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ORIGINAL PAPER

Prognostic value of aortic valve calcification in non-severe aortic stenosis with preserved ejection fraction

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Aims Aortic valve calcification (AVC) is prognostic in patients with aortic stenosis (AS). We assessed the AVC prognostic value in non-severe AS patients.

Methods and results We conducted a retrospective study of 395 patients with non-severe AS, LVEF ≥ 50%. The Agatston method was used for CT AVC assessment. The log-rank test determined the best AVC cut-offs for survival under medical surveillance: 1185 arbitrary unit (AU) in men and 850 AU in women, lower than the established cut-offs for severe AS (2064 AU in men and 1274 AU in women). Patients were divided into 3 AVC groups based on these cut-offs: low (<1185 AU in men and <850 AU in women), sub-severe (1185–2064 AU in men and 850–1274 AU in women), and severe (>2064 AU in men and >1274 AU in women). Of 395 patients (mean age 73 ± 12 years, 60.5% men, aortic valve area 1.23 ± 0.30 cm^2, mean pressure gradient 28 ± 8 mmHg), 218 underwent aortic valve intervention (AVI) and 158 deaths occurred during follow-up, 82 before AVI. Median survival time under medical surveillance was 2.1 (0.7–4.9) years. Compared with the low AVC group, both sub-severe and severe AVC groups had higher risk for all-cause death under medical surveillance after comprehensive adjustment including echocardiographic AS severity and coronary artery calcium score (all $P \leq 0.006$); while mortality risk was similar between sub-severe and severe AVC groups (all $P \geq 0.2$). This mortality risk pattern persisted in the overall survival analysis after adjustment for AVI. AVI was protective of all-cause death in the sub-severe and severe AVC (all $P \leq 0.01$), but not in the low AVC groups.

Conclusion Sub-severe AVC is a robust risk stratification parameter in patients with non-severe AS and may inform AVI timing.

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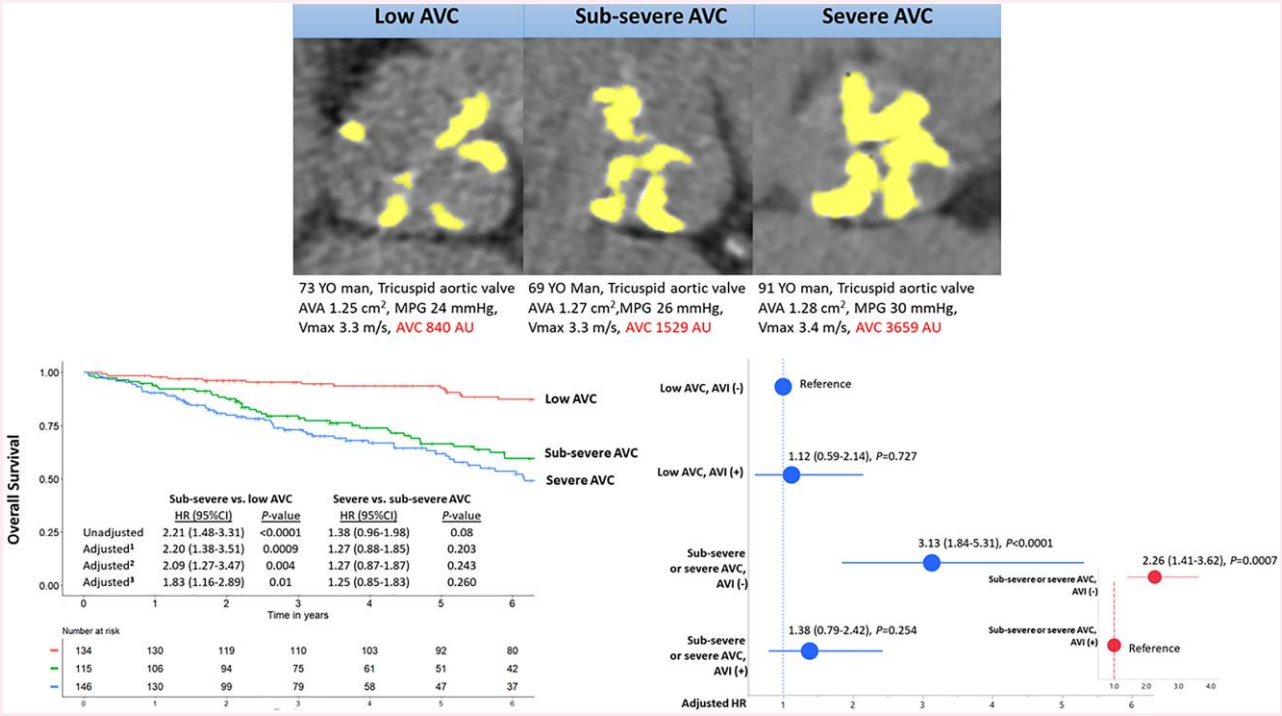
Graphical Abstract



CT AVC examples (upper), overall survival of three AVC groups (middle), and AVI impact on the sub-severe or severe AVC as a single group vs. low AVC group (bottom).

Keywords aortic valve calcification • sub-severe aortic valve stenosis • survival • computed tomography

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, affecting 11.9% of all adults referred for clinical echocardiographic evaluation.[1] The only treatment option to relieve valvular obstruction is aortic valve intervention (AVI), indicated in severe AS upon the presence of symptoms or a drop in LVEF below 50%, either through surgical or transcatheter approach.[2] However, recent studies highlighted worse survival in patients with non-severe AS compared with those without AS[1] or age- and sex-matched general population.[3] Supported by evidence from several retrospective studies showing significant mortality risk in patients with moderate AS,[4–6] ongoing clinical trials seek to determine whether earlier intervention may offer better outcomes in carefully selected symptomatic patients with moderate AS if they have heart failure with reduced EF or additional risk factors (NCT 02661451, 04889872, and 05149755). No study has evaluated risk identifiers in patients with non-severe AS, preserved LV systolic function, and without heart failure symptoms. With the trend of expanding AVI indications to a lower grade of AS, there is a need to study individuals falling within this clinical profile to refine our knowledge of their prognosticators and potential treatment indications.

CT aortic valve calcification (AVC) has become an important imaging biomarker to detect severe AS when echocardiographic AS severity is inconclusive.[2] The established severe AVC threshold [2065 arbitrary unit (AU) in men and 1274 AU in women] also has prognostic value independent of AVI status, likely linked to its association with severe AS, which in turn is associated with worse survival.[7,8] Higher AVC has also been associated with all-cause death and incident severe AS in individuals free of known coronary artery disease and overt aortic valve disease.[9,10] Whether AVC carries echocardiographic-independent prognostic information in patients with non-severe AS is unknown. We assessed whether AVC could differentiate patients with increased risk for death in the context of non-severe AS (e.g. mild, moderate, and moderate-to-severe AS). For this purpose, we studied AVC–mortality association in patients with non-severe AS, no or minimal symptoms (NYHA Class I or II), and preserved LVEF. The primary aim was to assess the association of AVC with all-cause death under medical surveillance (before AVI). The secondary aim was to assess whether the AVC–mortality association was independent of AVI status and whether AVI modified the association.

Methods

Study cohort

This study's patients are part of a larger previously published cohort.[11] In brief, all patients were identified from two valve clinic–based prospective studies of AS or patients with AS referred for clinical cardiac CT evaluation. Echocardiographic AS severity and AVC assessment were performed within 6 months, LVEF was ≥50%, and patient had at least mild AS [peak transvalvular velocity (V_{max}) ≥ 2 m/s and mean transvalvular pressure gradient (MPG) ≥ 10 mmHg). Patients with more than moderate mitral or aortic valve regurgitation or more than mild mitral stenosis, history of radiation therapy, or rheumatic valve disease were excluded. Among the original 1957 patients, 1344 had severe AS [aortic valve area (AVA) ≤ 1.0 cm^2 or indexed AVA < 0.6 cm^2/m^2 plus MPG ≥ 40 mmHg or V_{max} ≥ 4.0 m/s]. Of the remaining 613 patients with non-severe AS, we further excluded 190

with NYHA Class III–IV and 28 with low-flow low-gradient severe AS (AVA ≤ 1.0 cm^2 or indexed AVA < 0.6 cm^2/m^2 plus MPG < 40 mmHg or V_{max} < 4 m/s plus stroke volume index < 35 mL/m^2), resulting in 395 with non-severe AS for the current study. Of them, 215 (54.4%) were from prospective valve clinic research studies and 180 (45.6%) were from patients referred for clinical cardiac CT evaluation. CT indications of 180 patients included AS severity evaluation ($n = 161$, 89.4%), coronary artery disease or chest pain ($n = 13$, 7.2%), valve morphology evaluation ($n = 3$, 1.7%), and aortic aneurysm ($n = 3$, 1.7%). The study was approved by the Mayo Clinic Institutional Review Board.

Clinical and echocardiographic variables

Demographic information was ascertained at echocardiographic evaluation. Medical history, NYHA class, AVI status, death information, and clinical visits were abstracted from electronic medical records. Age-adjusted Charlson comorbidity index was calculated as previously reported.[12] All patients underwent two-dimensional and Doppler echocardiographic assessment of LV function and AS severity according to current guidelines.[2,13,14] Images were clinically acquired and reviewed by level 3 echocardiography-trained board-certified cardiologists.

CT AVC and coronary artery calcium

Both AVC and coronary artery calcium (CAC) scoring were performed offline using commercially available and validated software (Aquarius Intuition from TeraRecon, San Mateo, CA, USA), with the use of the Agatston method, and expressed in AU.[15] AVC and CAC_{score} measurements (Z.Y.) were compared with measurements by another investigator (M.-A.C.) for inter-observer variability assessment and repeated by the same investigator (Z.Y.) ≥2 months after the original measurement for intra-observer variability assessments, which were defined by the absolute difference between two measurements divided by the average of the two measurements. Inter- and intra-variability of AVC were 4.0 ± 6.0% and 2.3 ± 2.8%, and CAC_{score} were 3.9 ± 5.4% and 2.0 ± 2.1%, respectively.

Statistical methods

Data are expressed as mean (SD) or median (IQR) for continuous variables and as count (percentages) for categorical variables. Comparisons between groups were assessed by ANOVA t test for continuous variables and likelihood χ^2 test for categorical variables. AVC and CAC_{score} were square root–transformed for all the analyses due to skewed data distribution.

The log-rank test was used to determine the best prognostic cut-offs of AVC for their association with survival under medical surveillance in men and women separately (AVC, 1185 AU in men and 850 AU in women). Since our cut-offs were lower than the established cut-offs for severe AS (2064 in men and 1274 in women)[7] that showed prognostic value in previous studies,[8,16] we characterized patients into 3 AVC groups: low (<1185 AU in men and <850 AU in women), sub-severe (1185–2064 AU in men and 850–1274 AU in women), and severe (>2064 AU in men and >1274 AU in women).

Associations of AVC with all-cause death were assessed by unadjusted and then multivariable-adjusted Cox proportional hazard (PH) analysis. Adjustment included variables with a $P < 0.05$ on both univariable and multivariable analyses. Candidate variables included age-weighted Charlson comorbidity index score, sex, systolic and diastolic BP, LVEF, stroke volume index, LV hypertrophy,[13] elevated LV filling pressure,[17] bicuspid aortic valve, echocardiographic AS severity parameters (MPG, V_{max}, AVA, and indexed AVA), and CAC_{score}. Cox PH assumption was assessed via examination of the Schoenfeld residual. To assess associations with all-cause death under medical surveillance, patients were censored at AVI or latest clinical visit. To assess associations with overall survival, patients were censored at death or latest clinical visit, and AVI was introduced as a time-dependent variable. Improvement in prognostication and model performance for all-cause death by AVC was assessed by ANOVA likelihood χ^2 test and C-statistics. To explore the AVI impact on the AVC–mortality association, an interaction term of AVI with AVC was introduced in the regression analysis.

Both the absolute AVC score and $AVC_{density}$ (AVC divided by LV outflow tract area from transthoracic echocardiography) were analysed. However, we only present detailed results of AVC score in the main text because current guidelines[2] and a recent experts' review[18] only use AVC score to diagnose AS. Moreover, a previous multicentre study reported a lack of reproducibility of the diagnostic value of $AVC_{density}$[16] that was possibly related to the elliptical configuration of the LV outflow tract and associated measurement variability by echocardiography.[19] A summary of $AVC_{density}$ analysis is presented in the supplementary data. We refer to the absolute AVC score as AVC.

All tests were two-sided, with a $P < 0.05$ considered statistically significant. Data were analysed using JMP 14 (SAS Institute Inc., Cary, NC) and R programming version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Of our 395 patients, 344 (87%) had at least 1 criterion for echocardiographic moderate AS (AVA 1.0–1.5 cm^2, MPG 20–39 mmHg, or V_{max} 3–3.9 m/s)[2,14,18]; 56% of them had concordant AVA–MPG or AVA–V_{max} (see Supplementary data online, *Table S1*) and 44% discordant. The remaining 13% (51/395) of patients had mild AS: MPG 10–19 mmHg plus V_{max} 2.0–2.9 m/s. Scatterplots of AVC vs. echocardiographic AS severity parameters are shown in Supplementary data online, *Figure S1*, suggesting moderate correlations between them.

Table 1 shows patient characteristics of the entire group and three AVC groups. In the entire group, the mean age was 73 ± 12 years, 60.5% were men, and 73.7% NYHA Class I. Mean AVA, MPG, and V_{max} were consistent with moderate AS. The median AVC was below the established threshold of severe AVC for both men and women.[2,7,16] In general, patients with higher AVC were older, were mostly men, and had smaller AVA and higher V_{max} or MPG (all ANOVA $P < 0.0001$). Mean V_{max} and MPG in the sub-severe AVC group were within the moderate AS range, while mean V_{max} and MPG in the severe AVC group were in the 'moderate-to-severe' range (according to usual clinical practice). Mean AVAs were similar between sub-severe and severe AVC groups, both close to 1.1 cm^2 ($P = 0.365$), that may be clinically reported as moderate-to-severe but also moderate AS considering the upper SDs. Therefore, within non-severe AS, there was an overlap between moderate AS and moderate-to-severe AS. Conversely, median AVCs across three groups showed distinct differences: The median AVC of low AVC group was only 50% of that of sub-severe AVC group. The median AVC of the sub-severe AVC group was only ~60% of that observed in the severe AVC group. As for prevalence of cardiovascular risk factors and comorbidities, there were no significant differences between the sub-severe vs. severe AVC groups and the sub-severe vs. low AVC groups (all $P \geq 0.161$), except for a higher prevalence of atrial fibrillation in the sub-severe AVC compared with the low AVC groups (20.9 vs. 7.5%, $P = 0.002$).

Survival under medical surveillance by AVC group

After a median total follow-up of 4.8 (2.2–9.8) years, 218 (55%) patients had AVI [123 (56.4%) by surgical and 95 (43.6%) by transcatheter approach] and 158 (40%) died. Of 158 deaths, 82 occurred before AVI. Median survival time under medical surveillance was 2.1 (0.7–4.9) years.

Kaplan–Meier survival under medical surveillance of three AVC groups is shown in *Figure 1*. Patients with sub-severe and severe AVC both had worse survival than those with low AVC (both log-rank

Table 1 **Patient characteristics in all and three AVC groups**

	All ($N = 395$)	Low AVC ($N = 134$)	Sub-severe AVC ($N = 115$)	Severe AVC ($N = 146$)	*P*-value		
					ANOVA	Sub-severe vs. low AVC	Severe vs. sub-severe AVC
Age, year	73 ± 12	68 ± 12	74 ± 10	76 ± 10	<0.0001	0.0003	0.120
Men	239 (60.5%)	60 (45.1%)	76 (66.1%)	102 (69.9%)	<0.0001	<0.0001	0.516
BMI, kg/m^2	28.99 ± 6.05	29.85 ± 6.98	28.75 ± 5.75	28.38 ± 5.29	0.108	0.314	0.880
Systolic BP, mmHg	131 ± 18	132 ± 19	131 ± 18	130 ± 18	0.537	0.747	0.949
Diastolic BP, mmHg	72 ± 11	73 ± 11	72 ± 11	71 ± 11	0.424	0.740	0.871
LVEF, %	64 ± 6	65 ± 6	63 ± 6	63 ± 6	0.020	0.076	0.955
LV hypertrophy	147 (37.3%)	40 (30.3%)	35 (30.4%)	72 (49.3%)	0.0008	0.951	0.002
Elevated LV filling pressure[a]	146 (37.0%)	45 (33.8%)	44 (38.3%)	57 (39.0%)	0.601	0.443	0.898
AVA, cm^2	1.23 ± 0.30	1.38 ± 0.33	1.17 ± 0.27	1.14 ± 0.22	<0.0001	<0.0001	0.430
Indexed AVA, cm^2/m^2	0.64 ± 0.15	0.72 ± 0.17	0.61 ± 0.13	0.59 ± 0.11	<0.0001	<0.0001	0.216
V_{max}, m/s	3.4 ± 0.5	3.1 ± 0.5	3.4 ± 0.4	3.7 ± 0.4	<0.0001	<0.0001	<0.0001
MPG, mmHg	28 ± 8	22 ± 8	28 ± 7	32 ± 7	<0.0001	<0.0001	<0.0001
Stroke volume index, mL/m^2	49 ± 9	49 ± 9	49 ± 9	50 ± 11	0.283	0.564	0.840
NYHA Class I	291 (73.7%)	110 (82.0%)	86 (74.8%)	95 (65.1%)	0.005	0.161	0.089
Bicuspid aortic valve	97 (24.5%)	33 (24.6%)	28 (24.4%)	36 (24.7%)	0.998	0.959	0.954
Atrial fibrillation	73 (18.5%)	10 (7.5%)	24 (20.9%)	39 (26.7%)	<0.0001	0.002	0.271
Hypertension	269 (68.1%)	94 (70.2%)	80 (69.6%)	95 (65.1%)	0.611	0.920	0.442
Diabetes	86 (21.8%)	25 (18.7%)	29 (25.2%)	32 (21.9%)	0.457	0.211	0.532
Smoking (current)	32 (8.1%)	8 (6.0%)	11 (9.6%)	13 (8.9%)	0.514	0.287	0.855
Hyperlipidaemia	235 (59.5%)	86 (64.2%)	70 (60.9%)	79 (54.1%)	0.216	0.591	0.273
CKD stage ≥ 3	54 (13.7%)	15 (11.2%)	16 (13.9%)	23 (15.8%)	0.534	0.518	0.678
Chronic lung disease	51 (12.9%)	9 (6.8%)	13 (11.3%)	29 (19.9%)	0.004	0.204	0.058
Coronary artery disease	153 (38.7%)	39 (29.3%)	43 (37.4%)	71 (48.6%)	0.003	0.166	0.069
Age-adjusted Charlson comorbidity index score	5.36 ± 3.49	4.17 ± 3.21	5.72 ± 3.33	6.18 ± 3.57	<0.0001	0.001	0.516
CAC score, AU	489 (85–1799)	206.5 (17–763)	667 (119–1906)	1132 (147–2493)	<0.0001	<0.0001	0.093
Aortic valve calcium score, AU							
Men	1864 (1180–2757)	706 (422–984)	1560 (1344–1858)	2860 (2447–3552)	/	/	/
Women	868 (552–1350)	527 (225–718)	1021 (902–1132)	1640 (1410–2010)	/	/	/

Continued

Table 1 Continued

	All (N = 395)	Low AVC (N = 134)	Sub-severe AVC (N = 115)	Severe AVC (N = 146)	P-value		
					ANOVA	Sub-severe vs. low AVC	Severe vs. sub-severe AVC
Aortic valve calcium index, AU/cm^2							
Men	443 (273–602)	168 (111–232)	365 (326–445)	632 (548–775)	/	/	/
Women	249 (148–368)	145 (67–198)	282 (251–308)	465 (390–587)	/	/	/

Values expressed as mean ± SD/median (IQR) or count (%). Comparisons of sub-severe vs. low and severe vs. sub-severe AVC groups by Tukey HSD or Wilcoxon test or for continuous variables and χ^2 test for categorical variables. Severe AVC, >2065 AU in men vs. >1274 AU in women; sub-severe AVC, 1185–2065 AU in men vs. 850–127 AU in women; low AVC, <1185 AU in men vs. <850 AU in women.
LV, left ventricular; AVA, aortic valve area; MPG, mean transvalvular pressure gradient; V_{max}, aortic valve peak transvalvular velocity.
[a]Based on 2016 ASE recommendations for the evaluation of diastolic function.

$P < 0.0001$), while survival between the severe and sub-severe AVC groups was similar ($P = 0.21$). Their 1-, 2-, and 5-year survival were 98 ± 1.1%, 98 ± 1.4%, and 94 ± 2.5% in the low; 95 ± 2.1%, 86 ± 3.9%, and 61 ± 7.3% in the sub-severe; and 90 ± 2.9%, 79 ± 4.5%, and 57 ± 7.4% in the severe AVC groups, respectively.

Association of AVC with all-cause death under medical surveillance

AVC was associated with all-cause death as a continuous variable, with adjusted HRs for all-cause death 40–60% higher per square root SD change of continuous AVC (see Supplementary data online, *Table S2*; all $P < 0.005$). *Figure 1* shows HRs (95% CI) of the severe vs. sub-severe and sub-severe vs. low AVC groups; in both unadjusted and multivariable-adjusted analyses, the HR for death was higher in the sub-severe than the low AVC groups (all $P \leq 0.001$). Associations remained significant after adjustment for indexed AVA or V_{max} instead of AVA or MPG (all $P < 0.004$). Conversely, multivariable-adjusted mortality risks were similar between the sub-severe and severe AVC groups (all $P > 0.2$).

Incremental prognostic value for all-cause death under medical surveillance by sub-severe and severe AVC

Improvement in prognostication by different models is shown in *Figure 2*. Addition of the sub-severe and severe AVC groups (vs. low AVC group) to models of clinical and echocardiographic variables, AS severity measurement (AVA or MPG), and CAC_{score}, increased χ^2 of the models (both $P < 0.001$). AVC improved Cox PH model performance in all the multivariable-adjusted analysis, either as a continuous variable or a dichotomized variable (*C*-statistics in Supplementary data online, *Table S3*).

AVC–mortality association accounting for AVI status (overall survival)

Similar to the association with all-cause death under medical surveillance, AVC was associated with higher risk for all-cause death in multivariable-adjusted analysis when AVI was introduced as a time-dependent variable (adjustment in *Figure 3* legend, all $P \leq 0.004$). Supplementary data online, *Table S4*, shows overall mortality rates and cumulative AVI rates for the three AVC groups; compared with the other two groups, more patients received AVI at shorter follow-up time in the severe AVC group, likely due to this group's more severe AS. However, AVI rates in all three groups increased during follow-up, and differences in AVI rates attenuated between sub-severe and severe AVC groups, likely reflecting AS progression of the sub-severe group.

Figure 3 shows overall survival of three AVC groups (log-rank $P < 0.0001$) with unadjusted and adjusted HR (95% CI) from Cox PH analysis. Overall survival of the three AVC groups showed a similar pattern as that of all-cause death under medical surveillance analyses. Both the severe and sub-severe AVC groups had higher risks for all-cause death than the low AVC group (both $P < 0.001$), while survival between the severe and sub-severe AVC groups was similar ($P = 0.39$). After comprehensive adjustment, patients with sub-severe AVC had two times higher risk for death than those with low AVC independent of AVI status (all $P < 0.0001$). Associations remained significant when adjusted for indexed AVA or V_{max} instead of AVA or MPG (all $P \leq 0.0006$). Conversely, both unadjusted and adjusted mortality risks were similar between the high and severe AVC groups (all $P > 0.2$).

AVI impact on AVC–mortality association

AVI was associated with decreased risk for all-cause death after multivariable adjustment including AVC (all *P*-value of AVI ≤ 0.02,

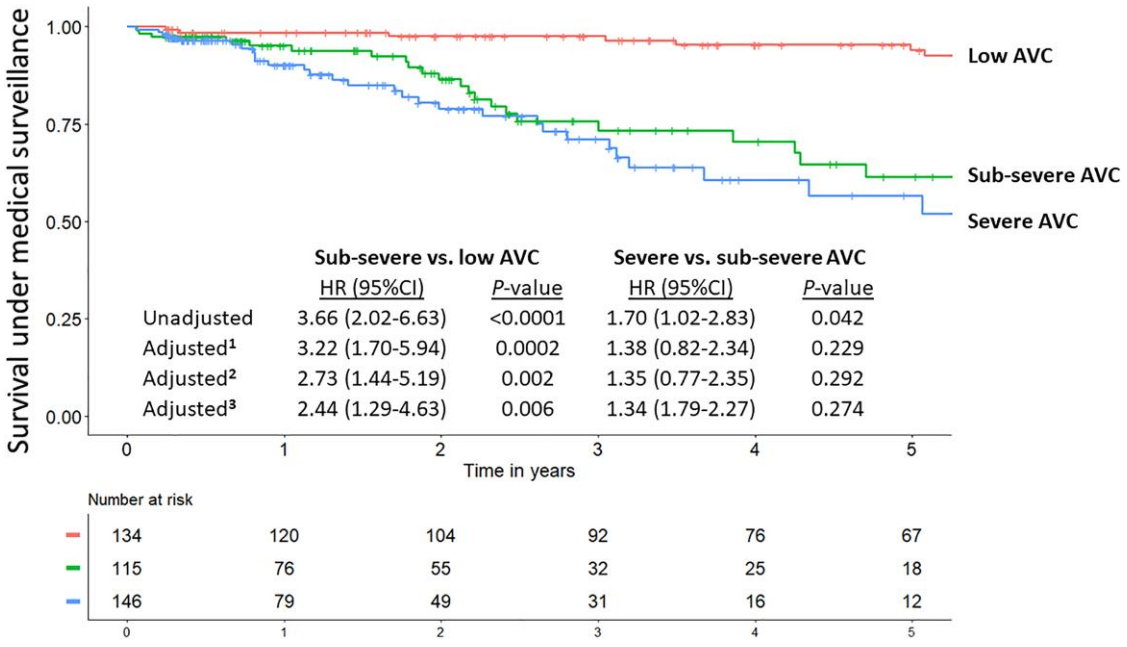


Figure 1 Kaplan–Meier survival under medical treatment of three groups: low, sub-severe, and severe AVC groups. HR from Cox PH analysis. Adjustment in Adjusted[1], age-adjusted Charlson comorbidity index score, NYHA class, LVEF, LV hypertrophy, and elevated LV filling pressure; Adjusted[2], Adjusted[1] + MPG + CAC_{score}; Adjusted[3], Adjusted[1] + AVA + CAC_{score}.

adjustment in *Figure 3* legend). Interestingly, we found an interaction of AVI with the sub-severe and severe (vs. low) AVC groups in unadjusted and multivariable-adjusted analyses (all $P \leq 0.01$). When the low AVC group was the reference, AVI had a protective effect in severe AVC–mortality association (all *P*-value of interaction term ≤ 0.01) and sub-severe AVC–mortality association (all *P*-value of interaction term ≤ 0.04). However, when the sub-severe AVC group was the reference, there was no interaction of AVI with severe AVC–mortality association anymore (all $P > 0.2$).

Given the similar AVI impact on AVC–mortality associations in the sub-severe and severe AVC groups, we combined them together as a single group (sub-severe or severe AVC) and then showed adjusted HR for all-cause death in four groups of patients based on AVI status and AVC levels in *Figure 4*: low AVC and AVI (−), low AVC and AVI (+), sub-severe or severe AVC and AVI (−), and sub-severe or severe AVC and AVI (+). In patients with low AVC, mortality risk was similar between AVI (+) and AVI (−) groups ($P = 0.727$). Conversely, in patients with sub-severe or severe AVC, mortality risk was higher in AVI (−) group compared with AVI (+) group ($P = 0.0007$). Moreover, compared with patients with low AVC and AVI (−), patients with sub-severe or severe AVC and AVI (−) had three times more risk for death ($P < 0.0001$); however, patients with sub-severe or severe AVC were not associated with excessive risk for death if they had AVI (HR = 1.38, $P = 0.254$).

Discussion

In our study of 395 patients with non-severe AS, preserved LVEF, mean AVA 1.2 cm^2, and MPG 28 mmHg, and without heart failure symptoms at rest, our main findings include the following: (i) AVC was associated with all-cause death under medical surveillance and overall death independent of AVI status; (ii) the best AVC cut-offs for predicting all-cause death, i.e. 1185 AU in men and 850 AU in women, both were below the severe AVC thresholds suggested by current guideline[2] or previous studies[7,16]; (iii) these cut-offs (>1185 AU in men and >850 AU in women) were robust prognosticators and improved prognostication beyond echocardiographic AS severity and CAC_{score}; (iv) patients with sub-severe AVC had a higher risk of all-cause death than those with low AVC, with their mortality risk being similar to patients with severe AVC; and (v) AVI was associated with a greater survival benefit in patients with sub-severe AVC than those with low AVC, and this benefit was similar between patients with sub-severe and severe AVC.

Our study suggests that sub-severe AVC scores in patients with echocardiographic non-severe AS identify a group of patients with a similarly high mortality risk as that conferred by current severe AVC cut-offs. In these high-risk patients, AVI was associated with a mortality-protective effect that was similar between sub-severe and severe AVC groups. Therefore, we propose that AVC may serve as a critical second-line risk-stratifying test to inform AVI timing, when evaluating patients with echocardiographic moderate and moderate-to-severe AS. Nonetheless, whether AVI improves survival in these patients needs to be proven by randomized clinical trials.

Heterogeneity in echocardiographic AS severity

AS grading does not always result in a black–white diagnosis. In the real-world clinical setting, it is common to encounter ambiguous terms like moderate-to-severe AS, a term not defined by current guidelines. A recent large-scale US real-world observational AS study[1] found that 44% of patients with an echocardiographic diagnosis of moderate AS and 82% of patients with a diagnosis of moderate-to-severe AS met at least one criterion for severe AS, reflecting real-world challenges and variability in AS grading. Although the majority of our patients had concordant moderate AS, 44% of our patients with possible moderate AS (at least one echocardiographic criterion for moderate AS)[18] had discordant AVA–MPG or AVA–V_{max} grading (see Supplementary data online, *Table S1*). However, the prevalence of sub-severe and severe

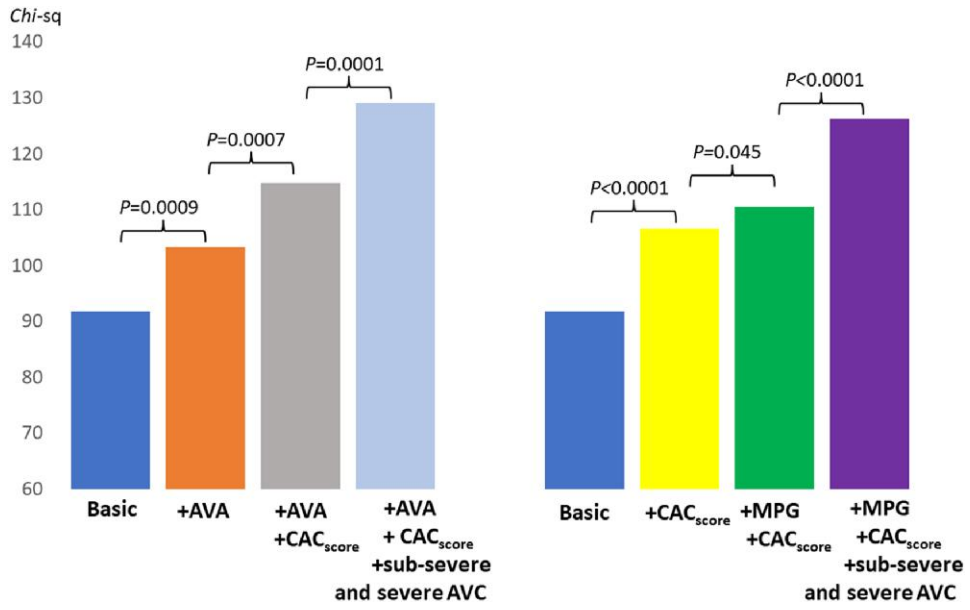


Figure 2 Improved prognostication for all-cause death under medical surveillance by sub-severe and severe AVC. *P*-value from ANOVA χ^2 change test. χ^2 of models from Cox PH models. Basic model including variables: age-adjusted Charlson comorbidity index score, NYHA class, LVEF, LV hypertrophy, and elevated LV filling pressure.

AVC was high across all subgroups, regardless of whether AS grading was concordant or discordant (see Supplementary data online, *Table S1*), suggesting that AVC may be a haemodynamic-independent measurement.[7] Interestingly, among patients with discordant AS grading, the subgroup with severe AVA plus moderate MPG or V_{max} (see Supplementary data online, *Table S1*) exhibited sub-severe or severe AVC in 84.5% of cases, such that AVA < 1.0 represents a red flag in patients with haemodynamically moderate AS.[20]

Clinical implications

Our findings represent a potential resolution to two common clinical questions: (i) What to do with discordant moderate AS patients? and (ii) What to do with concordant moderate and moderate-to-severe AS patients? The answer to both questions is likely to further risk-stratify them with CT AVC: discriminating between low- and high-risk moderate AS patients. A recent expert review[18] suggested using CT AVC to refine AS grading in cases of possible moderate AS with preserved LVEF. According to their recommendation, which set AVC cut-offs for diagnosis of moderate AS at 800–2000 AU in men and 400–1200 AU in women,[18] 81% of patients with discordant moderate AS and non-severe CT AVC could be reclassified as moderate AS. Although this is a reasonable diagnostic approach, there remains a clinical need to prognosticate these patients, and our study provides prognostic cut-offs within the moderate AVC range.

The prognostic value of severe AVC was demonstrated in two previous studies, both of which included a significant number of patients with severe AS.[8,16] Their results established diagnostic values of AVC for severe AS, which were also associated with increased mortality risk. Our study found lower AVC cut-offs, which is not unexpected since we studied patients with non-severe AS. It is reasonable to assume that a study with larger number of patients with non-severe AS including mild or mild-to-moderate AS might result in lower optimal thresholds for survival prediction. However, our study provided prognostic cut-offs for the moderate and moderate-to-severe categories of non-severe AS. Previous population-based studies have shown that the prognostic value of AVC was not independent of CAC_{score} in the general population (not AS-focused).[21–23] However, our study corroborates that for AS patients,[8,16] the prognostic value of AVC is independent of CAC score. Recent guidelines and expert reviews also favour AVC as a diagnostic tool for severe AS,[2,15,18] rather than a screening tool to predict atherosclerotic cardiovascular events for primary prevention.

The prognostic value of AVC for AS patients has been shown to attenuate post-AVI.[8] We also showed mortality risk attenuation in patients with severe or sub-severe AVC if they had AVI (*Figure 4*). Therefore, our results, together with previous studies,[8,16] suggest the main function of AVC remains as risk stratification in patients with AS, likely through its association with AS severity, rather than through its association with clinical comorbidities, i.e. not a prognostic biomarker in general.

Limitations

This study is retrospective and observational in nature; therefore, it is subject to selection bias and unable to establish causality between AVC and all-cause death. Our patients represent an equal mix of research-indicated and clinically indicated CT AVC evaluations and therefore are not consecutive patients, and this could be a source of bias. Nonetheless, the rate of discordant grading of moderate AS in our study is similar to previous consecutive patient observations.[18,24] Mortality of our patients is high, i.e. 40% after a median follow-up of 4.8 years. However, it is similar to previous studies of moderate AS (45% at median 4.3 years and 40% at 5 years).[25,26] Higher AVI rates (55%) in our study likely reflect referral bias to a tertiary medical centre. We observed a significant survival benefit associated with AVI in the sub-severe AVC group. However, this represents a statistical association, and causality can only be determined in a randomized clinical trial. In addition, our findings should be externally validated.

Conclusion

In patients with non-severe AS and preserved LVEF, those with sub-severe AVC had a mortality risk comparable with those with severe

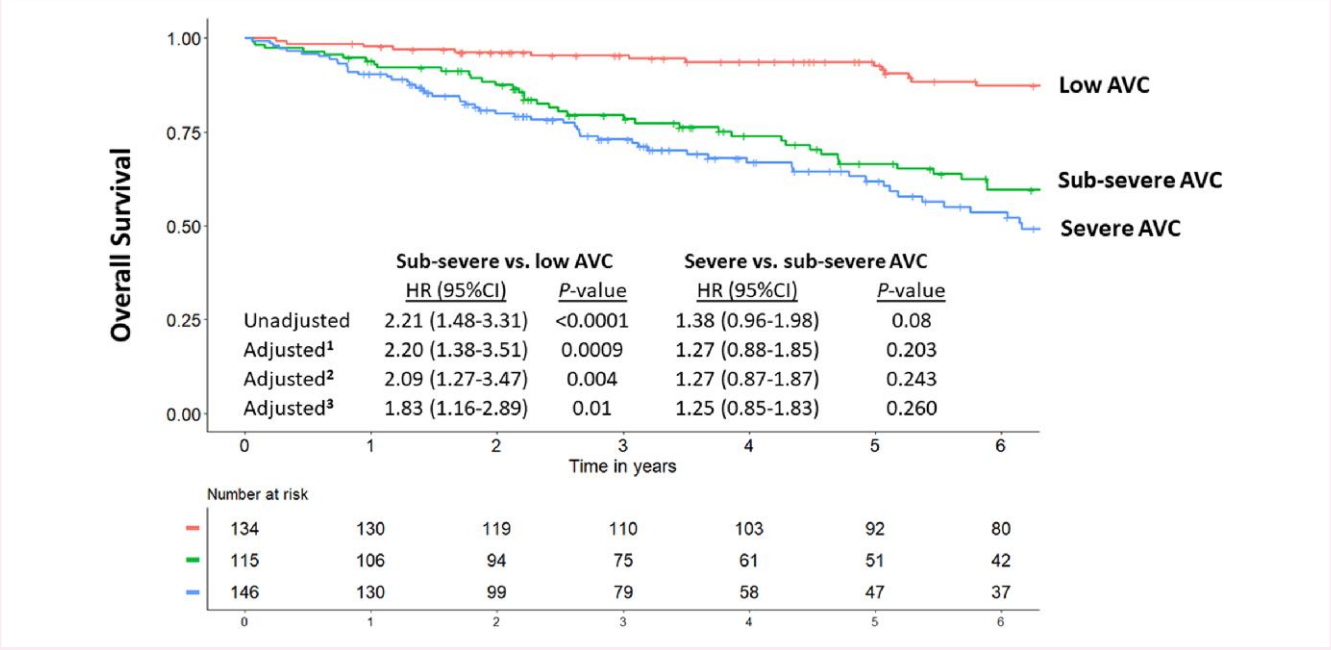


Figure 3 Kaplan–Meier overall survival of three AVC groups. HR from Cox PH analysis. Adjustment in Adjusted[1], age-adjusted Charlson comorbidity index score, diastolic BP, NYHA class, atrial fibrillation, bicuspid aortic valve, LVEF, elevated LV filling pressure, and AVI as time-dependent variable; Adjusted[2], Adjusted[1] + MPG + CAC_{score}; Adjusted[3], Adjusted[1] + AVA + CAC_{score}.

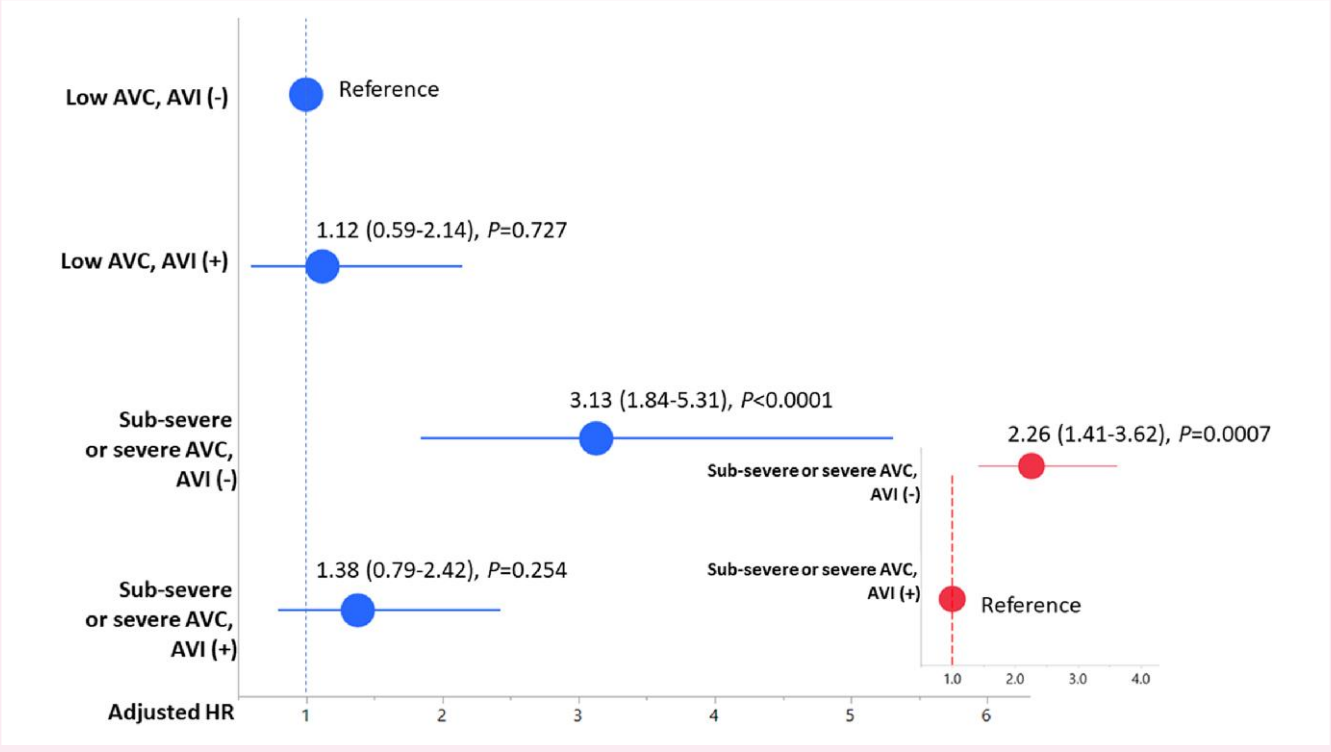


Figure 4 Adjusted HR for all-cause death of four groups based on AVC levels (sub-severe or severe AVC as a single group vs. low AVC group) and AVI status. Adjustment included: age-adjusted Charlson comorbidity index score, diastolic BP, NYHA class, atrial fibrillation, bicuspid aortic valve, LVEF, elevated LV filling pressure, AVA, and CAC_{score}.

AVC, independent of their comorbidities, LV function, echocardiographic AS severity, and CAC_{score}. The survival benefit associated with AVI was notable and similar for both sub-severe and severe AVC groups, but not significant for the low AVC group. Therefore, sub-severe AVC may serve as a new prognosticator for risk stratification in patients with non-severe AS and potentially inform AVI timing.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

Fully de-identified raw data from this manuscript could be made available upon reasonable request and specific permission from the Mayo Clinic research and legal departments.

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