echocardiographic aortic sclerosis. The
prognostic importance of the calcification phenotype in mul-
tiple cardiac locations underscores the importance of under-
standing the genetic and environmental determinants of
cardiac calcification.

Acknowledgments

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National Institutes of Health.

References

1. D’Cruz I, Panetta F, Cohen H, et al. Submitral calcification or sclerosis in
elderly patients: M-mode and two-dimensional echocardiography in
2. Hirschfeld DS, Emelson BB. Echocardiogram in calcified mitral annulus.
3. Bonninger M. (a) Bluttransfusion bei perniziöser anämie: (b) Zwei Falle
4. Burnsie JD, Desanctis RW. Bacterial endocarditis on calcification of the
5. Jeon DS, Atar S, Brasch AV, et al. Association of mitral annulus calci-
fication, aortic valve sclerosis and aortic root calcification with abnormal
myocardial perfusion single photon emission tomography in subjects age
6. Tenenbaum A, Shemesh J, Fisman EZ, et al. Advanced mitral annular calci-
fication is associated with severe coronary calcification on fast dual
transsthoracic echocardiography is a marker for high prevalence and
severity of coronary artery disease in patients undergoing coronary
and of aortic cuspal calcium with coronary artery disease in older patients.
predictors of six- to seven-year incidence of coronary heart disease,
stroke, congestive heart failure, and mortality in an elderly cohort (the


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