# Angiotensin-Converting Enzyme Inhibitors and Change in Aortic Valve Calcium

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**Background:** Calcium accumulation in the aortic valve is a hallmark of aortic sclerosis and aortic stenosis. Because lipoproteins, angiotensin-converting enzyme, and angiotensin II colocalize with calcium in aortic valve lesions, we hypothesized an association between angiotensin-converting enzyme inhibitor (ACEI) use and lowered aortic valve calcium (AVC) accumulation, as measured by electron beam computed tomography.

**Methods:** Rates of change in volumetric AVC scores were determined retrospectively for 123 patients who had undergone 2 serial electron beam computed tomographic scans. The mean (±SD) interscan interval was 2.5 (±1.7) years; 80 patients did not receive ACEIs and 43 received ACEIs. The relationship of ACEI use to median rates of AVC score change (both unadjusted and adjusted for baseline AVC scores and coronary heart disease risk factors) was determined. We also examined the relationship of ACEI use to the likelihood of and adjusted odds ratio for definite progression (AVC change >2 times the median interscan variability).

**Results:** Unadjusted and adjusted median rates of AVC score change were significantly higher in the no-ACEI group than in the ACEI group (adjusted median AVC changes [95% confidence interval]: relative, 28.7%/y [18.9%-38.5%/y] vs 11.0%/y [−1.9% to 24.0%/y], $P=.04$; absolute: 25.1/y [19.7-30.5/y] vs 12.2/y [4.5-19.9/y], $P=.02$). The adjusted odds ratio (95% confidence interval) for definite AVC progression was significantly lower for patients who received ACEIs (0.29 [0.11-0.75], $P=.01$).

**Conclusions:** This retrospective study finds a significant association between ACEI use and a lower rate of AVC accumulation. The results support the need for prospective, randomized trials of ACEIs in calcific aortic valve disease.

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Although calcific aortic valve disease is common in elderly individuals, there currently are no medical therapies that have been shown, in prospective, randomized trials, to slow its progression. Calcific aortic valve disease includes aortic sclerosis, in which the aortic valve is calcified but does not obstruct left ventricular outflow, and aortic stenosis, in which obstruction to left ventricular outflow is present.[1,2] Aortic sclerosis has a prevalence of 25% in patients older than 65 years[3] and has been associated with a 50% increase in risk for cardiovascular mortality.[4] Aortic stenosis carries an 80% 5-year risk of heart failure, valve replacement, or death.[5]

Histopathological studies now have demonstrated that aortic valvular disease is an active process, in which inflammation,[6-8] lipoprotein deposition,[9,10] molecular mediators of calcification,[11,12] and matrix metalloproteinases[13-15] all may participate. Recently, electron beam computed tomography (EBT) has been established as a highly reproducible method for quantifying aortic valve calcium (AVC).[16,17] Recent studies have used EBT to demonstrate associations between elevated low-density lipoprotein levels and an increased rate of AVC accumulation[18] and between statin use and a lower rate of AVC accumulation.[19] Increased EBT AVC score also has been shown to correlate with an increased likelihood of the presence of aortic stenosis[20,21] and to independently predict clinical events in patients with aortic stenosis.[21]

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Because of the recent demonstration that angiotensin-converting enzyme (ACE) is present in aortic valve lesions,[22] we hypothesized that ACE inhibitor (ACEI) use also might be associated with a lower rate of AVC accumulation, as assessed by serial EBT. The present study retrospec-

tively examined the relationship between ACEI use and rates of AVC accumulation in 123 patients who had undergone serial EBT for coronary calcium screening. Rates of change also were compared after adjustment for differences in baseline AVC scores and after further adjustment for coronary heart disease (CHD) risk factors.

## METHODS

### STUDY PARTICIPANTS

The study group consisted of 123 patients who had undergone 2 serial EBT scans and who had an AVC score by the volumetric method of 10 or greater on the initial image. Of these 123 patients, 65 had been included in a previous analysis of the relationship of statin use to rate of change in AVC scores.[19] All patients were identified from a subset of 980 patients in the EBT database at Harbor-UCLA Medical Center, Torrance, Calif, who had undergone 2 serial EBTs for the purpose of coronary calcium screening. All patients were asymptomatic for coronary artery disease. The Harbor-UCLA institutional review board approved the research protocol, and all participants gave written, informed consent.

Information on the presence or absence of traditional cardiovascular risk factors, including hypertension, family history of premature coronary artery disease, hyperlipidemia, smoking, diabetes mellitus, and statin use, was obtained before the initial and follow-up EBT. Smoking was defined as the use of 10 or more cigarettes per day. Patients receiving insulin or oral hypoglycemic agents were classified as having diabetes mellitus. Patients were classified as having hypertension if they were receiving antihypertensive medications or had known, but untreated, hypertension (blood pressure >140/90 mm Hg). Hyperlipidemia was defined as use of cholesterol-lowering medication or, in the absence of such medication, as a total serum cholesterol level greater than 240 mg/dL. Patients were classified as receiving ACEIs if they were receiving an ACEI drug at the time of both the initial and follow-up EBT. The remaining patients were classified as "no ACEI"; none of the patients in this group was receiving an ACEI at the time of either scan. One patient received an angiotensin receptor type 1 antagonist. This patient was included in the ACEI group.

### SCANNING PROCEDURE

Electron beam computed tomography was performed with an EBT scanner (Imatron C-150XL Ultrafast Computed Tomographic Scanner; GE Imatron, South San Francisco, Calif) with an acquisition time of 100 milliseconds per image, electrocardiographic triggering at 40% of the RR interval, and a section thickness of 3 mm. A total of 30 consecutive images were obtained during 2 breath-holding periods from the aortic arch to the apex of the heart. Foci with a density of greater than 130 Houndsfield units and an area of 3 or more contiguous pixels were regarded as calcification. Calcium scores for the coronary arteries and the aortic valve were quantified by the calcium volumetric score determined by the method of isotropic interpolation.[23] The aortic valve was identified as the structure between the left ventricular cavity and the ascending aorta and usually was present in 3 or 4 consecutive images. Aortic valve leaflet calcium was defined as present if calcium was seen in the continuous plane between the left ventricular cavity and the ascending aorta.[17,19] Calcium not in the leaflets, such as that within the aortic sinuses or the aortic wall, was not included.

### CLASSIFICATION OF PATIENTS WITH PROGRESSION VS NO CHANGE IN VOLUMETRIC AVC SCORES

Patients were classified as having definite AVC score progression if they had rates of volumetric AVC score change of 12.4%/y or more, which is 2 times the median interscan variability for volumetric AVC scores.[17] Patients with volumetric AVC score rates of change less than 12.4%/y were classified as having no change in AVC score.

### STATISTICAL ANALYSIS

Continuous variables are presented as median (interquartile range) or mean±SD. Adjusted values are presented as the median with the 95% confidence interval. The changes in the amount of AVC were assessed by subtracting the values measured in the second EBT scan from those measured in the first EBT scan, dividing the difference by the actual number of days that passed between scan 1 and scan 2, and multiplying this fraction by 365 (annualized change). The percentage change was obtained by dividing the annualized absolute change by the amount of the first scan (annualized percentage change). A $\chi^2$ analysis with Fisher exact test was used to test for differences in distribution of qualitative variables between groups.

The annualized percentage rates of AVC change as well as the annualized absolute rates of AVC change were not normally distributed, as evaluated by the Kolmogorov-Smirnov test. Therefore, the Mann-Whitney test was used to analyze differences between the first and second images according to treatment. Quantile (median) regression was used to estimate the adjusted medians of the annualized percentage AVC change as well as the annualized absolute AVC change according to ACEI use conditional on the confounding variables. This is similar to least-squares regression, where the objective is to estimate the mean of the dependent variable; however, median regression finds the regression plane that minimizes the sum of the absolute residuals rather than the sum of the squared residuals. Initially, medians were estimated adjusted for baseline AVC scores (model 1) and then estimated with further adjustment for traditional risk factors including age, sex, diabetes mellitus, elevated total cholesterol level, hypertension, current cigarette smoking, and family history of premature heart disease as well (model 2). Association of ACEI use with progression of AVC (as defined in the "Methods" section) also was assessed in multivariate modeling by means of logistic regression analyses.

Finally, interaction terms were used to investigate whether the associations of ACEI use with annualized percentage AVC change or absolute AVC change differed according to baseline AVC as well as conventional CHD risk factors. The statistical analyses were carried out with the *STATA V8* statistical package (Stata Corp, College Station, Tex). All statistical tests were 2-tailed, with significance defined as $P<.05$.

## RESULTS

### PATIENT CHARACTERISTICS

A total of 123 patients (81% male; mean±SD age, 68±9 years) were identified who had an AVC score of 10 or greater on the initial EBT image and who had 2 EBTs performed at least 6 months apart. The study group was followed up for 2.6±1.8 years. Baseline characteristics of the no-ACEI and ACEI groups are shown in **Table 1**.

**Table 1. Baseline Patient Characteristics**

| Characteristic | No ACEI (n = 80) | ACEI (n = 43) | *P* Value |
|---|---|---|---|
| Age, mean ± SD, y | 67 ± 9.8 | 69.3 ± 8.4 | .21 |
| Sex, No. (%) M | 68 (85) | 31 (72) | .09 |
| Family history of coronary disease, No. (%) | 41 (51) | 23 (53) | .81 |
| Hypertension, No. (%) | 31 (39) | 27 (63) | .01 |
| Diabetes, No. (%) | 7 (9) | 9 (21) | .06 |
| Smoking, No. (%) | 11 (14) | 3 (7) | .26 |
| High cholesterol, No. (%) | 48 (60) | 32 (74) | .11 |
| Receiving statin, No. (%) | 37 (46) | 23 (53) | .44 |
| Baseline AVC score, median (IQR) | 69.5 (35.5-164.5) | 146.3 (78.3-344) | .001 |
| Interscan interval, mean ± SD, y | 2.54 ± 1.72 | 2.89 ± 1.91 | .31 |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AVC, aortic valve calcium; IQR, interquartile range.

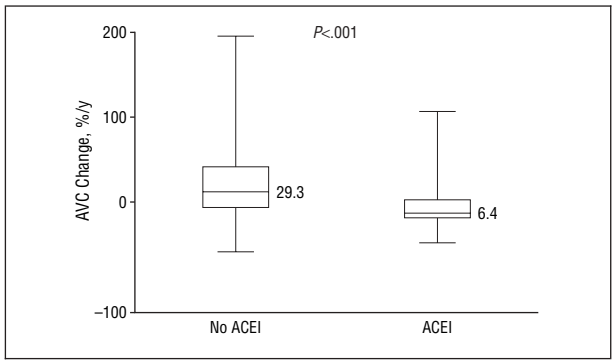


**Figure 1.** Association of angiotensin-converting enzyme inhibitor (ACEI) use with lower rate of change in aortic valve calcium (AVC) scores. Box plots display the median and 25th and 75th percentiles, and bars show the 10th and 90th percentiles. Median values are shown to the right of each box. Median rate of change was significantly lower for the ACEI group (Mann-Whitney test).

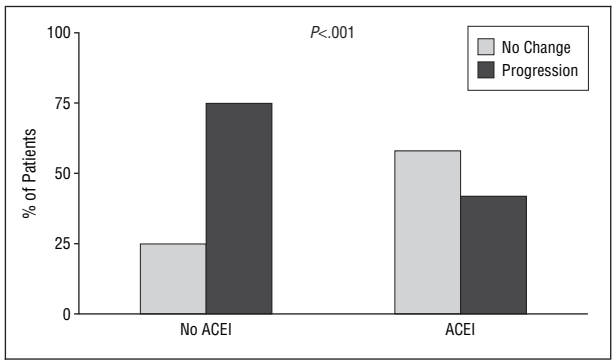


**Figure 2.** Association of angiotensin-converting enzyme inhibitor (ACEI) use with lower likelihood of definite progression in AVC scores (Fisher exact test).

The prevalence of hypertension was higher in the ACEI group (*P*=.01), as may be expected, since ACEIs are commonly used for the treatment of hypertension. However, there was a significant difference in baseline AVC scores between the 2 groups (Table 1).

**Table 2. Adjusted, Annualized Relative and Absolute Changes in AVC by ACEI Use**

| Variable | Median Change (95% CI) | | *P* Value |
|---|---|---|---|
| | No ACEI (n = 80) | ACEI (n = 43) | |
| Relative AVC change, %/y | | | |
| Model 1* | 30.2 (22.8 to 37.6) | 10.4 (0.3 to 20.5) | .003 |
| Model 2† | 28.7 (18.9 to 38.5) | 11.0 (−1.9 to 24.0) | .04 |
| Absolute AVC change/y | | | |
| Model 1* | 24.2 (18.6 to 29.9) | 10.4 (2.7 to 18.2) | .007 |
| Model 2† | 25.1 (19.7 to 30.5) | 12.2 (4.5 to 19.9) | .02 |

Abbreviations: See Table 1; CI, confidence interval.
*Adjusted for baseline AVC.
†Adjusted for baseline AVC, age, diabetes mellitus, sex, elevated total cholesterol level, hypertension, current cigarette smoking, and family history of premature coronary disease.

## PROGRESSION OF AORTIC VALVE CALCIFICATION

Overall, the median AVC score of all 123 patients increased from 86 (42-211) in the initial scan to 124 (66-301) in the follow-up scan, corresponding to a median annualized progression of 19% (interquartile range, 5%-51%). Seventy-eight patients (63%) demonstrated an annualized AVC score change of 12.4% or greater, which we had defined as definite AVC progression.

## DIFFERENCES IN AVC CHANGE ACCORDING TO ACEI USE

**Figure 1** demonstrates the crude annualized relative AVC change whether patients were or were not receiving ACEI therapy. For all 123 patients, the no-ACEI group had a significantly higher median rate of AVC score change than did the ACEI group, expressed as percentage change per year (*P*<.001). The crude median annualized absolute change was marginally different in the 2 groups (18.6/y [interquartile range, 4.8-37.6/y] in the no-ACEI group vs 8.2/y [1.4-28.8/y] in the ACEI group; *P*=.05). Also, as shown in **Figure 2**, the proportion of patients with definite AVC score progression was significantly higher in the no-ACEI group than in the ACEI group (75% vs 42%; *P*<.001).

## MULTIPLE REGRESSION ANALYSES

**Table 2** provides the adjusted medians of annualized relative and absolute change in AVC according to ACEI therapy. In models adjusted for baseline AVC (model 1), both percentage and absolute median AVC changes were significantly lower among individuals receiving ACEI therapy (*P*=.003-.007). After further adjustment for clinical covariates, the relationships of ACEI therapy to annualized percentage and absolute median AVC changes remained significant (*P*=.02-.04).

Also, after adjustment for baseline AVC score, ACEI use was associated with a significantly lower odds ratio

for definite AVC progression (0.28; $P=.002$) (**Table 3**). The association of ACEI use with a lower odds ratio for definite AVC progression was similar after further adjustment for all CHD risk factors (odds ratio, 0.29; $P=.01$).

The relationships described in the preceding paragraphs were essentially unaltered with additional adjustment for statin use. In the quantile multivariate regression, statin use also was significantly associated with a lower median progression of annualized percentage AVC (regression coefficient, –19.9; $P=.002$) as well as with progression of absolute AVC (regression coefficient, –16.0; $P=.01$). In addition, statin use was associated with an adjusted odds ratio of 0.3 (95% confidence interval, 0.1-0.9; $P=.04$) for definite AVC progression.

Further analyses to exclude the effect of modification by presence or absence of conventional CHD risk factors, as well as by baseline AVC scores with ACEI therapy, were performed. No significant interactions were observed (all $P>.1$), confirming the consistency of the results regardless of the absence or presence of CHD risk factors as well the magnitude of baseline AVC scores.

**Table 3. Adjusted ORs for Definite AVC Progression**

| Variable | ACEI Use, OR (95% CI) | *P* Value |
|---|---|---|
| Definite AVC progression | | |
| Model 1* | 0.28 (0.10-0.73) | .002 |
| Model 2† | 0.29 (0.11-0.75) | .01 |

Abbreviations: See Table 1; CI, confidence interval; OR, odds ratio.
*Adjusted for baseline AVC.
†Adjusted for baseline AVC, age, diabetes mellitus, sex, elevated total cholesterol level, hypertension, current cigarette smoking, and family history of premature coronary disease.

## COMMENT

In this retrospective, observational study, there was an association between ACEI use and lower rate of AVC accumulation, as assessed by serial EBT. The results suggest that ACEI therapy may have promise in the treatment of calcific aortic valvular disease, a process that is common in the elderly population[3,24] but for which there presently is no definitively proven pharmacologic therapy.

It is perhaps surprising, given the prevalence of calcific aortic valve disease, that so little progress has been made in identifying pharmacologic therapies for this process. Progress likely has been slowed by the misconception that calcific aortic valve disease is a "degenerative," and, by implication, unmodifiable, process. It only recently has been suggested that inflammatory cells,[6,7] cytokine receptors,[8] plasma lipoproteins,[9,10] and calcification mediators[11,12] may participate in disease pathogenesis. Moreover, for many years, the lack of an animal model of calcific aortic valve disease made it difficult to investigate the potential utility of pharmacologic therapies that might interrupt these processes. Only recently have 2 animal models been described in which several of the pathologic features of calcific aortic valve disease are replicated.[25,26] Thus, there has been interest using other means, primarily nonrandomized, retrospective studies, to determine whether specific pharmacologic agents, such as statins, might have utility in treating aortic valvular disease.[19,27,28]

Recently, the renin-angiotensin system also has been implicated in aortic valve disease pathogenesis.[22] Angiotensin-converting enzyme is present in aortic valvular lesions, where it colocalizes with its enzymatic product, angiotensin II, and with retained plasma lipoproteins.[22] This observation formed the basis of the present study. Furthermore, 3 recent clinical trials have demonstrated unequivocal clinical benefit of treatment with agents that block renin-angiotensin system components in patients who either have had, or are at high risk for, atherosclerotic complications.[29-31] Thus, the renin-angiotensin system might be an attractive target for therapy in aortic valve disease because patients with calcific aortic valve disease are also at high risk for cardiovascular events.[4]

The present study now suggests that ACEIs also may slow aortic valve calcification. One characteristic for which patients were not well matched was baseline AVC scores. However, the association of ACEI use with lower median rates of AVC change remained after adjustment for differences in baseline AVC score as well as after further adjustment for CHD risk factors. Statin therapy[19,27,28] retained its independent associations with both lower relative and absolute adjusted median rates of AVC progression, as well as with a lower adjusted odds ratio for definite progression.

It is noteworthy that ACEIs, which are of proven benefit in lowering coronary atherosclerosis risk,[29-31] were associated with decreased rates of aortic valve calcification in this retrospective study. Several authors have commented on the similarities between atherosclerosis and aortic valve disease,[32] in terms of both epidemiologic risk factors[3,33] and pathological features.[6-9,11,12,15,22,34] However, the identification of apparently novel risk factors, such as vitamin D receptor polymorphisms,[35] may provide clues to additional strategies that might specifically target calcific aortic valve disease.

The study has limitations. It is retrospective and nonrandomized and includes only a modest number of patients. It examines a surrogate end point, AVC as assessed by EBT, rather than "hard" clinical end points, such as progression to clinical heart failure, valve replacement, or death. Nevertheless, there were significant differences in the median rates of AVC change between these groups, particularly after adjustment for differences in baseline AVC scores. Moreover, when the results were examined on a per-patient basis, ACEI use was associated with significantly lower odds ratios for definite AVC score progression. Finally, in light of the recent demonstration that ACE and the angiotensin II type 1 receptor are present in aortic valve lesions,[22] the results of the present study are biologically plausible. These results support the need for prospective, randomized trials of ACEIs and/or angiotensin receptor type 1 antagonists to confirm the possibility that inhibition of angiotensin II may be of clinical benefit in patients with calcific aortic valve disease.

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