Aortic Valve Calcification

Determinants and Progression in the Population


Background—Aortic valve calcification (AVC) is considered degenerative. Recent data suggested links to atherosclerosis or coronary disease (CAD).

Methods and Results—AVC and coronary artery calcifications (CAC) were prospectively assessed by Electron-Beam-Computed-Tomography in 262 population-based research participants ≥60 years. AVC was frequent (27%) with aging (P<0.01) and in men (P<0.05). AVC was associated with diabetes, hypertension, higher body-mass-index, and serum glucose (all P<0.05). AVC was a marker of higher prevalence (P<0.01) and severity of CAD (CAC score: 441±802 versus 265±566, P<0.05) independently of age. After follow-up of 3.8±0.9 years, AVC score increased (94±271 versus 54±173, P<0.01, +11±32 U/year), faster with higher baseline AVC score (P<0.01). Compared with participants remaining free of AVC, de novo acquisition of AVC was associated with higher LDL-cholesterol (141±31 versus 121±27 mg/dL, P<0.05) and faster CAC progression (+78±87 versus +28±47 U/year, P<0.05). In multivariate analysis, LDL-cholesterol independently determined AVC acquisition while higher baseline AVC scores determined faster progression of existing AVC.

Conclusion—In the population, AVC is frequent with aging and atherosclerotic risk factors. AVC is a marker of subclinical CAD. AVC is progressive, appearing de novo with progressive atherosclerosis whereas established AVC progresses independently of atherosclerotic risk factors and faster with increasing initial AVC loads. (Arterioscler Thromb Vasc Biol. 2007;27:642-648.)

Key Words: aortic valve ■ computed tomography ■ calcification ■ atherosclerosis ■ epidemiology

With the striking decrease in the prevalence of rheumatic disease, calcification of the aortic valve (AVC) is the most frequent cause of aortic stenosis (AS) in Western countries (Monckeberg disease).1 Calcific AS has long been considered as a passive and degenerative process but recent data challenged this concept, showing that AVC is an active and highly regulated process,2–4 with histological similarities to atherosclerosis.5,6 The interpretation of AVC as an atherosclerotic phenomenon is supported by the 50% increased risk of cardiovascular death and myocardial infarction in subjects with aortic sclerosis (aortic valve thickening without obstruction to left ventricular outflow) and no known cardiovascular disease,7 which is presumed to be attributable to associated coronary artery disease (CAD). This interpretation was extended to all AVC grades by observational studies reporting diffuse atherosclerosis with aortic sclerosis,8–10 and suggesting that statin treatment reduced AS progression.11–13 Thus, AS and AVC have been mostly considered atherosclerotic processes potentially preventable by lipid-lowering treatment using statins.14 However, important discordant data have surfaced. Patients with the most extreme form of AVC, ie, AS, often have normal coronary angiograms,15 and the proof of association of AVC with coronary atherosclerosis remains circumstantial16 and uncertain. The link of hyperlipidemia to AS progression17 appears weak18 or even insignificant.12 Most importantly, the only available clinical trial of high-dose statin treatment for AS, recently published, demonstrated no association between lipids and AS progression and showed no effect of statin therapy on AS or AVC progression.19 Thus, to date, the determinants of AS and AVC progression remain unclear.

Another source of uncertainty relates to AVC assessment by standard Fluoroscopy or Echocardiography, both subjective and qualitative. Thus, Echocardiographic data, although pioneering,7 warrant population assessment of reliably measured AVC to assess their determinants and progression which are uncertain. Electron-Beam Computed Tomography (EBCT) is a reliable, objective, and quantitative method to measure simultaneously AVC20 and...
coronary arteries calcifications (CAC)\textsuperscript{21,22} an established marker of CAD.\textsuperscript{23,24}

The Epidemiology of Coronary Artery Calcification study is a population-based study in which randomly selected Olmsted County residents are prospectively followed with sequential evaluation of risk factors and EBCT.\textsuperscript{25,26} This epidemiological study offers the unique opportunity to evaluate AVC prevalence, progression and link to CAD.

Methods

Study Population

In the Epidemiology of Coronary Artery Calcification (ECAC) study,\textsuperscript{25,26} 1376 randomly selected adult Olmsted County residents of all ages gave written informed consent and were prospectively and repeatedly examined by EBCT for heart calcifications along with comprehensive clinical and cardiac risk factors assessment. Participants were excluded from the study if they were pregnant or lactating at enrollment or had previous cardiac surgery. The present substudy limited enrollment to participants \( \geq 60 \) years of age who had baseline and follow-up EBCT performed after 1995 (date after which scans were electronically saved). The Aortic Valve Calcification substudy was approved by our Institutional Review Board. At baseline and follow-up, cardiovascular risk factors were prospectively determined by participants' interview, physical examination, and fasting blood sampling. Fibrinogen levels and Creatinine clearance were measured at follow-up. Follow-up to assess AS development was obtained clinically with physical examination in all patients and with clinically indicated Doppler-Echocardiography in 129 participants.

Measures and Definitions

Participants reported current medication use, education, history of smoking, and physician-diagnosed hypertension, myocardial infarction, stroke, or diabetes. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were measured in the right arm with a random-zero sphygmomanometer (Hawksley and Sons). Three measures at least 2 minutes apart were taken and the average of the second and third measurements was used. Participants were considered hypertensive if the average SBP was \( \geq 140 \) mm Hg and/or the average DBP was \( \geq 90 \) mm Hg, or if they reported a prior diagnosis of and treatment for hypertension and were currently using antihypertensive medications. Participants were considered diabetic if they were using insulin or oral hypoglycemic agents. Body mass index was calculated as weight/height\(^2\) (kg/m\(^2\)).

Standard enzymatic methods were used to measure total cholesterol, HDL cholesterol, and triglycerides after overnight fasting. 15\,LDL cholesterol was calculated with the Friedwald equation. Plasma glucose was measured by the glucose oxidase method after overnight fasting. Creatinine clearance was calculated using the Cockroft formula and the fibrinogen measured by immunoturbidimetric assay.

Electron-Beam-Computed-Tomography

We and others have demonstrated the accuracy and reproducibility of EBCT for AVC\textsuperscript{26} and CAC quantification.\textsuperscript{25,26} Acquisition with Imatron C-100 or C-150 was triggered at 80\% of RR interval for two adjacent pixels nodule with density \( > 130 \) Hounsfield units. Integrative scores were calculated (accounting for pixel density)\textsuperscript{27} in Agaston units (AU) separately for aortic valve and coronary artery calcifications, using a dedicated software\textsuperscript{28,29} by observers blinded to all other data. Calcium scoring was semi-automated: areas of calcification are highlighted and those corresponding to the aortic valve or the coronary arteries are selected by the operator. Two runs were scored separately and averaged and calcification was considered present on the basis of this final score. Annualized progression rates of AVC and CAC were calculated as the difference between baseline and follow-up score divided by the follow-up duration. Progression, stability, or regression were also defined categorically based on a previously validated regression approach,\textsuperscript{25} which avoid misdiagnosis of change in regard to inter-run variability. Follow-up score (average of the 2 runs) is compared with the 95\% confidence limits of the baseline score (based on inter-run variability specific to the specific baseline score). This 95\% confidence interval increases with the baseline score (eg, [78 to 123] for a score of 100 and [440 to 580] for a score of 500). Progression was defined by a follow-up score \( > 95 \) CI upper limit, regression by a follow-up score \( < 95 \) CI lower limit and stability by a follow-up score between the 95\% CI lower and upper limits.

Statistical Analysis

Data are presented as mean\( \pm \)SD or percent. Comparisons between groups used Student \( t \) test or \( \chi^2 \) test as appropriate and the Wilcoxon rank sum test for non-normally distributed variables. Bivariate logistic regressions assessed the association between AVC presence and each cardiovascular risk factor after adjustment for age and gender. Correlations between AVC and CAC scores or annualized progression rates used Spearman correlations. Determinants of AVC progression overall and in patients with no AVC at baseline were assessed by logistic regression. Stepwise multiple linear regression analysis using logarithmic transformation of baseline AVC score (which was close to normally distributed) identified determinants of AVC progression with established AVC at baseline. To assess whether CAC score was higher in patients with AVC after adjustment for age and gender, CAC score was divided into quartiles and a proportional odds model was performed. A proportional odds model was also used to compare annualized CAC progression rate after adjustment for baseline CAC quartiles. For both analyses, proportional odds assumptions were verified and not violated. \( P<0.05 \) was considered significant.

Results

Baseline Characteristics

Two hundred sixty two participants aged 60 or older were enrolled, and their characteristics are summarized in Table 1. History of smoking was observed in 124 participants (47\%), hypertension in 179 (68\%), and diabetes in 25 (10\%). Fourteen participants (5\%) had clinical history of CAD and 8 (3\%) of cerebrovascular disease. AVC and CAC scores varied widely, respectively: 54\pm173 (range 0 to 1944) and 312\pm640 (range 0 to 5711) AU.

Determinants of AVC and Association With Cardiac Risk Factors

Baseline AVC prevalence was 27\% and increased with age: 19\% between 60 and 69 years (\n=171) and 42\% after 70 years (\n=91) (Odds ratio 1.12 [1.06 to 1.18] per year, \( P<0.01 \)). AVC prevalence was higher in men than in women (33 versus 22\%, \( P=0.05 \)) despite similar age (68 \pm 5 versus 68 \pm 5 years, \( P=0.94 \)), but AVC prevalence increased with age both in men and women (23\% and 16\% between 60 and 69 years and 50\% and 35\% after 70 years, respectively). Higher prevalence of AVC in men persisted after adjustment for age (OR=1.79 [1.01 to 3.19], \( P<0.05 \)). Participants with AVC had higher prevalence of cardiovascular risk factors (Table 1), with more frequent diabetes, higher body mass index, systolic blood pressure, serum glucose, and marginally more frequent hypertension (\( P=0.06 \)). No difference in tobacco-pack-years consumed or cholesterol levels was observed. After adjustment for age and gender, diabetes (OR=2.9 [1.2 to 6.9], \( P<0.05 \)), hypertension (OR=2.0 [1.1 to 3.9], \( P<0.05 \)), serum glucose (OR=4.5 per mg/dl increment [1.2 to 16.9], \( P<0.05 \)), and body mass index (OR=1.12
After 3.8±0.9 years (range 1.8 to 5.8) AVC prevalence and overall progression of Aortic Valve Calcification per kg/m² increment [1.06 to 1.19], *P*<0.01) remained independently associated with the presence of AVC. Diabete s, serum glucose, and body mass index were also significantly associated with AVC score (used as a continuous variable) (all *P*<0.05).

**Progression of Aortic Valve Calcification**

**Overall**

After 3.8±0.9 years (range 1.8 to 5.8) AVC prevalence and score increased (respectively, 34 versus 27% and 94±271 versus 54±173 AU, *P*<0.01) with an annualized score progression rate of +11±32 AU/year. Based of the regression approach described in methods, progression was noted in 74 participants (28%). No regression was observed. Progression was observed in 55/70 participants with baseline AVC and in 19/192 participants with no AVC at baseline (acquisition of AVC or de novo AVC) (79 versus 10%, *P*<0.01, OR=33,[1672] *P*<0.01). Participants with AVC at baseline had also higher annualized aortic progression rate (+39±53 versus +1±4 U/year, *P*<0.01) (Figure, left panel). No atherosclerotic factor showed linear association to AVC progression. Using a logistic regression, presence of baseline AVC (*P*<0.001) and LDL (*P*=0.01) predicted AVC progression but with a significant interaction AVC-LDL (*P*=0.04). Thus, determinants of AVC progression were analyzed separately in participants with and without AVC at baseline.

**Progression in Participants With no AVC at Baseline**

Among the 192 participants with no AVC at baseline, 19 developed de novo AVC at follow-up (10%). Total- and LDL-cholesterol were higher in participants with de novo AVC than in those who remained free of AVC at follow-up (235±39 versus 209±33 mg/dL, *P*<0.001 and 141±31 versus 121±27 mg/dL, *P*=0.003 respectively). Triglycerides was of borderline statistical significance (209±101 versus 175±77 mg/dL, *P*=0.07) while age (67±4 versus 67±5 years, *P*=0.85) and male gender (37% versus 40%, *P*=0.80) were not different. These participants showed also at follow-up a trend for higher fibrinogen level (351±65 versus 318±75 mg/dL, *P*=0.08) but no difference in creatinine clearance (51±17 versus 55±17 mL/min, *P*=0.34). In multivariate analysis, the only independent baseline predictor of AVC acquisition was LDL-cholesterol (RR=1.29 per 10 mg/dL increment [1.08 to 1.55], *P*<0.01).

**Progression in Participants With Baseline AVC**

In participants with baseline AVC, aortic score increased at follow-up (337±441 versus 197±291, *P*<0.01) and faster progression from baseline to follow-up was displayed stratified according to presence or absence of AVC at baseline, showing that AVC score progression is higher in participants with baseline AVC. In panel B (right), displaying only participants with established baseline AVC, the AVC score (mean±SE) progression from baseline to follow-up is stratified according to baseline AVC score tertile showing faster progression with higher AVC load.
with baseline aortic score tercile (+11±12, +20±17, and +86±71/year, respectively in the lowest, mid, and highest AV score tercile, P<0.01) (Figure, right panel). AVC progression rate was not different according to age, gender, or cardiovascular risk factors (Table 2). There was no association with follow-up Fibrinogen (P=0.53) and creatinine clearance (P=0.16). In multivariate analysis, the only independent determinant of faster annualized AVC progression was higher baseline AVC score (P<0.01).

Clinical Correlates
Progression to AS (mean gradient ≥10 mm Hg) was observed in 10 participants at last follow-up. These 10 participants reached a lower aortic valve area (AVA) (1.66±0.48 versus 2.28±0.56 cm², P<0.01) and had faster AVC progression rates than the remaining population (96±80 versus 8±24 AU/year, P<0.01). Participants with baseline AVC compared with those with no AVC at baseline developed AS more frequently during follow-up (13% versus 0.5%, P<0.0001). Five participants developed moderate or severe AS (mean gradient ≥20 mm Hg or AVA <1.5 cm²) and were only noted among those with AVC at baseline (7% versus 0%, P<0.001).

Association With Subclinical Coronary Atherosclerosis (CAC)

Baseline
Although correlation between AVC and CAC scores was weak (Rho=0.28, P<0.01), AVC was associated with higher prevalence of CAC (94 versus 72%, P<0.01; OR=6.3 [2.4 to 21.4], P<0.01), higher prevalence of CAC score ≥200AU (47 versus 27%, OR=2.5 [1.4 to 4.4], P<0.01), and with higher CAC score (441±802 versus 265±566, P<0.01). CAC score increased with age (r=0.26, P<0.01), but prevalence of CAC score ≥200 was higher in participants with AVC irrespective of age (41 versus 23% under 70 years and 53 versus 36% after 70 years, P=0.01). Adjusting for age and gender, AVC was independently associated with high odds of CAC presence (Odds-Ratio 4.7[1.7 to 16.6], P<0.01), high odds of CAC score ≥200 (Odds-Ratio 1.9[1.0 to 3.5], P=0.05), and with higher CAC score (P=0.01). The independent association of AVC with high odds of CAC presence persisted unchanged (Odds-Ratio 4.4[1.5 to 15.9], P<0.01) after further adjustment for cardiovascular risk factors (blood pressure, hypertension, smoking, diabetes, cholesterol) and persisted (P=0.01) even after exclusion of diabetic participants.

CAC and AVC Progression
Coronary score also increased (422±705 versus 312±640, P<0.01) with an annualized progression rate of +38±55 AU/year. There was a modest but significant correlation between AVC and CAC progression rates (Rho=0.35, P<0.01).

Compared with participants remaining free of AVC, participants with de novo AVC had higher CAC score at baseline (643±901 versus 223±503 AU, P=0.04) and at follow-up (967±1214 versus 328±637 AU, P=0.008), and most importantly had the faster CAC annualized progression rate (78±87 versus 29±47 AU per year, P=0.003) even after adjustment for baseline coronary score (P<0.05). In contrast, adjusting for baseline CAC, annualized CAC progression rate was not different in participants with established AVC and in those remaining free of AVC (P=0.41).

Discussion
This first population-based study with prospective EBCT performance allows determination of AVC, CAC, and atherosclerotic risk factors, and allows analysis of the determinants of AVC progression in the population. After the age of 60 years, AVC prevalence is high (27%), increases with age, and is higher in men than women. AVC presence is associated with cardiovascular risk factors, is a marker of subclinical CAD revealed by CAC independently of age and diabetes, and is associated with a higher risk of developing AS. AVC is progressive, with two distinctive patterns. Acquisition of AVC (de novo AVC) is characterized by high lipid...
and fibrinogen levels and fast CAC progression suggestive of rapidly progressive atherosclerosis. Conversely, progression of established AVC is fastest with highest baseline calcification score and unrelated to cardiovascular risk factors. These data emphasize the importance of diagnosing AVC as a marker of subclinical CAD, which may lead to more intense risk factor management. It is also essential to monitor AVC progression to AS and to devise new strategies of prevention of AVC progression.

Prevalence and Determinants of AVC
In our population based study, AVC measured by EBCT was common, present in 27% of subjects 60 or older, similar to the Cardiovascular Health Study aortic valve sclerosis prevalence after 65 (29%), showing that this observation is not an echocardiographic artifact. AVC is an active valve lesion and not simply a consequence of aging. Indeed, prevalence of AVC increases with age and is higher in men than women, but shows strong association to cardiovascular risk factors, even after adjustment for age and gender. Our study provides novel insights in demonstrating the association of AVC to diabetes, body mass index, and elevated serum glucose. Vascular calcification is a hallmark of diabetes and insulin resistance, and our study extends this observation to aortic valve calcification. The mechanistic link between glycemic dysregulation and AVC is yet undefined and appears unrelated to diabetic nephropathy.

Progression of AVC
AVC progression is the mechanism by which the intrinsic valvular complication of AVC, ie, progression to AS, occurs. Our study shows that the observation of AVC is not benign and that progression to AS occurs frequently. Although it is known that AS hemodynamically progresses over time, with valve area declining approximately by 0.1 cm²/year, the processes and determinants leading to this progression are poorly known. The concept of “degenerative” passive calcific valvular deposition is no longer accepted, and AS is considered an active atherosclerotic disease. AVC progression was even found in pilot data, directly linked to hyperlipidemia. However, the link AS-atherosclerosis was challenged by the lack of association between cholesterol levels and AS progression, and most importantly, by the lack of effect of the strongest antiatherosclerotic treatment available, high-dose statins, on AS and AVC progression. Our study provides insights dissociating two different phases of AVC progression and allows reconciling apparently discordant data.

The early phase fits well the atherosclerotic concepts of aortic calcification with hyperlipidemia, inflammation, and rapid coronary calcification. This phase is consistent with previous studies on early aortic lesion pathology, characterized by inflammation and oxidized lipoproteins deposition, colocalized with early calcium deposit, and with recent experimental data. The secondary phase of calcium accumulation with ultimately ossification, is unrelated to vascular risk factors and AVC grows faster with calcification load. This phase fits the biological concept of centripetal expansion of calcific nodules, which are surrounded by osteoblast-like cells, and fits the observed independence of AS progression from lipid profile. This concept of two different phases of AVC progression is essential in comprehending statin effect and properly targeting a clinical trial. Observational retrospective studies suggested that statins may reduce AS progression, but a recent clinical trial showed that, at an advanced stage, statins prevented neither AS progression nor calcium deposition. Thus, when AVC grows independently of lipid levels as shown by our study, statins do not prevent calcium accumulation. Conversely, at an early stage of aortic sclerosis, when de novo calcification is lipid-dependent and inflammatory, statins may prevent AVC progression, as shown experimentally and may prevent the frequent progression to AS. Thus our study, as well as the most recent data, provide essential support for a clinical trial of statins in patients with early rather than advanced valve lesions, sclerosis or early AVC, to prevent progression to AS.

Clinically, calcified valves accumulate calcium faster but the relationship between calcification load and hemodynamic AS severity is non-linear. The same calcium accumulation may result in smaller valve area reduction in patients with more severe AS. Combinations of these various factors explain the large variability of AS progression between individuals. However, faster calcific growth with AVC load noted in the present study, suggests that for any given AS severity, a larger baseline calcific load may lead to faster calcific and hemodynamic progression and worse prognosis. Therefore, monitoring AVC load in patients with aortic valve disease is an important part of the clinical monitoring.

Recent ACC/AHA guidelines underline the importance of risk stratification by calcium measurements, especially in asymptomatic patients with severe AS or in patients with less severe AS undergoing coronary artery bypass graft. The method for AVC assessment is not specifically mentioned. Echocardiography versus CT is simple but qualitative, subjective, depends on gain settings, and is not specific (reflects both fibrosis and calcification), resulting in more severe estimation of AVC grade.

AVC and Subclinical Coronary Artery Atherosclerosis
Recently, the Cardiovascular Health Study reported increased cardiac mortality in participants with aortic valve sclerosis, a finding quite surprising with nonobstructive valve lesions. Whether echocardiographic underestimation of the valve stenosis or true linkage of minor AVC with subclinical CAD explained the excess mortality remained mysterious as most studies attempting to address this issue were subject to referral and selection bias. Our study provides novel population-based information on the association independent of age between CAD and AVC. The association of AVC to cardiovascular risk factors led to the suspicion of a CAD-AVC association, but our study proves the excess CAD burden with AVC in the general population even accounting for atherosclerotic risk factors. CAC assessed by EBCT is a sensitive and reliable marker of presence and extent of CAD, and a high score predicts high rate of subsequent coronary events. Thus, by demonstrating that AVC is a...
marker of higher prevalence and severity of CAC in the population independently of age and gender, the present study links formally AVC to the CAD that leads to poor outcome. Also, the rapidly progressive CAD accompanying AVC acquisition emphasizes the link of AVC presence to subsequent risk. Future prospective studies should evaluate whether AVC presence and/or acquisition identify groups at high risk for coronary events and whether active treatment prevents these events.

However, our study also provides important insights regarding association between CAD and AVC. Indeed, in a purely atherosclerotic hypothesis of calcification progression, the fact that most patients with severe AS attributable to massive valve calcification present without obstructive CAD, would be incomprehensible. AVC, after the initial atherosclerotic phase, grows independently of most risk factors. Thus, AVC presence is a marker of presence and extend of CAD but massive AVC is not a marker for extensive CAD.

Limitations
The present study is, with the Cardiovascular Health Study (CHS), the only population-based study of early aortic valve lesions. Nevertheless biases cannot be ruled out, either because of the methods (echocardiography for CHS) or the requirement of a second EBCT (excluding patients who died in the interim). However, both studies are consistent regarding the high prevalence of aortic valve sclerosis or calcification, and the association to cardiovascular risk factors. Thus, this consistency underscores the public health problem detected. Our study is smaller in size and the association of risk factors of lesser significance to AVC may not be detected. However, our sample provides 84% power to detect correlations of Rho=0.18, so that the major determinants of AVC presence and progression can be detected. Only patients ≥60 years old were considered in the present study. Whether our findings can be extended to younger patients, especially those with bicuspid aortic valve, needs further evaluation. Importantly, although we cannot assess prognosis because participants with both baseline and follow-up CT were enrolled, we can demonstrate AVC progression leading to aortic stenosis, its determinants, and association to CAD, which represent novel information of particular value because population-based.

We did not perform repeated coronary angiography to assess coronary disease, but CAC burden is a reliable surrogate of subclinical coronary atherosclerosis. Coronary and aortic calcifications appear with aging, but their association is not incidental and is independent of age, gender, and diabetes, and as such may be a marker of future coronary events.

Also, to assess for AS development, Doppler-Echocardiography was performed when clinically indicated in only 129 participants. In addition, anatomy of the aortic valve (bicuspid or tricuspid) was not available. Finally, for AVC and CAC quantification, we used the previously validated Agatston score. Similar results were obtained using a volumetric method.

Conclusion
In the population, AVC prevalence is high, increases with age, and is higher in men than women. However, AVC is not a passive, degenerative phenomenon. AVC is associated with cardiovascular risk factors, particularly diabetes, and is a marker of subclinical CAD. AVC is progressive leading frequently to AS, with two different patterns. De novo AVC occurs in a context of hyperlipidemia and progressive atherosclerosis. Progression of established AVC is unrelated to cardio-vascular risk factors and is faster with high AVC load suggesting exponential calcification growth. These new epidemiologic data emphasize the importance of detecting and of testing new approaches for preventing AVC.

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Disclosures
None.

References
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