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Baseline Aortic Valve Calcium Score and Use of Anticoagulants are associated with Rapid Progression of Aortic Valve Calcification

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Abstract

Background: Factors associated with rapid progression of aortic valve calcification (AVC) remains insufficiently addressed. The aim of this study was to identify risk factors that predict the progression of AVC and whether there is an association with coronary artery calcification (CAC).

Methods: We retrospectively identified patients with two non-contrast, gated x-ray computed tomography (CT) scans for AVC scoring. Medical records were reviewed, rate of increase in AVC over time was calculated, and a multivariable model was used to determine predictors.

Results: In 360 patients studied, the mean rate of increase in AVC per year was incrementally higher according to baseline AVC. For patients with baseline AVC score <250 AU, the mean AVC rate per year was 15.8±26.8; and for >1000 AU the mean rate was 280.3±284.2 (p-value <0.001). Use of warfarin anticoagulation was found to be significantly associated with a higher rate of AVC score increase (12.0% in patients with baseline AVC <250 Vs 33.3% patients with baseline AVC >1000) (p <0.05). After adjustment for age, factors noted to have an increased rate of AVC include baseline AVC and oral anticoagulant use (both p <0.05).

Discussion: The initial CAC score was higher in patients with higher AVC, but the mean rate of increase in CAC score was not found to be statistically significantly related to AVC. There was no statistically significant association between conventional risk factors or CACS. These data may help determine appropriate follow up intervals and risk stratification of patients with AVC.

Conclusion: The rate of change in AVCS increases according to higher baseline AVC. The rate of calcification is also associated with the use of oral anticoagulants. These data may help determine appropriate follow up intervals and risk stratification of patients with AVCS.

Keywords: Aortic valve calcification • X-Ray computed tomography • Anticoagulation

Introduction

Calcific aortic valve disease (CAVD) is a common disorder affecting up to 13% of the United States population [1] and which is anticipated to double over the next 50 year [2]. Progressive cardiovascular disease (CAVD) results in hemodynamically significant aortic stenosis (AS), which is associated with heart failure and reduced survival. The association between traditional cardiovascular disease risk factors and the development of aortic stenosis (AS) in the general population remains insufficiently addressed, despite the increased risk of AS with cumulative age [3-5]. CAVD is characterized by progressive fibro-calcific remodeling and thickening of the aortic valve leaflets that evolves over years to cause severe obstruction to cardiac outflow [6]. Until recently, CAVD and vascular calcification were considered degenerative and unregulated processes, but it has become increasingly apparent that CVAD is not a passive process of calcium deposition, but rather a complex process that involves genetic factors, lipoprotein deposition, and oxidation, chronic inflammation, as well as osteoblastic transition of cardiac valve interstitial cells and active leaflet calcification [6]. Calcification in the aortic valve can be measured non-invasively on gated x-ray computed tomography [1,7,8]. As the calcium largely causes the obstruction, the amount of calcium roughly correlates with the severity of obstruction in aortic valve stenosis and the aortic valve calcium score has an established role as an adjunctive test for determining the severity of aortic valve stenosis [9]. The temporal progression of aortic valve calcification has not been well studied, however, and risk factors for progression of aortic valve calcification are not well known. Better understanding of such progression might allow for greater insights into the mechanism of the disease of aortic stenosis and individualization of patient follow up, especially in the pre-clinical phase. The primary aim of this study was to identify risk factors that predict progression in patients who have aortic valve calcification/early aortic stenosis.

Research Methodology

This is a single-center retrospective longitudinal study involving the chart review of patients at Saint Luke's Mid America Heart Institution (MAHI), Kansas City, Missouri. Subjects who had undergone screening gated x-ray non-contrast CT scanning of the coronary arteries for coronary calcium scoring were eligible for inclusion. The MAHI coronary calcium scoring database was queried (total n=112,665, 1/2005-12/31/2019) and individuals who had aortic valve calcium identified on a coronary calcium score study (aortic valve calcium score >0) and had at least one other gated CT calcium score at another point in time between 2005 to 2019 were included (n=360). Baseline demographics including age, gender, history of hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, coronary artery disease (CAD), myocardial infarction (MI), stroke, peripheral vascular disease, history of the bicuspid aortic valve (BAV), and medications use such as angiotensin-converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB's), statin use, and anticoagulation use were obtained from electronic health records (EHR). Saint Luke's Hospital Institutional Review Board granted a waiver of informed consent for this retrospective study.

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Aortic valve calcium (AVC) scoring was obtained as has been previously described [1,7,8]. AVC was defined as any calcified lesion localized to the AV leaflets and aortic annulus. Calcification in the ascending aorta, subaortic annulus space or coronary arteries was excluded. AVC was quantified using Agatston methodology [10], which accounts for both lesion area and calcium density (using Hounsfield brightness). If AVC was not detected, the Agatston score was recorded as zero. All CT scans were scored on the same workstation (Singo. via coronary calcium scoring program, Siemens Healthineers, Erlangen Germany) by one of the authors (AS) and reviewed and confirmed by the senior author (RCT). The study participants were categorized into four groups based on Agatston score of their first CT scan as follows: <250 AU, 250-500 AU, 500-1000 AU, and those with scores >1000 AU.

Continuous variables are expressed as mean +/- standard deviation and categorical variables as proportions. Patients were divided into 4 groups based on their baseline AV calcium scores as mentioned above. Continuous variables were analyzed with a one-way ANOVA test, and categorical variables were compared with Chi-square tests. We then performed a multivariable linear regression model predicting the rate of AVCS using the following variables: age, sex, smoking, AC use, HTN, DM, FH of CAD, statin use, bicuspid aortic valve, creatinine, baseline CACS, and baseline AVCS. Output from this model is shown graphically with the linear beta weights and 95% confidence intervals (Figure 1). Statistical analyses were performed using SAS 9.4 (Cary, NC). Statistical significance was defined as $p < 0.05$.

Results

A total of 360 patients with at least two separate gated coronary calcium scoring chest CT scans between 2005 and 2019 were identified from the MAHI cardiovascular CT scan database. The mean between-scan days was 2381 +/- 1274 sd. Demographic and clinical characteristics are presented in Table 1. The mean baseline age was 73.4 +/- 8.4 years sd with 62.8% being male. Hypertension was present in 80.6% of the cases, diabetes in 33.0% and 50.7% of cases had an abnormal coronary artery calcium score. About 50.3% of individuals had a family history of CAD. The prevalence of chronic kidney disease (CKD) stage I, II, III, IV and V was 17.0%, 46.1%, 16.4%, 3.1%, and 2.8% respectively. About 50% of the cohort was on ACE/ARBs, 73.6% on statins, and 20.3% on anticoagulants.

Table 1. Baseline characteristic and demographic data.

Baseline Characteristics	N= 360	AVCS <250 N = 201	AVCS 250-500 N = 67	AVCS 500-1000 N = 38	AVCS>1000 N = 54	P-value
Age						
Mean ± SD	73.4 ± 8.4	71.9 ± 8.1	73.7 ± 8.3	76.1 ± 7.2	77.0 ± 8.9	< 0.001
Median (IQR)	74.0 (68.0, 79.0)	73.0 (66.0, 77.0)	74.0 (69.0, 79.0)	77.0 (71.0, 81.0)	77.5 (69.0, 84.0)	
Sex						
Female	134 (37.2%)	82 (40.8%)	25 (37.3%)	12 (31.6%)	15 (27.8%)	0.308
Male	226 (62.8%)	119 (59.2%)	42 (62.7%)	26 (68.4%)	39 (72.2%)	
Diabetes	114 (33.0%)	65 (33.9%)	14 (21.2%)	12 (33.3%)	23 (45.1%)	0.052
Hypertension	278 (80.6%)	148 (77.1%)	53 (80.3%)	33 (91.7%)	44 (86.3%)	0.150
Family History of CAD	172 (50.3%)	91 (47.9%)	34 (51.5%)	20 (57.1%)	27 (52.9%)	0.739
Bicuspid aortic valve	12 (3.5%)	4 (2.1%)	1 (1.5%)	1 (2.8%)	6 (11.8%)	0.017
Previous CAD	175 (50.7%)	82 (42.7%)	41 (62.1%)	18 (50.0%)	34 (66.7%)	0.003
Rheumatic heart disease	2 (0.6%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	0.474
Smoking	10 (2.9%)	6 (3.1%)	3 (4.5%)	0 (0.0%)	1 (1.9%)	0.757
Statin	254 (73.6%)	141 (73.1%)	48 (73.8%)	27 (75.0%)	38 (74.5%)	1.000
Use of ACE/ARB	173 (49.9%)	99 (51.0%)	30 (45.5%)	21 (58.3%)	23 (45.1%)	0.556
Use of Anticoagulants	73 (20.3%)	24 (12.0%)	21 (31.3%)	10 (26.3%)	18 (33.3%)	< 0.001
Warfarin	29 (8.4%)	8 (4.0%)	8 (12.1%)	7 (18.9%)	6 (14.6%)	0.001
Serum phosphorus						
Mean ± SD	3.8 ± 0.8	3.8 ± 0.9	4.0 ± 0.7	3.9 ± 0.6	3.7 ± 0.8	0.602
Median (IQR)	3.7 (3.3, 4.1)	3.7 (3.3, 4.1)	3.9 (3.5, 4.2)	3.6 (3.5, 4.4)	3.7 (3.2, 4.1)	
Serum creatinine (mg/dl)						
Mean ± SD	1.1 ± 0.9	1.0 ± 0.6	1.2 ± 1.4	1.2 ± 0.8	1.2 ± 1.1	0.240
Median (IQR)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	1.0 (0.7, 1.1)	
Serum calcium (mg/dl)						
Mean ± SD	9.4 ± 0.5	9.4 ± 0.5	9.3 ± 0.5	9.3 ± 0.6	9.2 ± 0.7	
Median (IQR)	9.4 (9.1, 9.7)	9.5 (9.1, 9.7)	9.4 (9.1, 9.7)	9.4 (8.9, 9.7)	9.3 (8.8, 9.5)	0.016
CKD-eGFR						
0	47 (14.6%)	18 (10.0%)	7 (11.7%)	8 (23.5%)	14 (28.6%)	
I	55 (17.0%)	30 (16.7%)	10 (16.7%)	3 (8.8%)	12 (24.5%)	
II	149 (46.1%)	94 (52.2%)	32 (53.3%)	14 (41.2%)	9 (18.4%)	
III	53 (16.4%)	33 (18.3%)	5 (8.3%)	5 (14.7%)	10 (20.4%)	
IV	10 (3.1%)	3 (1.7%)	3 (5.0%)	2 (5.9%)	2 (4.1%)	
V	9 (2.8%)	2 (1.1%)	3 (5.0%)	2 (5.9%)	2 (4.1%)	
Elevated cholesterol	62 (18.6%)	42 (22.8%)	9 (14.1%)	3 (8.6%)	8 (16.0%)	0.150
Elevated LDL	90 (27.3%)	56 (30.6%)	16 (25.4%)	9 (26.5%)	9 (18.0%)	0.359
Hypertriglyceridemia	93 (27.8%)	50 (27.0%)	18 (28.1%)	11 (31.4%)	14 (28.0%)	0.952

Predictors of higher baseline aortic valve calcium and predictors of progression of aortic valve calcium

Higher baseline aortic valve calcium score was associated with older age (Table 2). AVCS mean age was 71.9 ± 8.1 in individuals < 250 AU and 77.0 ± 8.9 in individuals AVCS > 1000 AU (p-value <0.001). The mean rate of increase in AVCS per year was incrementally higher according to baseline AVCS (Figures 2 and 3). For patients with baseline AVCS <250 AU, the mean ACVS rate per year was 15.8± 26.8; for 250-500 AU, the mean rate was 39.9 ± 36.9, for 500-1000 AU, the mean rate was 96.8 ± 76.0, and for > 1000 AU, the mean rate was 280.3 ± 284.2 (p-value <0.001). The difference between the old and new scan AVCS was also significant across all the groups – a mean difference of 80.9 +/- 55.6 in group 1 to 1326 +/- 1170.8 in group 4. Use of anticoagulation (33.3% in group 4 vs 12.0% in group 1, p<0.05) was found to be significantly associated with a higher rate of AVCS score at baseline and associated with faster rate of AVCS increase. In our full multivariable model, only two variables were noted to have an increased rate of AVCS - baseline AVCS and oral anticoagulant use (both p <0.05).

With regards to CACS, the initial CAC scores were noted to be higher in individuals with higher baseline AVCS; 182.3±319.0 in individuals with AVCS <250, and 689.2±734.5 in individuals with ACVS >1000 (p-value of <0.001). However, the mean rate of increase in CAC score was not found to be statistically significantly related to aortic valve calcium. The median rate of change in AVCS per year is higher in patients with higher baseline calcium score and the rate of increase seems to level off between baseline scores of 1000-2000 (Figure 3). Only baseline aortic valve calcium score and use of warfarin predicted the progression of AVCS (Figure 1). The rate of AVCS change per year rises with an increased baseline AVCS reaching the peak at ~1100 baseline score (Figure 3).

Discussion

Our study aimed to determine the rate of progression of AV calcium using CT and to evaluate and identify the risk factors associated with the progression of AV calcification. Since valvular calcification is the intrinsic mechanism leading to AS development, and in the light of the fact that it may be precisely estimated by computed tomography (CT) [11], aortic valve calcification load assessment has been of significant interest. Prior studies have demonstrated that the prevalence of AVC and the degree of valve calcification depend on age [12,13]. In the study by Walsh, the incidence of AVC was 3% for subjects <50 years of age, 6% for subjects 50–59 years of age, 17% for subjects 60–69 years of age, and 34% for subjects ≥70 years of age (p <0.0001) [14]. However, AV calcification is not simply a consequence of aging, but rather a complex mechanism involving deposition of lipoproteins, chronic inflammation and the calcification cascade [15]. In our study, increasing age was associated with increasing prevalence of AVCS in univariable analysis, but not in multivariable analysis. Our study also did not reveal a significant correlation between gender and the prevalence and degree of AVC, similar to the study by Koos et al. analyzing AVC in 402 individuals [16].

It is known that AS hemodynamically progresses over time, with valve area declining approximately by 0.1 cm^2/year [17]. The processes and determinants leading to this progression are poorly known. While prior epidemiologic investigations have reported cross-sectional associations between AVC and traditional cardiovascular risk factors, including male gender, smoking, hyperlipidemia, diabetes, metabolic syndrome [18-20] and hypertension [18,21,22], as well as bicuspid aortic valves [23], our study did not find any significant correlation between these factors and the progression of AVCS, after correcting for age.

Despite the favorable effects of statins observed in some studies [24,25],

Table 2. Rate of progression of AVCS across four groups.

Predictors of progression	Total	Group				P-value
	N= 360	AVCS <250 N = 201	AVCS 250-500 N = 67	AVCS 500-1000 N = 38	AVCS>1000 N = 54	
Initial Aortic valve Calcium Score						
Mean ± SD	212.4 ± 439.2	52.1 ± 50.7	134.3 ± 92.4	226.5 ± 145.9	896.0 ± 830.5	< 0.001
Median (IQR)	74.1 (22.9, 162.9)	37.5 (11.1, 76.0)	124.2 (68.0, 182.0)	203.5 (112.7, 334.0)	779.9 (233.0, 1241.9)	
Initial Coronary artery Ca score						
Mean ± SD	342.5 ± 613.3	182.3 ± 319.0	446.9 ± 582.2	550.9 ± 1168.5	689.2 ± 734.5	< 0.001
Median (IQR)	103.4 (18.5, 410.4)	61.8 (4.5, 204.5)	288.2 (57.7, 569.0)	229.4 (36.0, 452.5)	564.5 (90.2, 976.1)	
New Aortic valve Calcium Score						
Mean ± SD	532.1 ± 859.5	132.9 ± 57.7	336.2 ± 66.7	700.6 ± 138.6	2237.2 ± 1243.8	0.001
Median (IQR)	214.0 (120.2, 488.7)	128.1 (85.2, 180.4)	321.4 (280.7, 390.0)	706.0 (578.1, 783.0)	1625.7 (1389.0, 2857.0)	
New Coronary Cal score						
Mean ± SD	787.2 ± 2519.5	642.6 ± 3081.0	924.5 ± 913.9	880.7 ± 1689.4	1311.7 ± 1236.5	0.515
Median (IQR)	325.8 (89.2, 864.6)	205.6 (69.1, 597.3)	682.0 (268.1, 1440.2)	465.5 (208.5, 978.6)	970.0 (221.9, 2008.9)	
Rate of change in AVCS						
Mean ± SD	67.2 ± 145.0	15.8 ± 26.8	39.9 ± 36.9	96.8 ± 76.0	280.3 ± 284.2	< 0.001
Median (IQR)	21.6 (9.5, 59.2)	11.5 (6.0, 18.4)	32.3 (24.5, 38.9)	82.0 (61.7, 106.7)	187.5 (114.8, 387.1)	
Rate of change in CAC						
Mean ± SD	93.9 ± 688.7	100.7 ± 887.4	80.9 ± 91.5	72.6 ± 91.6	101.6 ± 108.9	0.994
Median (IQR)	25.7 (7.1, 75.1)	18.8 (5.5, 47.4)	51.0 (10.4, 117.9)	52.2 (14.6, 84.6)	59.9 (12.7, 172.7)	
Differences in Days between initial and new scan						
Mean ± SD	2381.1 ± 1274.2	2495.0 ± 1229.2	2262.8 ± 1143.1	2289.8 ± 1207.0	2172.2 ± 1588.5	0.284
Median (IQR)	2127.0 (1503.0, 3135.5)	2181.0 (1543.0, 3234.0)	2071.0 (1436.0, 2878.0)	1905.5 (1627.0, 2489.)	2385.5 (1000.0, 3360.0)	
Difference in CAC between initial and new scan						
Mean ± SD	478.3 ± 2327.3	459.0 ± 2952.1	477.6 ± 637.6	401.7 ± 664.0	686.6 ± 820.1	0.958
Median (IQR)	158.1 (38.4, 416.4)	109.8 (31.3, 354.1)	248.2 (75.1, 657.2)	270.0 (99.6, 404.6)	258.7 (76.0, 1395.1)	
Difference in AVCS between initial and new scan						
Mean ± SD	323.3 ± 617.6	80.9 ± 55.6	201.9 ± 99.0	474.1 ± 167.3	1326.1 ± 1170.8	< 0.001
Median (IQR)	120.1 (58.3, 294.4)	75.1 (38.7, 113.7)	205.6 (140.5, 262.3)	490.4 (395.1, 596.0)	1060.0 (640.0, 1422.5)	

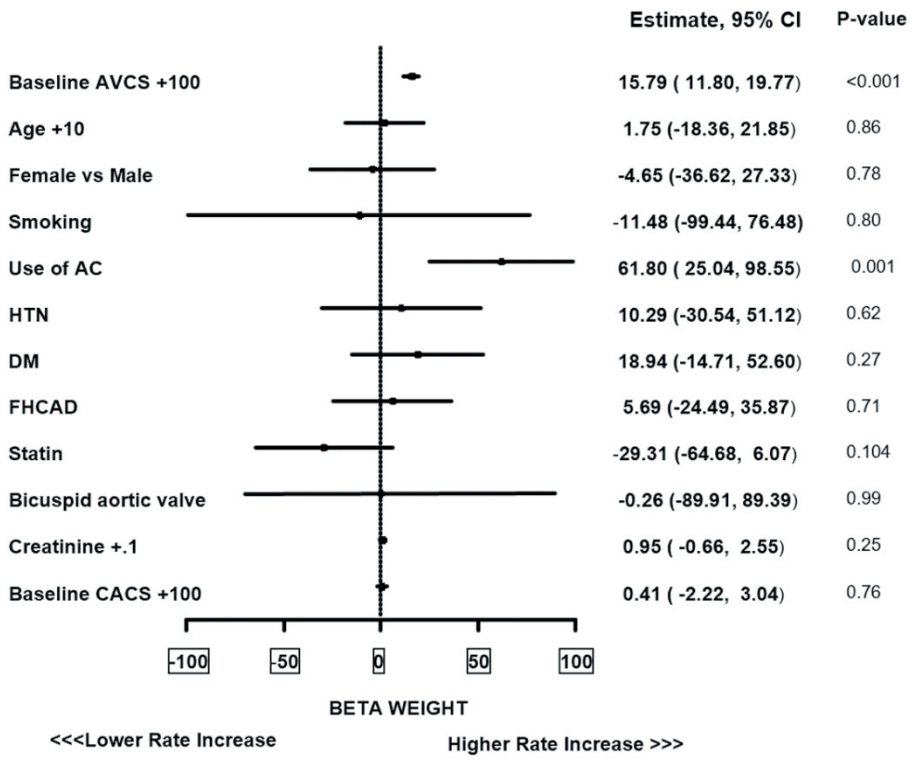

Figure 1. In the multivariable module only baseline AVCS and anticoagulant use predicted more rapid increase in AVCS.

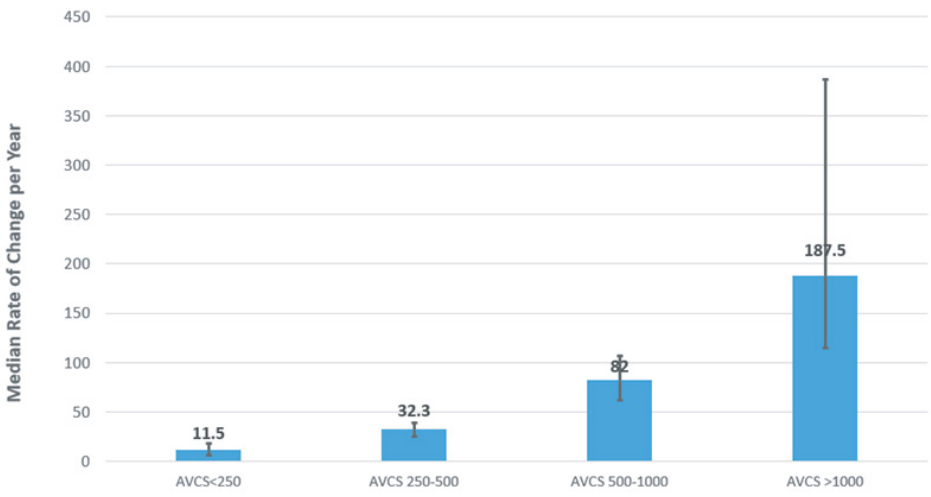

Figure 2. Rate of AVCS change by baseline AVC category.

conflicting and predominantly no significant association has been reported in the two largest trials [26]. Similar somewhat conflicting results were observed in our study. For example, we found that the participants with higher baseline AVCS also had higher baseline coronary artery calcium score (CACS) supporting the theory that the CVD risk factors are perhaps responsible for the initiation of AVC. However, baseline CACS was not associated with more rapid progression of AVCS. These findings could be explained if the risk factors associated with initial aortic stenosis differ from those associated with disease progression due to pathophysiological differences in the initiation and the progression of the process [27]. This early phase fits well with the atherosclerotic concepts of aortic calcification with hyperlipidemia, inflammation, and rapid coronary calcification, consistent with previous studies on early aortic lesion pathology [28], characterized by inflammation and oxidized lipoproteins deposition [29,30], and colocalized with early calcium deposit [28,30].-The secondary phase of calcium accumulation with ultimately ossification [31], is unrelated to vascular risk factors and AVC grows faster with calcification load [32], thus reflecting the biological concept of centripetal expansion of calcific nodules, which are surrounded by osteoblast-like cells [33], and fits the observed independence of AS progression from lipid profile [17,34].

We found that for any given aortic valve calcium score severity, a larger baseline calcific load leads to faster calcification, emphasizing that as the disease progresses, there is near exponential calcium deposition and the rate of calcification is independent of conventional cardiovascular risk factors. Lipoprotein a (Lp(a)) increases expression of key osteogenic genes in human valvular interstitial cells (VIC), committing them to an osteoblastic-like cell type [35]. Although our study did not evaluate the Lp(a), prior studies have shown that in AS, patients with elevated Lp(a) and OxPL-apoB plasma levels demonstrate increased valvular calcification activity, faster disease progression, and an increased risk of AV replacement (AVR) or death than subjects with lower levels. The pro-osteogenic effects of Lp(a) and OxPL on VIC are potentially

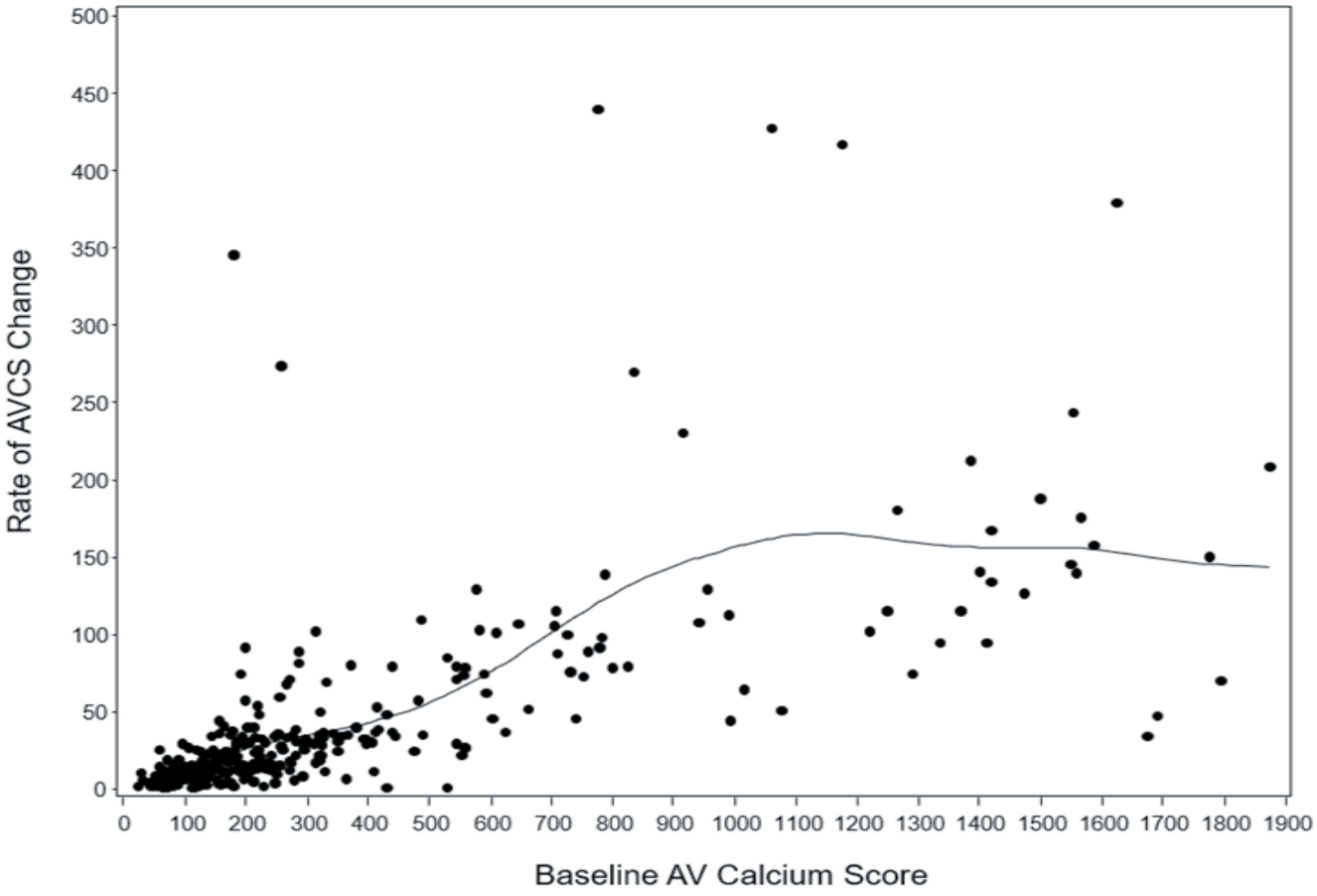

Figure 3. Rate of AVCS change by baseline AVCS.

reversible with targeted treatment inactivating OxPL [2]. These findings provide a rationale for clinical studies aiming to reduce elevated Lp(a) and OxPL levels in patients with AS as a means of slowing disease progression and delaying the need for AVR. Lp(a) is unaffected by statin therapy, but levels can now be reduced with novel compounds [36], making Lp(a) a potential therapeutic target in AS.

Our study also demonstrates a strong association of the level of AVC with the use of anticoagulants (3.3% in group 1 vs 12.0% in group 4, p <0.05), especially warfarin (18.9% in group 3 and 14.6% in group 4 vs 4.0% in group 1, p <0.05). Oral anticoagulants were also independently associated with a more rapid progression of aortic valve calcium over time (beta weight 71.06 ci 28.47-113.66). Vitamin K antagonist (VKA) have been previously implicated in the progression of AS and our results confirm and expand upon this finding [37,38]. This observation is theoretically supported by the fact that VKA inactivates matrix γcarboxyglutamic acid protein (MGP), through its incomplete γcarboxylation by antagonization of vitamin K [39]. MGP is a potent inhibitor of vascular calcification. Only the carboxylated form of MGP (c-MGP) is protective towards calcium deposition whereas the uncarboxylated (uc-MGP) is ineffective in protecting the vascular tissue from mineralization [40,41] and the carboxylation of MGP is dependent on vitamin K. MGP prevents both the crystal complexes nucleation and the Bone Morphogenic Protein-2 (BMP-2) induced osteogenic differentiation of vascular cells [40].

Koos et al. used CT imaging to quantify coronary and AV calcification in patients on long-term oral anticoagulation with VKA and compared it to those not on anticoagulation [40]. The patients on VKA had higher coronary calcium (p=0.024) as well as AV calcium (p=0.002) [38]. Similar results have been reported in a series of 430 subjects where a significantly greater incidence of AVC was found to be associated with the use of warfarin (18.0% vs 6.9% in warfarin vs non-warfarin-treated subjects; p=0.014) [37], findings similar to our study. Direct oral (DOAC) anticoagulants that do not act via the vitamin K pathway conceivably would solve this problem, and this possibility is supported in several studies.

Tastet et al. assessed the advancement of AS by measuring progression of peak aortic jet velocity (Vpeak) on Doppler echocardiography and AVCS on MDCT in participants who had at least mild aortic stenosis and were taking warfarin versus DOAC versus no anticoagulant group. The median annualized increase in Vpeak was larger in the warfarin group compared with the DOAC and no anticoagulant therapy groups. The median follow-up time between the first and last MDCT examinations was 2.0 years (25th to 75th percentile: 1.5 to 3.9 years). In the subset of patients who also underwent MDCT, the annualized increase in AVC score was at least 2-fold larger in the warfarin compared with the DOAC and no anticoagulation therapy groups [42]. Our study extends the findings by Tastet et al. and magnifies their observation to include individuals who have milder levels of aortic valve disease – those who have lower levels of aortic valve calcification likely prior to hemodynamic aortic stenosis.

AVC as measured by MDCT is low risk, noninvasive, and highly reproducible [8]. MDCT is not indispensable in patients with an obvious surgical indication of AVI but is helpful in considering transcatheter AVI. Thus, the measurement of AVC by MDCT should be considered for not only diagnosis, but also risk-stratification purposes in the evaluation of and therapeutic decision making in some patients with AS [8]. For example, in patients with echocardiographic findings which could be possibly be explained by either low-gradient- severe AS or moderate aortic stenosis, heavy AVC load is helpful as it is consistent with severe calcified aortic valve disease [7]. Higher AVC load is also associated with worse outcome [11,43].

Limitations

This was a single center, retrospective, non-randomized study and has the limitations associated with such a design. Also, not all characteristics may be captured and some baseline characteristics such as kidney function and use of anticoagulation can change over time, limiting the accuracy of a predictive model. Likewise, while to a certain extent the reference ranges of AVCA are

dependent on the imaging protocol and CT equipment used [44], we performed aortic calcium scoring in a consistent manner on all our patients.

Conclusion

Our study showed that a high baseline AV calcium score and the use of warfarin oral anticoagulation are associated with a faster rate of progression of aortic valve calcium. We did not find any statistically significant association with the conventional CAD risk factors, emphasizing that progression of AVC seems to be unrelated to conventional CVD risk factors. The faster rise in individuals with high baseline AVC load suggest a positive feedback of calcium deposition with accelerated calcification growth over the years. The study confirmed, in a population of mostly pre-clinical aortic valve calcification, the rapid progression of AVCS previously described with warfarin use in patients with aortic stenosis, implying that alternative anticoagulation strategies should be considered as an alternative in individuals with CAVD. These data also could help determine appropriate follow up intervals for patients with aortic valve calcifications.

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Author Contributions

Annapoorna Singh: Data curation, writing-original draft preparation**; John Saxon:** conceptualization, visualization, supervision, reviewing and editing; **Kevin Kennedy:** Methodology, software and validation; **Randall Thompson:** Conceptualization, visualization, supervision, writing-reviewing and editing.

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