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ORIGINAL PAPER

Impact of age on aortic valve calcium progression and risk for aortic stenosis: multi-ethnic study of atherosclerosis

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Aims Aortic valve calcium (AVC) is strongly associated with the risk for severe aortic stenosis (AS). The prevalence of AVC increases with age, but the impact of age on the progression of AVC and its association with moderate-severe AS is unknown.

Methods and results Our study included 6810 participants (52.9% women) without overt cardiovascular disease between ages 45 and 84 from the Multi-Ethnic Study of Atherosclerosis. AVC was measured using non-contrast cardiac CT at Visit 1. Progression was calculated as the change in AVC divided by years between CT scans (2–10 years). Incident moderate-severe AS was adjudicated using medical chart review and echocardiogram data from Visit 6 (median follow-up of 16 years). The association between AVC and moderate-severe AS was assessed using multivariable adjusted Cox proportional hazards ratios. There were 5899 participants with AVC = 0 and 911 with AVC >0. There were 3834 participants age <65 years and 2979 age ≥65 years. The median AVC was 34.1 AU (IQR 13–1113) for participants <65 vs. 69.0 AU (IQR 23–2453) for participants ≥65. Participants <65 and ≥65 years had no significant difference in median annualized AVC progression within the baseline AVC categories of 1–99 (10 vs. 12 AU/year, $P = 0.303$) and AVC ≥100 (50 vs. 47 AU/year, $P = 0.846$). AVC >0 was associated with a similar significantly higher risk of incident moderate-severe AS for both younger (HR 13.37; 95% CI 5.67–31.52) and older participants (HR 10.59, 95% CI 6.77–16.56).

Conclusion AVC progression was significantly associated with baseline AVC burden and was similar for younger vs. older persons after accounting for baseline AVC. The presence of AVC was significantly associated with a higher long-term risk for moderate-severe AS among both younger and older participants.

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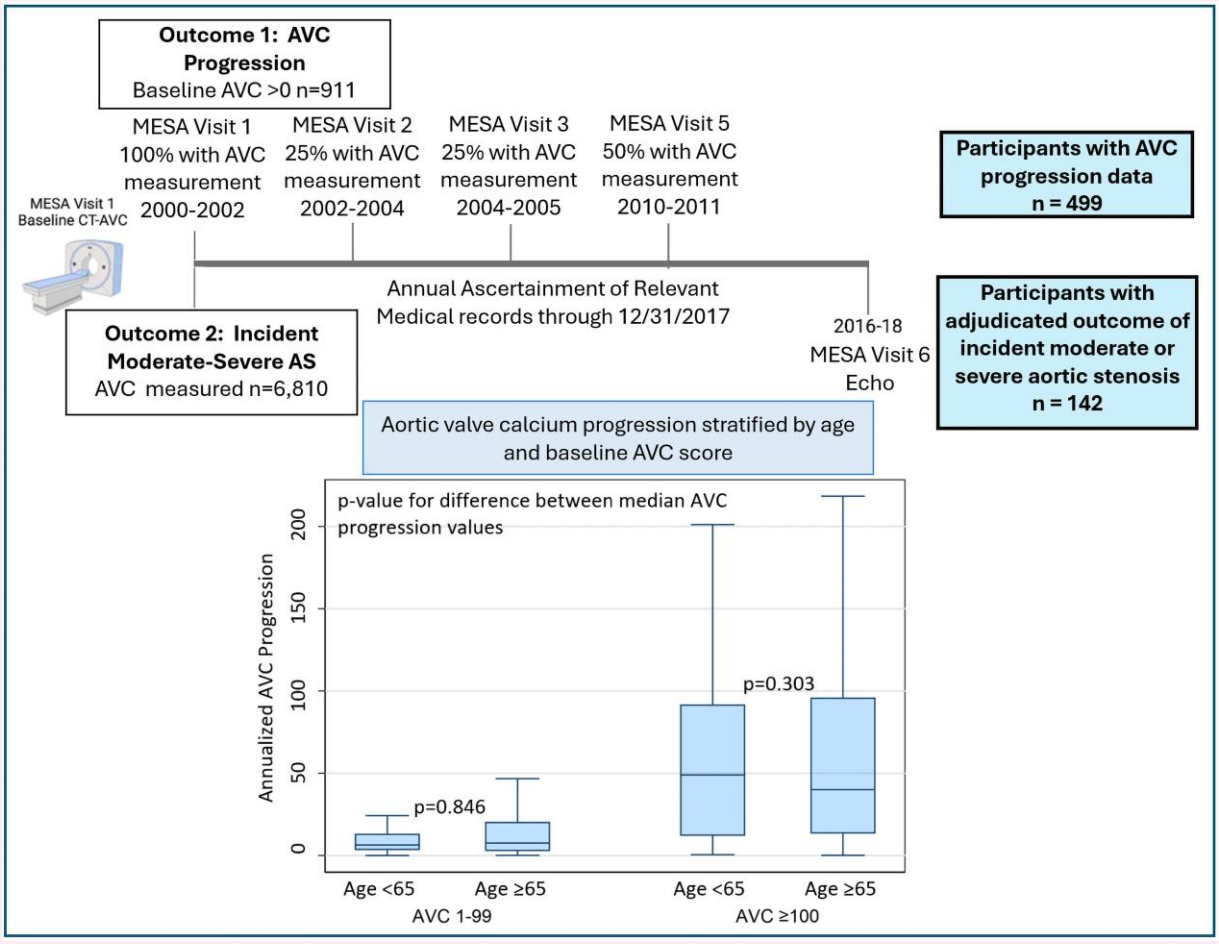
Graphical Abstract



Impact of age on aortic valve calcium progression and risk for aortic stenosis: Multi-Ethnic Study of Atherosclerosis

Keywords age • aortic valve calcium • aortic stenosis • incidence • cardiac computed tomography

Introduction

Calcific aortic valve disease (CAVD) is the most common valvular disease in the United States[1] with a prevalence that is expected to increase by up to three-fold over the next 25 years.[2] Currently, the only available treatment is aortic valve replacement (AVR), which has very high costs.[3,4] However, without AVR, patients face a poor prognosis with a 15% 5-year survival[5] and even with AVR, most patients already have irreversible myocardial damage, which has been associated with worse survival.[6,7] The poor prognosis associated with advanced CAVD emphasizes the need for better risk stratification and early detection to identify persons at higher long-term risk, who may be more likely to benefit from novel treatment approaches.

The prevalence of CAVD is higher among older persons[8–14] due to a higher prevalence of CAVD risk factors and longer exposure time to these risk factors.[10,15,16] CAVD, which is fundamentally characterized by aortic valve calcification (AVC), has a prevalence as high as 55% among participants ≥80 years.[8] AVC can be easily measured using cardiac computed tomography (CT), which is commonly used to measure coronary artery calcification (CAC). Greater AVC values are associated with a higher long-term incidence of severe aortic stenosis (AS), with AVC ≥300 associated with an over than 300-fold increase in the long-term risk for severe AS.[14]

While previous research has highlighted a higher prevalence of AVC >0 among older populations and a very strong association between AVC >0 and AS, limited data exists on (i) whether there is a difference in the rate of AVC progression for younger vs. older persons or (ii) if the association between AVC and moderate-severe AS differs by age. Therefore, in this study we examined the progression of AVC and the association of AVC with long-term risk of moderate-severe AS for younger vs. older persons in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study population

A total of 6810 MESA participants between 45 and 84 years old who were free of known CVD were included. Participants were from six different sites throughout the United States (Baltimore, New York, Chicago, Los Angeles, Forsyth County, and St. Paul). The MESA design has been previously described.[17] The Institutional Review Board reviewed and approved the MESA protocol at each institution, and written consent was obtained

from all participants. For this study, participants were excluded if they were missing a baseline AVC score ($n = 2$) or had severe AS at baseline ($n = 2$).

At MESA Visit 1 (2000–2002), data regarding age, sex, race/ethnicity, income, education, current smoking status, medical history, and current medications were self-reported by participants. Diabetes was defined as use of current anti-glycemic medication, fasting glucose ≥126 mg/dL, or self-report. Seated blood pressure was recorded a total of three times, and the average of the final two readings was used for analysis. LDL-C was calculated using the Friedewald equation.

Assessment of aortic valve calcification and aortic valve calcification progression

AVC was measured using non-contrast cardiac CT at MESA Visit 1 (2000–2002). ECG-gated cardiac CT scanners were used in the Chicago, Los Angeles, and New York Field Centers while a four-slice multidetector CT system was used in the Baltimore, Forsyth County, and St. Paul Field Centers. AVC was scored for calcified lesions in the aortic valve leaflets including those that extended into the aortic root, but not for those that were isolated to the aortic ring.[17,18] AVC was quantified using the Agatston method.[19] All scans were read centrally at the Harbor-UCLA Research and Education Institute core reading lab. AVC measured using cardiac CT has low intrareader and interscan variability, 4.4% and 9.7% respectively.[18]

A total of 911 participants at AVC >0 at MESA Visit 1. Follow-up CT scans were performed among participants with baseline AVC > 0 as follows: 25% of MESA participants were randomly selected to have follow-up CT scans conducted at MESA Visit 2 (2002–2004) and Visit 3 (2004–2005), and 50% of the participants were randomly selected to have a follow-up CT scan conducted at MESA Visit 5 (2010–2011). A total of 499 participants with AVC >0 at Visit 1 had a follow-up CT scan to measure AVC progression and were included in the AVC progression analysis. The same protocol for measuring and quantifying AVC was utilized for baseline and all follow-up scans.

Assessment of incident moderate-severe AS

Participants and/or families were contacted every 9 to 12 months and reported all hospital admissions, outpatient CVD diagnoses, or deaths. Incident moderate-severe AS was adjudicated as has previously been described.[14,20,21] In brief, medical records were then obtained for corresponding admission, outpatient diagnoses, or death. ICD codes were used to identify candidate moderate-severe AS events, and if present, complete medical records were obtained. Two Cardiologists from the MESA CVD Events Adjudication Committee independently reviewed the medical records, and any disagreements on event classification were discussed until a consensus was obtained. This was supplemented by MESA Visit 6 echocardiography data. Echocardiography was performed for 3032 of 3303 (91.8%) of participants attending exam 6 (2016–2018). A diagnosis of moderate-severe AS was based on standard clinical criteria: echocardiography (e.g. aortic valve area <1.5 cm^2, peak velocity ≥3.0 m/s, and mean gradient ≥30 mmHg), AVR for severe AS or moderate AS in patients undergoing coronary artery bypass graft surgery, or a documented diagnosis of moderate or severe AS. Moderate-Severe AS was identified in a total of 142 participants.

Statistical analysis

Participant demographic data was analyzed using descriptive statistics and stratified by AVC (AVC = 0 vs. AVC > 0) and age (age < 65 years vs. age ≥65 years). AVC score is 0 inflated and right skewed but normalizes with logarithmic transformation [ln (AVC + 1)]. Therefore, for continuous analyses AVC was analyzed as a logarithmically transformed variable. AVC was also examined as a categorical variable (AVC 0, 1–99, ≥100 AU).

AVC progression was calculated as the change in AVC divided by the number of years between CT scans (2–10 years). Linear regression was used to examine the association between age (per 10 years older and age ≥65 years) and AVC progression. The age threshold of 65-years as the prevalence of AVC increases with age, particularly above the age range of 65 to 70 years old.[9,11] We also conducted the analysis per 10 years older based on prior retrospective analyses showing two-fold increased risk of aortic valve disease per 10-year increase in age.[10] An analysis for the association between age and AVC progression was also conducted after adjusting for baseline AVC. Linear regression models were adjusted for the following adjustment variables that were selected based on variables most likely to impact the association of AVC with AS: age, sex, field centre, systolic blood pressure, diastolic blood pressure, hypertension medication, total cholesterol, HDL-C, lipid-lowering medication, fasting glucose, diabetes, body mass index, pack-years smoking, lipoprotein(a), education, and income.[14] Incident moderate-severe AS was selected as the primary outcome variable given strong association between AVC and long-term risk of severe AS. We also conducted linear regression analyses per one standard deviation higher annualized AVC progression. Cases of moderate AS were also included to maximize the power of the study and growing interest in earlier valve replacement strategies for patients with moderate AS, such as the ongoing PROGRESS trial.[22] Incident moderate-severe AS was assessed using event rate per 1000 person-years and Kaplan-Meier survival curves, both stratified by age (age < 65 years vs. age≥65 years) and AVC categories. The association between AVC with incident moderate-severe AS was assessed using multivariable adjusted Cox proportional hazards ratios as follows: model 1: unadjusted, model 2: adjusted for age, race/ethnicity, systolic blood pressure, LDL-C, diabetes, lipoprotein(a) with fewer variables included compared with linear regression analyses to avoid overfitting given the relatively small number of events. We also performed sensitivity analyses to examine the progression of AVC (i) stratified by gender and (ii) for participants with AVC = 0 at baseline. We also examined the association of AVC with (i) moderate-severe AS excluding participants with bicuspid aortic valve and (ii) with the outcome of all-cause mortality.

Results

Among both participants with AVC = 0 and AVC > 0, those who were age ≥65 years generally had a higher atherosclerotic burden (*Table 1*). However, older persons had lower low-density lipoprotein cholesterol and triglyceride levels and a higher proportion of lipid-lowering medication.

AVC progression

Participants <65 years and ≥65 years had no significant difference in median annualized AVC progression within the baseline AVC categories of 1–99 (10 vs. 12 AU/year, $P = 0.846$) and AVC > 100 (50 vs. 47 AU/year, $P = 0.303$) (Central Illustration). We observed similar findings when stratified by sex (see Supplementary data online, *Figure S1*). In multivariable adjusted regression modeling, there was a greater annualized AVC progression per every 10 years of older age (β coefficient 1.43, $P = 0.006$) and for participants ≥65 years compared with younger participants (β coefficient 26.37, $P = 0.001$). (*Table 2*). However, after adjusting for baseline AVC, the associations were attenuated. The results remained significant within specific AVC groups, but the overall results showed no significant difference in AVC progression per 10-years older (β coefficient 0.32, $P = 0.511$) or for older participants (β coefficient 9.67, $P = 0.134$).

In sensitivity analysis examining participants with AVC = 0, 433 developed incident AVC >0. Among these participants, we found no significant difference in AVC progression based on age <65 vs. ≥65 (β coefficient 8.97, $P = 0.079$) or per every 10 years older age (β coefficient 0.716, $P = 0.176$). We also found no significant difference in annualized AVC progression per every 10 years older age or for participants ≥65 years compared with younger participants for either women or men (see Supplementary data online, *Table S1*). There was no significant difference in AVC progression between older and

Table 1 Participant demographics stratified by age and absence or presence of AVC

	AVC = 0 (n = 5899)		*P*-value	AVC >0 (n = 911)		*P*-value
	Age <65 (n = 3645)	Age ≥65 (n = 2257)		Age <65 (n = 189)	Age ≥65 (n = 722)	
Age, years	54.3 (5.7)	71.4 (4.9)	<0.001	58.4 (4.3)	73.7 (5.3)	
Women	54.3%	55.8%	0.261	32.8%	41.8%	0.024
Race						
White	37.3%	37.6%	0.783	42.3%	46.1%	0.783
Black	27.7&	28.9%	0.287	24.4%	25.7%	0.287
Chinese	23.1%	20.2%	0.008	28.0%	20.3%	0.008
Hispanic	12.0%	13.3%	0.144	5.3%	7.9%	0.144
Systolic blood pressure, mm Hg	120.4 (18.7)	133.1 (22.3)	<0.001	130.1 (20.7)	136.3 (22.3)	<0.001
Diastolic blood pressure, mm Hg	72.4 (10.2)	71.0 (10.4)	<0.001	75.4 (10.4)	71.4 (9.8)	<0.001
Hypertension	46.7%	73%	<0.001	68.8%	80.9%	<0.001
Antihypertensive medication	23.4%	47.4%	<0.001	45.5%	58%	<0.001
LDL-C, mg/dL	118.0 (31.6)	115.3 (29.9)	0.001	129.2 (39.2)	115.9 (32.5)	<0.001
HDL-C, mg/dL	50.3 (14.6)	52.8 (15.2)	<0.001	47.0 (13.2)	49.5 (14.4)	0.036
Triglycerides, mg/dL[a]	112 (77, 164)	107 (76 155)	0.007	133 (92 186)	118 (82, 166)	0.017
Lipoprotein(a), mg/dL[a]	16.5 (7, 39)	17.5 (8, 38)	0.296	25.4 (9, 67)	19 (8, 52)	0.027
Hyperlipidemia	43.5%	47.8%	<0.001	63.0%	53.6%	0.001
Lipid-lowering medication	11.0%	20.7%	0.001	22.0%	27.2%	<0.001
Glucose, mg/dL	95.3 (30.8)	98.6 (25.9)	<0.001	103.5 (40.4)	102.5 (35.7)	0.739
Diabetes	9.8%	14.1%	<0.001	21.2%	19.5%	<0.001
Body mass index, kg/m^2	28.7 (5.7)	27.7 (5.2)	<0.001	30.0 (5.4)	28.1 (4.7)	<0.001
Current smoking	17.0%	7.6%	<0.001	20.1%	8.0%	<0.001
10-year ASCVD risk score, %	6.0 (6.1)	21.1 (12.9)	<0.001	12.0 (8.9)	28.0 (15.1)	<0.001
Coronary artery calcium [a]	0 (0, 9.6)	25 (0, 173)	<0.001	33 (0, 223)	155 (21, 536)	<0.001
Aortic valve calcium[a]	0	0	n/a	34.1 (13, 1113)	69.0 (23, 2453)	<0.001

[a]Median and interquartile range.

younger participants, after exclusion of those with bicuspid valves (see Supplementary data online, *Table S2*).

Incident moderate-severe AS

Over a median follow-up of 16.7 years, 142 participants developed moderate-severe AS. Higher unadjusted event rates per 1000 person-years for moderate-severe AS were observed among those age ≥65 years compared with those age <65 years within each AVC subgroup. However, the difference in moderate-severe AS event rate between older and young persons was only significant for those with AVC = 0 and both age groups with AVC = 0 had a very low event rate (*Figure 1*). In unadjusted Kaplan-Meier survival analysis, both participants age <65 years and age ≥65 years, had a significant reduction in survival free from moderate-severe AS for participants with AVC ≥100 compared with those with AVC = 0. Participants aged ≥65 years had a slightly lower survival free from moderate-severe AS with AVC ≥100 at ∼65% compared with ∼75% among age <65 (*Figure 2*).

Multivariable adjusted analysis demonstrated that AVC >0 was associated with a higher risk of long-term incident moderate-severe AS among younger HR 13.37 (95% CI 5.67–31.52) and older HR 10.59 (95% CI 6.77–16.56) participants. When analyzed as a categorical variable, higher AVC scores were significantly associated with an increased risk for moderate-severe AS among both younger and older participants, except for participants <65 years old with AVC 1–99 in whom there were only 2 moderate-severe AS events HR 2.68 (95% CI 0.54–12.52) (*Figure 3*).

There was a significant association between AVC and all-cause mortality for older patients and for younger patients in unadjusted, but not adjusted results (see Supplementary data online, *Table S3*).

Discussion

In this study, we demonstrate similar progression of AVC for younger vs. older persons and that the burden of AVC is the primary driver of AVC progression. Additionally, our results show that AVC is predictive of incident long-term moderate-severe AS for both younger and older persons. Accordingly, these results provide insight into the similar underlying pathophysiology for CAVD in both younger and older persons and further highlights the prognostic utility of AVC to identify persons at increased risk for moderate-severe AS regardless of age.

The prognostic role of CAVD severity has been reinforced using echocardiographic data as baseline haemodynamic severity of AS has been shown to predict faster progression to severe AS.[23–26] Older age has also been associated with incident AS using echocardiographic data. However, given age's association with a higher burden of CAVD[9] and the lack of adjustment for baseline CAVD disease severity in these studies, it is likely that the baseline severe CAVD of the older sample accounts for the observed association of age with incident AS.[27–29]

Table 2 Linear regression (β-coefficient) of annualized AVC progression stratified by age and AVC group

	Overall	Baseline AVC 1–99	Baseline AVC ≥100
Per 10 years old			
Unadjusted for baseline AVC	1.43 ($P = 0.006$)	0.35 ($P = 0.002$)	1.24 ($P = 0.474$)
Adjusted for baseline AVC	0.32 ($P = 0.511$)	0.31 ($P = 0.006$)	0.44 ($P = 0.735$)
Per 1 SD higher, adjusted for baseline AVC	0.003 ($P = 0.511$)	0.04 ($P = 0.006$)	0.01 ($P = 0.735$)
Age ≥65 years old			
Unadjusted for baseline AVC	26.37 ($P = 0.001$)	5.51 ($P = 0.015$)	49.65 ($P = 0.053$)
Adjusted for baseline AVC	9.67 ($P = 0.134$)	4.76 ($P = 0.034$)	46.18 ($P = 0.038$)
Per 1 SD higher, adjusted for baseline AVC	0.10 ($P = 0.134$)	0.05 ($P = 0.034$)	0.48 ($P = 0.038$)

All models adjusted for: sex, race/ethnicity, field centre, systolic blood pressure, diastolic blood pressure, hypertension medication, total cholesterol, HDL-C, LDL-C, lipid-lowering medication, lipoprotein(a), fasting glucose, diabetes, body mass index, pack-years smoking, education, and income.

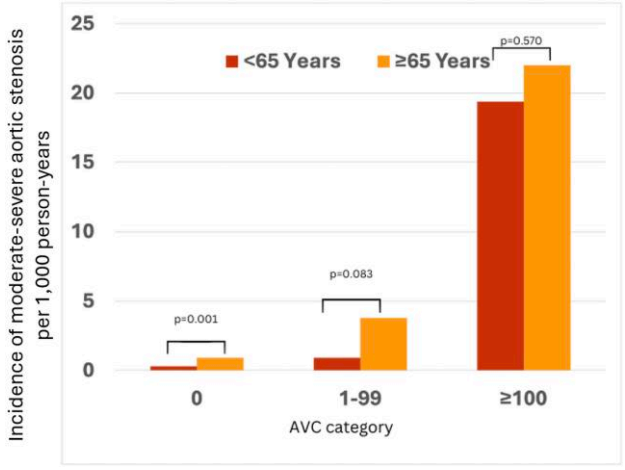


Figure 1 Age-specific incidence of moderate-to-severe AS by AVC categories per 1000 person-years follow-up. Participants aged ≥ 65 years had a significantly greater incidence of moderate-to-severe AS compared with those aged < 65 years among individuals with AVC = 0 ($P = 0.001$) with both age groups having a very low event rate. There was no significant difference in the incidence of moderate-to-severe AS between the two age groups among participants with AVC 1–99 ($P = 0.083$) or AVC ≥ 100 ($P = 0.057$). AVC, aortic valve calcium.

Echocardiography has demonstrated that greater baseline AVC predicts faster progression to severe AS and a higher mortality risk among patients with mild or moderate disease.[25] Our study, using CT measured AVC, further supports this finding by demonstrating that AVC burden is the predominant factor associated with rate of AVC progression regardless of age.

Our findings of no difference in AVC progression between age groups after adjusting for baseline AVC are consistent with other studies that have reported baseline AVC to predict AVC progression, not age[11] and extends these prior reports of 5-year progression data to 10-years. There are some studies that do report an association between age and disease progression,[27,30] but these studies used echocardiogram evaluation of patients with AS, which has several potential limitations, particularly among patients with low flow, low-gradient phenotypes, which can make the diagnosis of AS challenging.

In contrast, CT-quantified AVC is not subject to discordant hemodynamics and the use of sex-specific AVC thresholds (1200 AU in women and 2000 AU in men) has been recommended as a tie breaker for the diagnosis of severe AS.[31,32] Additionally, our study sample included a wider age range of 45 to 84 years and adjusted for cardiovascular risk factors and baseline AVC. Our findings replicate a similar phenomenon observed for coronary heart disease where CAC scores have been found to be the predominant predictor of CAC progression beyond age.[33–36]

We found a significant association between AVC and all-cause mortality for older patients, but only in unadjusted results for younger patients. However, the hazard ratio point estimates were similar for younger and older participants in the unadjusted results. The lack of a significant association among younger participants is likely due to lower power as among participants with AVC >0 there were only 37 deaths during follow-up for younger participants compared with 379 for older participants. These results are consistent other studies that have similarly shown a significant association of AVC with all-cause mortality.[37]

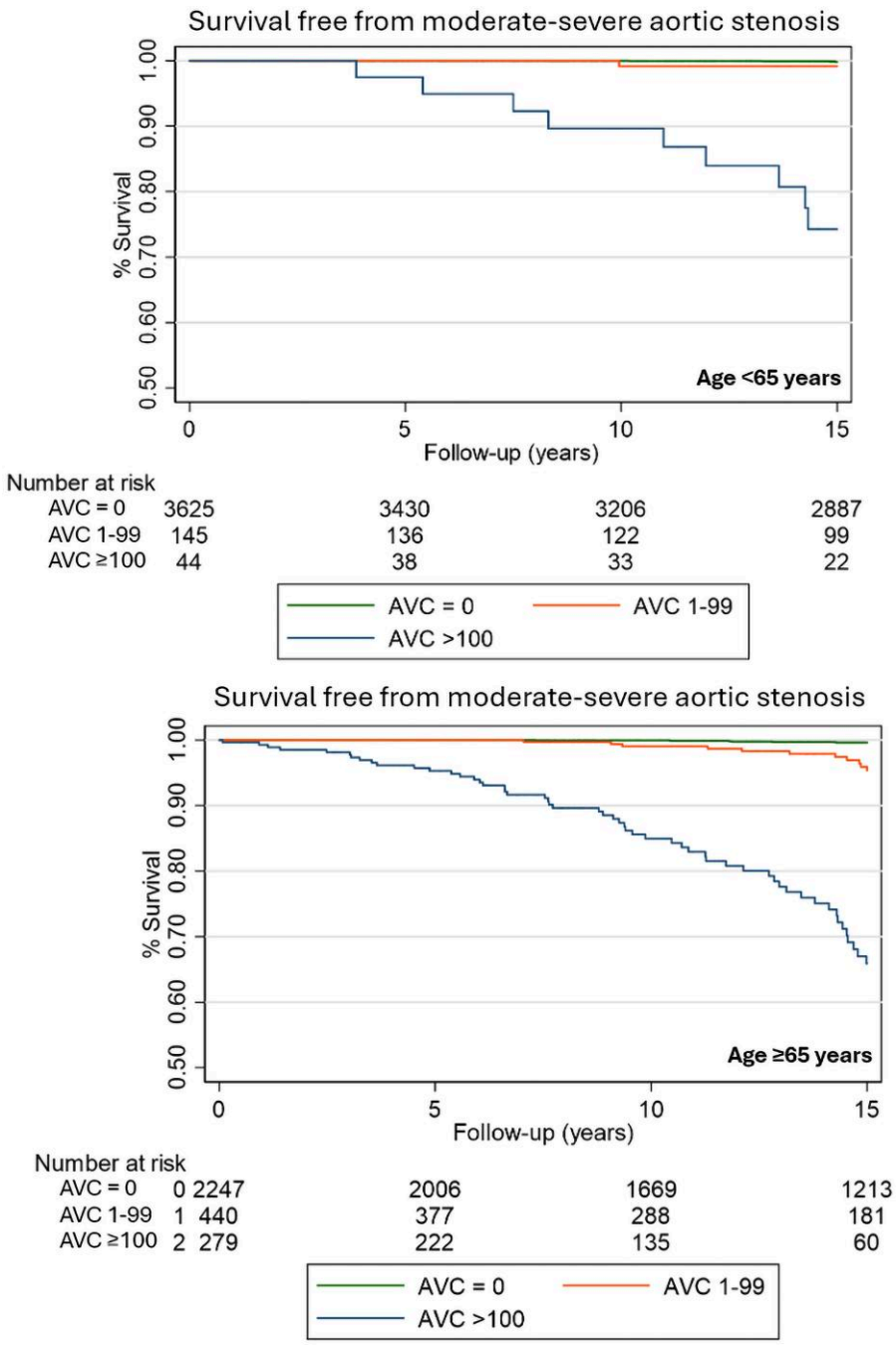


Figure 2 Kaplan–Meier curves demonstrating survival free from moderate-to-severe AS, stratified by age and AVC category. Top: Among participants aged < 65 years, there was a significant reduction in survival free from moderate-severe AS for participants with AVC > 100 compared with those with AVC = 0. Similarly, among participants aged ≥ 65 years, there was a significant reduction in survival free from moderate-severe AS for participants with AVC >100 compared with those with AVC = 0. AS, aortic stenosis; AVC, aortic valve calcium.

In addition to age, several prospective analyses have examined the impact of sex on disease progression. The COFRASA-GENERAC study found faster disease progression in females compared with males after adjusting for baseline AVC.[38] In contrast, in the PROGRESSA study, AVC progression was reported to be two-fold slower among females compared with males.[39] The discordance in findings between these studies and our study which showed no difference in AVC progression between sexes can be explained by several differences in the participants and methodology.[23,24,40] The participants included in the COFRASA-GENERAC study had higher baseline median AVC scores (median AVC 1168 AU) compared with our study, and even included participants with severe AS. The faster progression reported may be secondary to the higher baseline AVC scores. The participants of the PROGRESSA study had mild AS or low-gradient AS and the

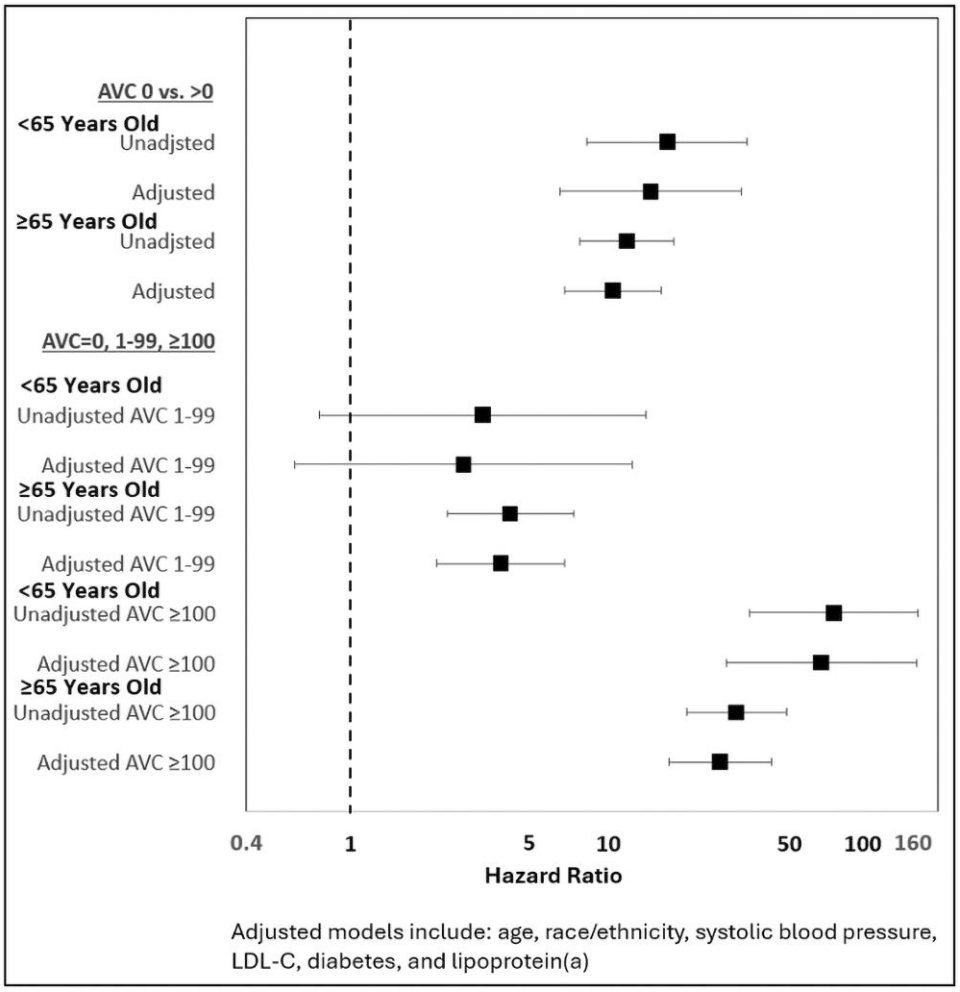


Figure 3 Association of AVC with incident moderate-to-severe AS, stratified by age. In both unadjusted and adjusted models, AVC > 0 was associated with higher risk of incident moderate-severe AS among younger and older participants. When analyzed as a categorical variable, higher AVC scores were significantly associated with increased risk for moderate-severe AS among both older and younger participants, except for participants <65 years with AVC 1–99. For this multivariable adjusted Cox proportional hazards ratios, the model adjusted for age, race/ethnicity, systolic blood pressure, LDL-C, diabetes, and lipoprotein(a). LDL-C, low-density lipoprotein cholesterol.

researchers examined AVC progression thresholds to identify moderate haemodynamic progression, which poses diagnostic limitations among those patients with low-gradient AS. Additionally, our study had a longer follow-up period of a median of 16.7 years, while the follow-up period in the COFRASA-GENERAC study was 3.2 years and in the PROGRESSA study was 2 years.

While there are currently no approved therapies for slowing AVC or preventing AS, our study provides AVC progression reference ranges that may be clinically helpful for estimating disease progression and timing of follow-up surveillance imaging. This framework may be useful for clinicians particularly when evaluating patients who are earlier in the disease process and asymptomatic. Our data suggests that AVC 1–99 is associated with ~10 AU/year AVC progression, while AVC >100 is associated with ~50 AU/year AVC progression. Therefore, it may be reasonable to consider follow-up echocardiogram imaging in 5–10 years among those with AVC 1–99, and 3–5 years among those with AVC >100 or even shorter for those with very high AVC scores. Combining our findings with prospective analyses on the impact of sex on AVC progression, it may be reasonable to consider even more frequent surveillance if the patient is female. Additionally, given the up to 75-fold increased risk of AS, the presence of AVC >100 may warrant consideration of echocardiography if not previously performed.

Study limitations

Limitations of this study include that not all participants had a follow-up CT scan and the relatively small number of participants who developed moderate-severe AS, particularly for those age <65 years old, which reduces the precision of our event rate, hazard ratio estimates, and confidence intervals. However, the lower limits of our 95% CI still demonstrate a significant association between AVC and moderate-severe AS. We acknowledge that use of another age cutoff could be justified. The small sample size also limits our ability to conduct further subgroup analysis, such as finer delineation of age categories. Lastly, our Cox model did not adjust for bicuspid aortic valves, however, sensitivity analysis found similar results after excluding patients with

bicuspid AS ($n = 10$) (see Supplementary data online, *Table S2*). Strengths of the study include the use of non-contrast CT for the measurement of AVC and the adjudication of severe AS,[41] as well as the long follow-up period for AVC progression analyses of 10 years and severe AS analyses of 16.7 years.

Conclusion

Our study found a similar rate of progression of AVC among younger and older age persons, which was predominantly based on baseline AVC burden. Additionally, our results demonstrate that AVC >0 is associated with a higher risk of long-term incident moderate-severe AS among both older and younger populations. These findings emphasize the prognostic importance of AVC in moderate-severe AS among individuals of all ages. Therefore, CT measured AVC is an important tool that should be more frequently utilized for risk stratification and considered for use in patient selection for novel clinical trials and therapeutics aiming to slow down disease progression and prevent moderate-severe AS.

Supplementary data

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

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Author contributions

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Data availability

The data underlying this article are available via the Multi-Ethnic Study of Atherosclerosis.

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