Published in final edited form as:

Am Heart J. 2009 October ; 158(4): 562–568. doi:10.1016/j.ahj.2009.07.027.

Association of Aortic Valve Calcification to the Presence, Extent, and Composition of Coronary Artery Plaque Burden: ROMICAT Study

Amir A. Mahabadi, BS^a, Fabian Bamberg, MD MPH^{a,b}, Michael Toepker, MD^a, Christopher L. Schlett, BS^a, Ian S. Rogers, MD MBA MPH^{a,c}, John T. Nagurney, MD MPH^d, Thomas J. Brady, MD^{a,b}, Udo Hoffmann, MD MPH^{a,b}, and Quynh A. Truong, MD MPH^{a,b,c}

^a Cardiac MR PET CT Program, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

^b Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

^c Division of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

^d Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Abstract

Background—Aortic valve calcification (AVC) is associated with cardiovascular risk factors and coronary artery calcification. We sought to determine whether AVC is associated with the presence and extent of overall plaque burden, as well as to plaque composition (calcified, mixed, and non-calcified).

Methods—We examined 357 subjects (mean age: 53 ± 12 years, 61% male) who underwent contrast-enhanced ECG-gated 64-slice multi-detector computed tomography from the ROMICAT trial for the assessment of presence and extent of coronary plaque burden according to the 17-coronary segment model and presence of AVC.

Results—Patients with AVC (n=37, 10%) were more likely than those without AVC (n=320, 90%) to have coexisting presence of any coronary plaque (89% vs. 46%, p<0.001) and had a greater extent of coronary plaque burden (6.4 segments vs. 1.8 segments, p<0.001). Those with AVC had over 3-fold increase odds of having any plaque (adjusted odds ratio [OR] 3.6, p=0.047) and an increase of 2.5 segments of plaque (p<0.001) as compared to those without AVC. When stratified by plaque composition, AVC was associated most with calcified plaque (OR 5.2, p=0.004), then mixed plaque (OR 3.2, p=0.02), but not with non-calcified plaque (p=0.96).

Conclusion—AVC is associated with the presence and greater extent of coronary artery plaque burden and may be part of the later stages of the atherosclerosis process, as its relation is strongest

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Address for Correspondence: Quynh A. Truong, MD MPH Cardiac MR PET CT Program Massachusetts General Hospital 165 Cambridge Street, Suite 400 Boston, MA 02114 Email: qtruong@partners.org (telephone) 617-726-0798, (fax) 617-724-4152.

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Disclosure: No conflicts of interest to be disclosed.

with calcified plaque, less with mixed plaque, and nonsignificant with non-calcified plaque. If AVC is present, consideration for aggressive medical therapy may be warranted.

Keywords

Aortic valve calcification; coronary artery disease; multi-detector computed tomography; calcified plaque; non-calcified plaque; mixed plaque

Introduction

Aortic valve calcification (AVC) has been considered a passive degenerative process, resulting from chronic mechanical shear stress.¹ However, recent data suggest that AVC may be caused by local inflammation^{2, 3} with implications that lipoproteins may play an essential role in the development and progression of AVC.^{2, 4-6} Additionally, AVC is associated with both cardiovascular risk factors and coronary artery calcification, which further supports a mechanistic relationship with atherosclerosis.⁷⁻¹¹

While AVC is believed to be associated to overall coronary plaque burden and the risk of cardiovascular disease, such studies have been primarily performed using non-contrast computed tomography (CT) with coronary artery plaque assessment from calcium scores.^{7, 11} To date, the association of AVC to overall coronary plaque burden and especially to non-calcified plaque components remains unknown. With the advent of contrast-enhanced multi-detector CT (MDCT) as a reliable technique for the non-invasive assessment of coronary plaque burden, detection and characterization of coronary atherosclerotic plaque into calcified and non-calcified plaque components^{12, 13} as well as reliable detection of AVC with high accuracies are possible.¹⁴

Thus, in the present analysis we aimed to determine whether AVC is associated with the presence and extent of overall coronary artery plaque burden, as well as to plaque composition (calcified, mixed, and non-calcified). Additionally, in a subgroup analysis of patients with AVC, we examined the relationship between AVC volume and the extent of coronary plaque burden.

Methods

Study population

Consecutive subjects for this analysis were prospectively enrolled between May 2005 and May 2007 as part of the ROMICAT (The Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. This study was a prospective observational cohort study of adult patients at low-to-intermediate likelihood for acute coronary syndrome who presented to the emergency department with acute chest pain whose initial electrocardiogram and biomarkers were negative or inconclusive and who were awaiting hospital admission. The details of the study have been previously reported.¹⁵

In brief, patients who were hemodynamically or clinically unstable (systolic blood pressure <80 mm Hg, clinically significant supraventricular or ventricular arrhythmias, persistent chest pain despite therapy), were known to have allergy to iodinated contrast agent, had an admission serum creatinine greater than 1.3 mg/dL, were on metformin treatment, had a history of hyperthyroidism, or who were unable to provide informed consent were excluded from this study. For this analysis, we also excluded subjects with prior aortic valve surgery, coronary artery bypass grafting, and coronary artery stent.

The Institutional Review Board of the Massachusetts General Hospital approved the study and all participants provided written informed consent. The ROMICAT trial was supported by research contracts from the National Institutes of Health (NIH) grant R01 HL080053. Amir Mahabadi is supported by a grant from the German National Academic Foundation. Drs. Rogers and Truong received support from NIH grant T32 HL076136 and L30 HL093896. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

MDCT Imaging Protocol

CT imaging was performed using a standard coronary artery 64-slice MDCT (Sensation 64, Siemens Medical Solutions, Forchheim, Germany) imaging protocol that included the administration of sublingual nitroglycerin (0.6 mg), if contraindications were absent and intravenous beta-blocker (5–20 mg of intravenous metoprolol), if the baseline heart rate was above 60 beats per minute.

Images were acquired during a single inspiratory breath hold in spiral mode with 330 ms rotation time, 32×0.6 mm collimation, tube voltage of 120 kVp, and maximum effective tube current-time product of 850 mAs, adjusted to the subjects body habitus. Tube modulation was employed when possible. On average, 80mL of iodinated contrast agent (Iodhexodol 320 g/cm³, Visipaque, General Electric Healthcare, Princeton, NJ), followed by 40mL saline solution was injected at a rate of 5mL/s. The beginning of image acquisition was delayed according to the contrast agent transit time, calculated from a test bolus scan (20 ml contrast agent followed by 40 ml saline, flow rate of 5 ml/s). The images were reconstructed offline using retrospectively ECG-gated half-scan algorithm. For coronary artery plaque assessments, on average, 3 transaxial data sets per subject were reconstructed with an image matrix of 512×512 pixels, a slice thickness of 0.75 mm, and an increment of 0.4 mm. For AVC assessments, multiphase reformats (MPR 5–95%, 10% interval, total of 10 phases) were reconstructed with a slice thickness of 1.5 mm and increment of 1.5 mm. All image analyses were performed offline on a dedicated cardiac workstation (Leonardo, Siemens Medical Solutions, Forchheim, Germany).

Coronary Artery Plaque Assessment

Two observers, each with more than 3 years of experience (more than 800 cases) in cardiac CT performed the plaque assessment. Both observers were blinded to the subject's clinical presentation and history. The presence and extent of calcified, mixed, and non-calcified coronary plaque was determined for each subject and evaluated according to the modified American Heart Association classification with 17-coronary segments.¹⁶ Details on plaque detection and characterization have been previously described and validated.^{15, 17} Briefly, segments were defined as having calcified plaque, if a structure with a density of greater than 130 Hounsfield units (HU) could be visualized separately from the contrast-enhanced coronary lumen (because its density was above the contrast-enhanced lumen), be assigned to the coronary artery wall, and be identified in at least 2 independent planes. Non-calcified plaque was defined as any clearly discernible structure that could be assigned to the coronary artery wall in at least 2 independent image planes and had a CT density less than 130 HU units but greater than the surrounding connective tissue. Mixed coronary atherosclerotic plaque was defined as the presence of calcified and non-calcified plaque components within any single coronary artery segment.

Aortic Valve Calcification Assessment

Two different readers qualitatively assessed for the presence of AVC. Both these readers had more than one year of experience in cardiac CT and were blinded to the clinical history and findings of the coronary artery evaluation. Cross-sectional planimetric short-axis images of the

aortic valve were reconstructed from the MPR data set. The presence of AVC was defined as a structure with a density of greater than 130 HU separately from the contrast and the valve leaflets in the closed position that could be visualized in all three planes and present throughout the cardiac cycle. For the subset of subjects with aortic valve calcification, the AVC volume was measured by one reader, based on the modified Simpson's method and using a dedicated volumetric software (Volume, Leonardo, Siemens Medical Solutions, Forchheim, Germany). Regions of interest were manually traced in axial planes to obtain the area of calcification in all slices containing calcification of the aortic valve (slice thickness 1.5mm). The AVC volume was automatically calculated by summation of the regions of interest multiplied by the slice thickness.

Covariates and Risk Factor Assessment

Covariates were assessed at the time of subject's enrollment. Presence of cardiovascular risk factors was established from actual measurements obtained during index hospitalization. Hypertension was defined as systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg or current antihypertensive treatment. Diabetes was defined as a fasting plasma glucose > 126 mg/dL or treatment with a hypoglycemic agent. Hyperlipidemia was defined as total cholesterol of > 200 mg/dL or treatment with a lipid lowering medication. Subjects were classified as smokers if they had smoked at least one cigarette per day in the last year. Body mass index (BMI) was defined as weight (in kilograms) divided by the height squared (in meters). Family history of coronary artery disease was defined as having a first-degree relative with a documented history of myocardial infarction or sudden cardiac death before 65 years of age for females or before 55 years of age for males. History of coronary artery disease was defined as documented prior myocardial infarction or percutaneous transluminal coronary angioplasty.

Statistical Analysis

Continuous variables are reported as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), as appropriate. Discrete variables are given in frequency and percentiles. We used t-test or Wilcoxon rank sum test for comparisons of continuous variables and Fisher's Exact or Chi-square test for binary variables, as appropriate. We used logistic regression analysis to determine the associations of AVC to the presence of any plaque and type of plaque. We used linear regression analysis to determine the relationship of AVC to the extent of plaque and plaque composition. Multivariable analyses included AVC and were adjusted for potential confounders based on *a priori* knowledge, which including age, gender, and traditional cardiovascular risk factors of BMI, hypertension, hyperlipidemia, diabetes, smoking, family history of premature coronary artery disease, and history of coronary artery disease. Correlations between AVC volume and extent of coronary plaque were assessed using the Spearman's correlation coefficient (95% confidence interval). Interobserver variability for the assessment of coronary plaque was excellent in 100 randomly selected subjects (kappa=0.92 for any plaque).¹⁷ Interobserver agreement for the detection of presence of AVC was assessed in a subset of 20 randomly selected cases with perfect agreement in detecting AVC between both readers (kappa=1.0). For AVC volume, inter- and intra-observer reproducibility were excellent on 20 cases with intra-class correlation coefficients (ICC) of > 0.99, both $p < 0.001$. A two-tailed p -value of < 0.05 was considered significant. All analyses were performed using the SAS software (Version 9.1.3, SAS Institute Inc) and SPSS 16.0 (Chicago, Illinois).

Results

We included 357 subjects in this analysis. Of those, 178 subjects (50%) had presence of coronary artery plaque. Out of 17 segments, there was an average of 2.32 ± 3.46 coronary

segments with plaque per subject. There were 37 subjects (10%) with presence of AVC and these patients were older, more likely to have hypertension, hyperlipidemia, and diabetes than those without AVC (Table 1).

AVC and Coronary Artery Plaque

Subjects with AVC had a higher frequency of presence of coronary plaque (89.2% vs. 45.6%, $p<0.001$) and a greater extent of coronary plaque than subjects without AVC (6.4 ± 4.3 vs. 1.8 ± 3.0 segments with any plaque, $p<0.001$). Table 2 summarizes the associations between AVC and the presence and extent of coronary artery plaque. As compared to patients without AVC, patients with AVC had a 10-fold increase odds of having any coronary plaque (odds ratio [OR] 9.96, $p<0.001$). After adjustment for age, gender, and traditional cardiovascular risk factors, there remained over 3-fold increase odds of having any plaque (OR 3.56, $p=0.047$). On a per segment basis, patients with AVC had 4.59 segments more coronary plaques ($p<0.001$) than those without AVC. After multivariable adjustment, patients with AVC still had a greater extent of plaque over those without AVC (2.47 segments more coronary plaque, $p<0.001$).

AVC and Coronary Artery Plaque Composition

Overall there were 141 subjects (39%) with presence of calcified plaque, 108 (30%) with mixed plaque, and 60 (17%) with non-calcified plaque. The average number of segments of plaque per patient was 1.25 ± 2.30 for calcified plaque, 0.78 ± 1.78 for mixed plaque, and 0.29 ± 0.78 for non-calcified plaque. When stratifying subjects by plaque composition, subjects with AVC were more likely to have calcified (86.5% vs. 35.1%, $p<0.001$) and mixed plaque (73.0% vs. 25.3%, $p<0.001$), while presence of non-calcified plaque was not significantly different between the two groups (24.3% vs. 15.9%, $p=0.24$).

Figure 2 illustrates the association between AVC and the presence of any coronary artery plaque burden and types of coronary plaque (calcified, mixed, and non-calcified coronary plaque). In unadjusted analysis, patients with AVC had a 12-fold increase odds of having any calcified plaque (OR 12.39, $p<0.001$) and an 8-fold increase of having any mixed plaque (OR 7.97, $p<0.001$) when compared to those without AVC. After adjustment for age, gender, and traditional risk factors, these increase risks of plaques were attenuated but remained significant with a 5-fold increase for calcified plaque (OR 5.23, $p=0.004$) and a 3-fold increase for mixed plaque (OR 3.24, $p=0.016$). There was no difference in OR for non-calcified plaque between patients with AVC and those without in both unadjusted ($p=0.20$) and adjusted ($p=0.96$) models.

On a per segment basis, patients with AVC had a median of 3.0 more segments containing calcified plaque ($p<0.001$) and 2.0 more segments of mixed plaque ($p<0.001$) when compared to subjects without AVC (median of 0 segment). There was no significant difference in the extent of non-calcified plaque ($p=0.25$) between subjects with AVC and those without. Table 3 summarizes the unadjusted and adjusted analyses for the association of AVC to the extent of coronary plaque burden by plaque composition. After adjustment for age, gender, and traditional risk factors, subjects with AVC had an estimated 1.55 more segments of calcified plaque ($p<0.001$) and 1.00 more segment of mixed plaque ($p=0.001$) over those without AVC, while there was no association between AVC and non-calcified plaque ($p=0.56$).

AVC Volume and Coronary Plaque

In the subjects with AVC, the median AVC volume was 0.05 cm^3 [IQR 0.02 cm^3 , 0.09 cm^3]. The median AVC volume was higher in subjects with presence of coronary plaque than in subjects without any plaque (0.05 cm^3 vs. 0.01 cm^3 , $p=0.006$). There were 4 subjects (11%) who had presence of AVC without evidence of any coronary artery plaque and a median AVC volume of 0.01 cm^3 (range $0.01\text{--}0.02 \text{ cm}^3$). These patients were 56.8 ± 8.7 years with a BMI

of $28.8 \pm 5.0 \text{ kg/m}^2$. Of the four, 3 were men (1 had both hypertension and hyperlipidemia, 1 was a smoker, and 1 had no cardiac risk factors). The one woman was 69 year-old with a BMI of 32 kg/m^2 but had no other cardiac risk factors.

When stratified by plaque composition, the median AVC volume was higher in subjects with presence of calcified plaque (0.05 cm^3 vs. 0.01 cm^3 , $p=0.027$) and mixed plaque (0.06 cm^3 vs. 0.02 cm^3 , $p=0.043$) than those without plaque. However, AVC volume was not significantly different in subjects with and without non-calcified plaque (0.05 cm^3 vs. 0.04 cm^3 , $p=0.96$). Figure 3 showed the median AVC volume in subjects with and without any coronary plaque and plaque by its composition. Moreover, AVC volume was correlated with the extent of plaque ($r=0.48$, $p=0.002$), but varied depending on composition (calcified: $r=0.34$, $p=0.04$; mixed: $r=0.31$, $p=0.056$) with no correlation to non-calcified plaque ($p=0.99$).

Discussion

In this analysis we examined the association of AVC to the presence and extent of overall coronary artery plaque burden using MDCT. In addition, CT angiography allowed us to assess the relationship between AVC and coronary artery plaque composition. The strength of our study is the large sample size of 357 patients where 64-slice MDCT was performed with evaluation for coronary artery plaque and its morphology as well as AVC. In our cohort, 89% of subjects with AVC had some degree of coronary artery disease. We found that patients with AVC had a 3-fold risk of having coronary plaque and had a greater degree of plaque burden (2.5 segments more) than those without calcification of the aortic valve. These associations were independent of age, gender, and traditional cardiovascular risk factors. Furthermore, we found that AVC volume correlated with the extent of coronary artery plaque, but was variable depending on plaque morphology. When stratifying into the different subtypes of plaque, there was a significant association between AVC with the presence and extent of calcified and mixed coronary plaque, but not with non-calcified plaque. These findings suggest a similar mechanism for development of both AVC and coronary artery disease.

AVC and coronary artery plaque burden

The association of AVC with coronary artery plaque may be caused by the shared risk factors and partially similar pathophysiologic pathway, as AVC has been associated to traditional risk factors such as age,^{8, 9} male gender,⁹ BMI,⁸ hypertension,^{8, 9} hyperlipidemia,⁹ diabetes,^{9, 10} the metabolic syndrome,¹⁰ and systemic inflammatory markers.¹⁸⁻²¹ Because of its overlap in risk factors of cardiovascular disease, presence of AVC is suspected to be associated with coronary artery disease and risk of cardiovascular events. This hypothesis is supported by the association of AVC with coronary calcification, as coronary artery calcification is a marker of overall atherosclerotic plaque burden^{22, 23} and significantly adds over traditional risk factors when predicting cardiovascular events.²⁴ Our study confirms these findings as we found that AVC is independently associated with coronary atherosclerosis, with more than 3-fold increase risk after adjustment for traditional risk factors. In addition, we found that subjects with AVC on average had more than 2 segments more of coronary plaque after adjustment for traditional risk factors. Together with our results, these findings may indicate a similar mechanism for development of both AVC and coronary artery disease. If AVC is present, then consideration for aggressive medical management (e.g. with statin therapy⁵) may be warranted to prevent progression of both coronary artery disease and aortic valve calcification.

In contrast to Yamamoto et al. who observed no statistically significant difference in the severity of coronary artery disease defined by invasive coronary angiography in subjects with and without AVC when looking at patients with clinically suspected coronary artery disease,²⁵ our findings of a significant association between AVC and the extent of coronary plaque are in keeping with Messika-Zeitoun et al. who found an association between the progression of

AVC and the progression of coronary artery calcification in an unselected population-based cohort.¹¹ One potential explanation for the difference in result with the invasive angiography study is that cardiac catheterization study allows only luminal assessment of coronary artery disease, while CT angiography enables full visualization of the coronary vessels and early disease detection, such as the process of positive remodeling. In addition, our study differs from the CT calcium study in that CT angiography allows for detection of not only calcified plaque but also other plaque type composition, including mixed and non-calcified plaque components.

AVC and coronary plaque composition

Contrast-enhanced MDCT is a reliable non-invasive technique for the assessment of coronary plaque burden.^{12, 13} When stratifying into subtypes of plaque, we found a significant association of AVC with the presence and extent of calcified and mixed coronary plaque, but not with non-calcified plaque. In adjusted analysis, there was a gradient effect with a 5-fold increase in risk for calcified plaque, 3-fold increase in risk for mixed plaque, but no difference for non-calcified plaque when comparing patients with and without AVC. Bamberg et al. recently reported that calcified coronary plaque was detected on CT more often in the advanced stage of coronary artery disease, while non-calcified plaque occurs early in the atherosclerosis process.¹⁷ Our study provides the unique opportunity to examine the different plaque morphologies, particularly non-calcified plaque, which was not possible with prior CT calcium scan studies.^{7, 11} Our results suggest that AVC may be part of the later stages of the atherosclerosis process, as it is associated strongest with calcified plaque, less with mixed plaque, and not with non-calcified plaque. It is likely that the relation with AVC and mixed plaque is driven by the presence of calcified plaque. Moreover, we found no association between AVC and non-calcified coronary plaque. This observation provides insight on the natural history of atherosclerosis which may be similar irrespective of different vascular beds, where calcification occurs later and during the chronic phase while non-calcified plaques may be prominent in early and active stage of cardiovascular disease.^{17, 26} Interestingly, in 4 of our patients with AVC, there was no coronary atherosclerosis. While the degree of AVC volume in these patients were minimal (ranged from 0.01 – 0.02 cm³), this finding suggests that other mechanisms for valvular calcification also exist.¹

Limitations

Our analysis was performed in the study cohort of the ROMICAT trial, which is based on a symptomatic study sample of patients presenting to the emergency department with the chief complaint of chest pain. Hence, the generalizability of our results may be limited to this patient population. We may be underpowered for the subgroup analysis with non-calcified plaque. Larger studies in population based collectives are needed to confirm our results. The radiation exposure from CT angiography should preclude its use for the sole purpose of AVC assessment. However, our study was performed for the primary purpose of suspected coronary artery disease and the images obtained allowed us to simultaneously evaluate the relationship between AVC with coronary artery plaque and its composition.

Conclusion

AVC is independently associated with the presence and extent of overall coronary artery plaque burden. It has a gradient association to plaque composition, with the strongest association to calcified then mixed plaque components, and no association with non-calcified plaque, suggesting that it may be related to the later stages of atherosclerosis. If AVC is present, consideration for aggressive medical therapy may be warranted to retard the atherosclerosis process.

Acknowledgments

We gratefully acknowledge the enthusiastic support in patient enrollment of the team of faculty, residents, nursing and administrative staff of the Emergency Department Services of the Massachusetts General Hospital.

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Figure 1.
MDCT images of the aortic valve in short-axis. (A) 48 year old male with no aortic valve calcification (AVC) and no coronary artery disease. (B) 64 year old male with AVC and calcified plaque in LAD (left anterior descending artery), LCX (left circumflex artery), and RCA (right coronary artery).

Figure 2.

Odds Ratio and 95% Confidence Interval for the presence of any coronary artery plaque burden and subtypes of coronary plaque (calcified, mixed, and non-calcified coronary plaque) in the presence and absence of aortic valve calcification in univariate and multivariable models, adjusting for age, gender, and traditional risk factors.

*in multivariable adjusted model

Figure 3.

Aortic valve calcification volume in subjects with presence and absence of coronary artery plaque burden as well as of subtypes of coronary plaque (calcified, mixed, and non-calcified plaque) in the subset of subjects with presence of aortic valve calcification.

CA plaque: calcified coronary plaque

NC plaque: non-calcified coronary plaque

Table 1

Patient characteristics of the study population and as stratified by presence of aortic valve calcification.

	Overall (N=357)	With AVC (N=37)	Without AVC (N=320)	p-value
Age (years)	53.0 ± 11.8	65.8 ± 13.7	51.5 ± 10.7	<0.001
Gender, male (%)	217 (60.8)	28 (75.7)	189 (59.1)	0.052
BMI (kg/m ²)	28.9 ± 5.7	28.4 ± 4.8	28.9 ± 5.8	0.54
Hypertension (%)	139 (38.9)	24 (64.9)	115 (35.9)	0.001
Hyperlipidemia (%)	131 (36.7)	20 (54.1)	111 (34.7)	0.030
Diabetes (%)	36 (10.1)	8 (21.6)	28 (8.8)	0.022
Smoking (%)	176 (49.3)	20 (53.9)	156 (48.8)	0.60
Family history of CAD (%)	86 (24.1)	8 (21.6)	78 (24.4)	0.84
History of CAD (%)	18 (5.0)	3 (8.1)	15 (4.7)	0.42

AVC: aortic valve calcification,

BMI: body mass index,

CAD: coronary artery disease.

Table 2

Unadjusted and adjusted models for the association of aortic valve calcification to the presence and extent of coronary plaque burden (number of segments with coronary plaque).

	Presence of coronary plaque		Extent of coronary plaque	
	Odds ratio (95% CI)	p-value	β estimate (95% CI)	p-value
Unadjusted	9.96 (3.45–28.76)	<0.001	4.59 (3.51–5.68)	<0.001
MV adjusted	3.56 (1.02–12.44)	0.047	2.47 (1.47–3.47)	<0.001

CI: confidence interval,

MV: multivariable model adjusted for age, gender, and traditional risk factors, including BMI, hypertension, hyperlipidemia, diabetes, smoking, family history of coronary artery disease, and history of coronary artery disease.

Table 3
Linear regression analyses for the association of aortic valve calcification to the extent of coronary plaque burden (number of segments) based on plaque composition in unadjusted and adjusted models.

	Calcified plaque		Mixed plaque		Non-calcified plaque	
	β estimate (95% CI)	p-value	β estimate (95% CI)	p-value	β estimate (95% CI)	p-value
Unadjusted	2.74 (2.01–3.47)	<0.001	1.82 (1.24–2.40)	<0.001	0.03 (–0.23–0.30)	NS
MV adjusted	1.55 (0.84–2.26)	<0.001	1.00 (0.41–1.59)	0.001	–0.08 (–0.38–0.26)	NS

CI: confidence interval; NS: nonsignificant.
MV: multivariable model adjusted for age, gender, and traditional risk factors, including BMI, hypertension, hyperlipidemia, diabetes, smoking, family history of coronary artery disease, and history of coronary artery disease.