Diagnosis and management of left valvular heart disease with advanced echocardiography and cardiac computed tomography

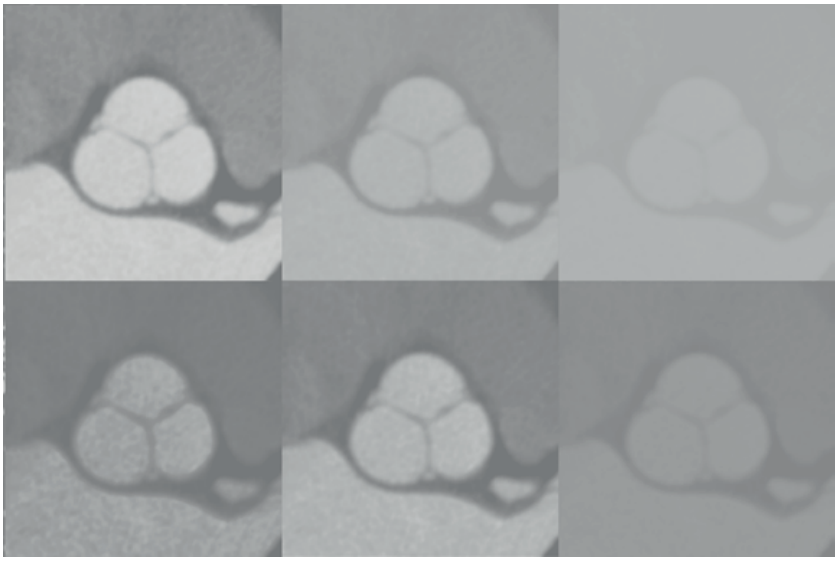
Kamperidis, V.

PART III

AORTIC STENOSIS AND MITRAL REGURGITATION: PROGNOSIS

CHAPTER 8

Prognostic Value of Aortic and Mitral Valve Calcium Detected by Contrast Cardiac Computed Tomography Angiography in Patients with Suspicion of Coronary Artery Disease



Vasileios Kamperidis, MD, MSc, Michiel A. de Graaf, Alexander Broersen, PhD, Wehab Ahmed, Georgios Sianos, MD, PhD, Victoria Delgado, MD, PhD, Jouke Dijkstra, PhD, Jeroen J. Bax, MD, PhD, and Arthur J. Scholte, MD, PhD

Am J Cardiol. 2014;113(5):772-8.

ABSTRACT

Aortic valve calcium (VC) detected on non-contrast cardiac computed tomography angiography (CCTA) is known to be associated with all-cause mortality in asymptomatic and primary prevention population. However, the clinical significance of aortic and mitral VC remains unknown in symptomatic patients with suspected coronary artery disease (CAD). The aim of the present study was to assess whether aortic and mitral VC is independently associated with cardiac events and all-cause mortality in symptomatic patients with suspected CAD. A total of 369 symptomatic patients (mean age 55 ± 11 years, 60% male) who were referred for CCTA because of suspected CAD were included in the study. Aortic and mitral VC was detected and quantified by volume on contrast CCTA. Median follow-up (FU) for events (coronary-events and all-cause mortality) was 2.8 (interquartile range: 1.6 to 4.0) with a maximum of 5.5 years. A total of 39 (11%) patients had VC. Increased age, hypertension and increased Agatston coronary artery calcium (CAC) score were associated with VC. During the FU, patients with VC had higher risk for a coronary event (38.8 vs. 11%, log-rank $p<0.001$) and worse survival (92.3 vs. 99.1%, log-rank $p=0.002$) compared to those without VC. Volume of VC was independently associated with outcome, after adjusting for clinical variables (hazard ratio 1.88, $p<0.001$), Agatston CAC score (hazard ratio 1.47, $p=0.03$) and significant CAD (hazard ratio 1.81, $p=0.001$). In conclusion, aortic and mitral VC volume quantified on contrast CCTA was independently associated with coronary events and all-cause mortality in patients with suspected CAD.

INTRODUCTION

Contrast enhanced cardiac computed tomography angiography (CCTA) is nowadays used for the anatomic evaluation of coronary artery disease (CAD) in symptomatic patients with chest pain and low to intermediate probability of CAD.[1,2] Besides CAD, valve calcium (VC) can be detected by contrast enhanced CCTA.[3,4] Aortic and mitral VC detected by CCTA has been associated with increased prevalence of CAD, cardiovascular events and all-cause mortality in asymptomatic patients.[5-8] However, little is known about the prognostic value of aortic and mitral VC detected by CCTA in symptomatic patients. Moreover, the value of VC quantification on contrast enhanced CCTA has never been explored. Therefore, the aim of the current study was to assess the independent association between VC, detected and quantified on contrast CCTA, and prognosis in symptomatic patients with suspected CAD.

METHODS

We included all symptomatic patients who underwent a clinically indicated contrast enhanced CCTA for the evaluation of CAD from November 2007 till April 2010. Patients with previous diagnosis of CAD, congenital heart disease, mechanical valve prosthesis and poor CCTA diagnostic image quality were excluded.

All scans were performed using a 64-detector row computed tomography scanner or a 320-row scanner according established guidelines and local protocol.[9,10] Scan parameters were: 120kV, 300mA (depending on BMI and thoracic anatomy) and collimation of 64x0.5mm; and 120kV, 400-580mA (depending on BMI and thoracic anatomy) and collimation of 320x0.5mm for 64- and 320-row scanners, respectively. Contrast-enhanced CCTAs were reconstructed at 75% of the R-R interval with a slice thickness of 0.3mm for the 64- and 0.5mm, increment 0.25mm for the 320-detector scanner. Non-enhanced CCTAs were also reconstructed at the 75% of the R-R interval but with a slice thickness of 3mm non-overlapping. Reconstructed images were transferred to a remote workstation (Vital Images, Plymouth, Minnesota) for post-processing with dedicated software.

The non-contrast scans were used to evaluate the total coronary artery calcium (CAC) score as described by Agatston et al. applying a threshold of ≥130 Hounsfield units (HU)[11] with commercially available software (Vitrea 2, Vital Images, Plymouth, Minnesota).

To quantify VC on contrast-enhanced CCTA, novel automated data post-processing software (customized research version of CalcScore V11.1 by Medis specials b.v.) was used. Since both calcium and contrast medium have a radio density of >130 HU, a cut-off value of >130 HU as used for non-contrast scans, is not suitable to quantify calcium on contrast enhanced CCTA images.[12] Therefore, in the present study we applied a predefined threshold of 800

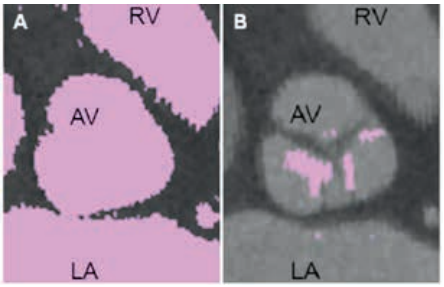


Figure 1. Aortic valve calcium assessed on contrast cardiac computed tomography angiography at the double oblique transverse view. A. Using a threshold of 130 HU detects all contrast, B. Using a threshold of 800 HU detects calcium on the aortic valve. AV=Aortic Valve, HU=Hounsfield Units, LA=Left Atrium, RV=Right Ventricle

HU to quantify calcium on the aortic and mitral valve.[3] An example of both

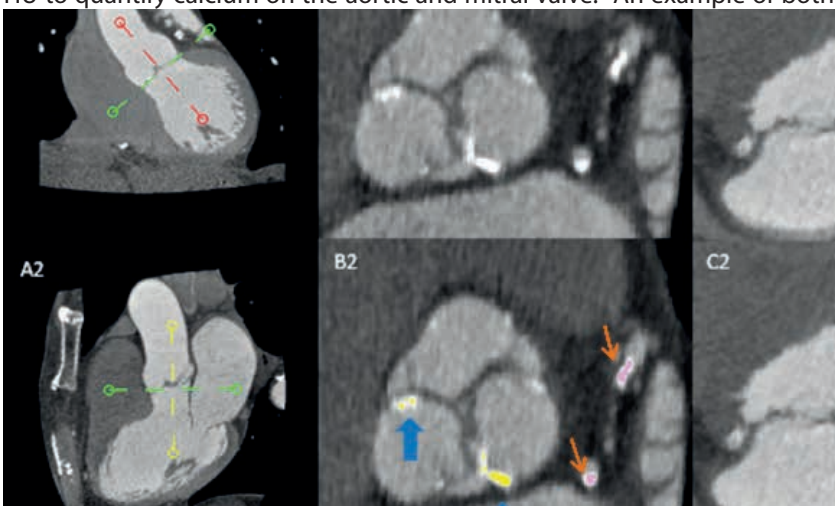


Figure 2. Aortic and mitral valve calcium assessed on contrast cardiac computed tomography angiography with the threshold of ≥800HU. By adjusting the 3 orthogonal multi-planar reformation planes (red, yellow and green dotted lines), based on aortic valve orientation, in the coronal (A1) and single oblique sagittal (A2) views, the double oblique transverse view depicting the real aortic valve short axis (B1) was created. By using the sequential axial images below the aortic annulus, the mitral valve could also be visualized in this view (C1). B2 demonstrates the calcium detected on the aortic valve. Blue arrows point the aortic valve calcium colored yellow after selecting it. Orange arrows point the coronary artery calcium colored pink (not selected). C2 demonstrates the calcium detected on the mitral valve. Red arrow points mitral valve calcium colored green after selecting it.

thresholds is depicted in Figure 1. Because the Agatston score is only suitable for assessing coronary artery calcium,[11] VC was quantified by assessing the volume (mm^3) of calcium on contrast-enhanced CCTA.[3,4]

To quantify VC we performed the following steps: because the aortic valve is depicted obliquely on the standard axial view,[3] the first step was to reorient the image based on the aortic valve. By using three multi-planar reformation planes (Figure 2.A1&A2), a double oblique transverse view was created. In this plane the aortic cusps were equally bisected allowing concomitant visualization of the insertion point of the aortic cusps (Figure 2.B1). Secondly, scrolling through sequential axial images below the aortic annulus, the mitral valve can be visualized in this view (Figure 2.C1). Next, 3mm slabs were created to facilitate accurate VC quantification. Subsequently, the aortic (Fig-

ure 2.B2) and mitral VC (Figure 2.C2) were manually selected. The aortic VC included all calcium within the level of the aortic annulus till the level of the coronary ostia. Mitral VC was defined as calcium of the mitral annulus and leaflets. Finally, the volume of the selected aortic and mitral VC was calculated automatically by the software.

Presence of significant CAD was evaluated from the contrast CCTA as previously described.[13] Significant CAD was defined as ≥50% stenosis.

Cardiovascular risk factors evaluated for this study were: hypertension, defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication; hypercholesterolemia, defined as serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl and/or treatment with lipid lowering drugs; diabetes, defined as fasting glucose ≥ 126mg/dl and/or on blood glucose lowering treatment; smoking, as current; obesity, as BMI ≥ 30 Kg/m^2 and family history: defined as the presence of CAD in first-degree family members diagnosed at the age of <55 years in men and <65 years in women.

Clinical information were recorded prospectively into the departmental Cardiology Information System (EPD, Vision, version 8.3.3.6, Leiden, The Netherlands) and analyzed retrospectively. Follow up was completed till January 2013. Patient follow-up data were gathered using clinical visits or standardized telephone interviews. The primary outcome was all-cause mortality. The secondary end-point was coronary events, including a composite of myocardial infarction (MI) and revascularization (percutaneous coronary intervention (PCI) and coronary artery by-pass grafting (CABG)). The combined (primary and secondary) end-point is described as events.

Statistical analysis was performed with the SPSS software version 20 (SPSS, Chicago, IL). Categorical variables are presented as number and percentages and continuous variables as mean ± standard deviation. Based on the distribution, continuous variables were compared with the Student t-test or the Mann-Whitney U-test. Categorical variables were compared with the x^2 test. Logistic regression analysis was used to evaluate the association between each cardiovascular risk factor and valve calcium as a categorical variable. In the multivariate adjusted analysis only the covariates with a p <0.10 in the univariate analysis were included. CAC Agatston score was introduced in the regression analysis as log(CAC Agatston score + 1). Cumulative event rates from the time of CCTA scanning were calculated using the Kaplan-Meier method. The log-rank test for time to event data with respect to the primary (all-cause mortality) and secondary end point (composite endpoint of MI and revascularization) were used for statistical comparison between the patient groups (VC group vs. the no-VC group). In addition, the Kaplan-Meier estimates of the primary and the secondary endpoints were calculated for patients included in the VC group divided according to the median value of calcium volume. Cox regression analysis was conducted for the evaluation of univariate and multivariate hazard ratios (HRs) for the occurrence of events. CAC Agatston score and valve calcium volume were both introduced in the Cox regression analysis as log(CAC Agatston score + 1) and log(valve calcium volume + 1). HRs were reported with 95% confidence interval (CI). Statistical significance was considered for p value < 0.05.

RESULTS

Of the 384 consecutive symptomatic patients referred for CCTA to detect and evaluate CAD, 369 patients (mean age 55 ± 11 years, 60% men) were finally included in the current analysis. Fifteen patients were excluded because of: mechanical aortic valve prosthesis (N=3, 0.8%) and adult congenital heart disease (N=12, 3%). VC was observed in 39 (10.7%) patients; 34 (9.3%) had aortic VC, 10 (2.8%) had mitral VC and 5 (1.4%) had calcium on both valves. Baseline characteristics are presented in table 1. Patients with VC were older, were more likely to have hypertension and had a higher CAC score. In addition, patients with hypertension and those with Agatston CAC score >100[6,14] had higher VC volumes compared to patients without hypertension and those with Agatston of ≤100, respectively (Table 2).

Table 3 demonstrates the univariate and multivariate analysis for the association of classical cardiovascular risk factors with the presence of VC. Increasing age and Agatston CAC score were the only factors independently associated with the presence of VC.

The median follow-up after the CCTA was 2.8 years (interquartile range 1.6 to 4.0) with a maximum of 5.5 years. During this follow-up period, the combined end-point was observed in 56 (15%) patients; 6 (1%) patients died, 11 (3%) suffered acute coronary syndrome, 32 (9%) underwent PCI, 4 (1%) underwent CABG and 3 (1%) suffered a myocardial infarction during the follow-up period after CCTA. Event-free survival was significantly worse for patients with VC in comparison to those without VC (event rate: 44% vs. 12% respectively, log-rank p<0.001) (Figure 3.A). Patients with higher VC volume had worse event-free survival (event rate: 12% for no VC patients vs. 33% for subgroup of patients with VC volume below the median value of 14 mm^3 [interquartile range 5 to 49] vs. 56% for subgroup of patients with VC volume above this median, log-rank p<0.001) (Figure 3.B). Focusing on the coronary-event-free survival, patients with VC had statistically significant more coronary events than those without VC (coronary-event rate: 39% vs. 11% respectively, log-rank p<0.001) (Figure 3.C). Focusing on all-cause mortality, the survival was significantly worse for those with versus those without VC (survival rate: 92% vs. 99% respectively, log-rank p=0.002) (Figure 3.D).

Table 4 presents the HRs of the univariate analysis for the association of cardiovascular risk factors and VC volume with events. Increasing age, significant CAD, Agatston CAC score and VC volume were significantly associated with events in the univariate cox-regression analysis. VC volume remained independently associated with the endpoint, after adjusting for age, hypertension, smoking and Agatston CAC score or significant CAD (Table 5).

Table 1. Baseline Demographics and Risk Factors According to the Presence of Valve Calcium.

Variable	All subjects	Valve Calcium		p* value
	N=369 (100%)	NO (N= 330)	YES (N=39)	
Age (years)	55 ± 11	54 ± 11	66 ± 9	<0.001
Men	221 (60%)	198 (60%)	23 (59%)	0.90
Body Mass Index (Kg/m^2)	26 ± 4.2	26 ± 4.1	26 ± 4.5	0.72
Diabetes Mellitus	103 (30%)	89 (29%)	14 (36%)	0.37
Hypertension	139 (40%)	117 (38%)	22 (56%)	0.02
Hypercholesterolemia	123 (35%)	105 (34%)	18 (46%)	0.13
Smoker	58 (17%)	50 (16%)	8 (21%)	0.50
Family History of CAD	144 (41%)	133 (43%)	11 (28%)	0.07
Obesity	70 (20%)	63 (20%)	7 (18%)	0.74
Agatston CAC Score	175 ± 478	114 ± 291	666 ± 1059	<0.001

Values are mean ± SD or n (%).

*p value for the comparison of Valve Calcium YES to NO.
Hypertension, defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication. Hypercholesterolemia, defined as serum total cholesterol ≥230 mg/dl and/or serum triglycerldes ≥200 mg/dl and/or treatment with lipid lowering drugs. Obesity, defined as BMI ≥30Kg/m^2. CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease

Table 2. Risk Factors according to Quantified Valve Calcium.

Variable		Valve Calcium Volume	p value
Diabetes Mellitus	+	44.5 ± 394.1	0.18
	0	8.79 ± 78.6	
Hypertension	+	45.6 ± 353.6	0.02
	0	1.8 ± 8.4	
Hypercholesterolemia	+	35.9 ± 360.6	0.18
	0	10.2 ± 82.2	
Smoker	+	21.8 ± 148.4	0.49
	0	18.9 ± 237.4	
Family History of CAD	+	3.6 ± 25.1	0.07
	0	30.4 ± 291.7	
Obesity	+	21.4 ± 137.6	0.65
	0	18.9 ± 242.0	
Agatston CAC Score	>100	74.2 ± 445.4	<0.001
	≤100	1.0 ± 8.1	

All values are mean ± SD in mm^3. +=Yes, 0=No, CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease

Table 3. Univariate and Multivariate Analysis of Risk Factors associated with Valve Calcium.

Variable	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age (years)	1.14	1.09 - 1.20	<0.001	1.11	1.06 - 1.17	<0.001
Diabetes Mellitus	1.37	0.68 - 2.76	0.37			
Hypercholesterolemia	1.66	0.85 - 3.25	0.14			
Hypertension	2.10	1.07 - 4.12	0.03	1.01	0.46 - 2.21	0.98
Family History of CAD	0.52	0.25 - 1.08	0.08	0.68	0.30 – 1.53	0.35
Smoking	1.33	0.58 - 3.06	0.50			
Obesity	0.87	0.37 - 2.05	0.74			
Agatston CAC Score	2.74	1.91 - 3.89	<0.001	1.88	1.28 - 2.76	0.001

Agatston CAC score has been introduced as log(Agatston CAC score + 1)
CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease, CI= Confidence Interval, OR= Odds Ratio

Table 4. Univariate Cox Regression Analyses of factors associated with the Combined End Point.

Variable	Univariate		
	HR	95% CI	p value
Age (years)	1.06	1.03 - 1.08	<0.001
Diabetes Mellitus	1.20	0.69 - 2.09	0.52
Hypercholesterolemia	1.20	0.70 - 2.05	0.51
Hypertension	1.60	0.94 - 2.71	0.08
Family History of CAD	1.45	0.85 - 2.45	0.17
Smoking	1.73	0.93 - 3.23	0.08
Obesity	1.33	0.72 - 2.48	0.36
CA stenosis ≥50%	2.63	1.55 - 4.45	<0.001
Agatston CAC score	2.58	1.98 - 3.38	<0.001
Valve Calcium Volume	2.26	1.71 - 2.99	<0.001

Agatston CAC score has been introduced as log(Agatston CAC score + 1)
Valve Calcium Volume has been introduced as log(Valve Calcium Volume + 1)
CA= Coronary Artery, CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease, CI= Confidence Interval, HR= Hazard Ratio

Table 5. Multivariate Cox-Regression Analyses for Valve Calcium Volume association to Combined End Point.

Variable	Baseline model	Baseline model + Agatston CAC score	Baseline model + CA stenosis ≥50%
	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value
Valve Calcium Volume	1.88 (1.35 - 2.62) <0.001	1.47 (1.04 - 2.08) 0.03	1.81 (1.27 - 2.56) 0.001

Baseline Model: included Age, Hypertension, Smoking and Valve Calcium Volume
Agatston CAC score has been introduced as log(Agatston CAC score + 1)
Valve Calcium Volume has been introduced as log(Valve Calcium Volume + 1)
CA= Coronary Artery, CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease, CI= Confidence Interval, HR= Hazard Ratio

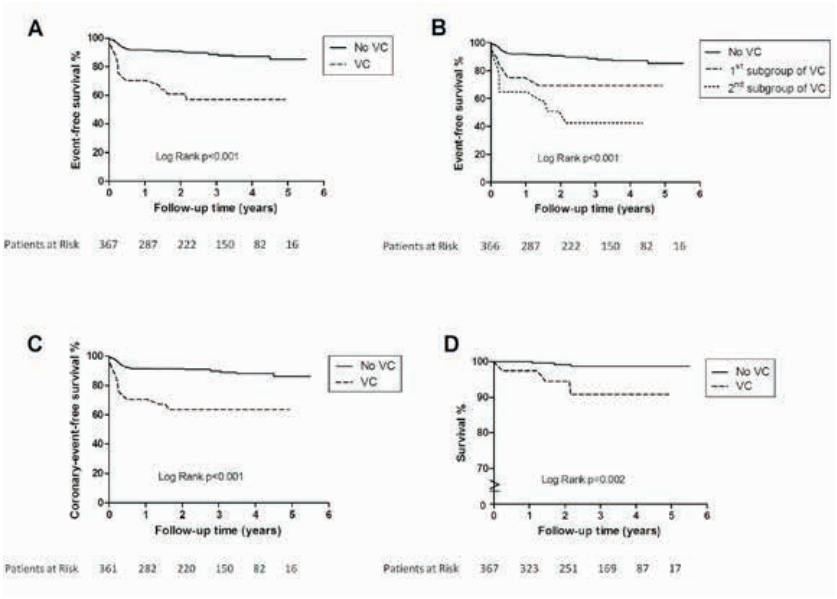


Figure 3. Kaplan-Meier curves for combined end-point (events), coronary-events and all-cause mortality in patients with and without VC. Patients with VC had worse outcome; A. event-free survival was significantly worse for the patients with VC (event rate: 11.8% in no-VC vs. 43.5% in VC, p<0.001). B. event-free survival was significantly worse for the patients with higher VC volume (event rate: 11.8% in no VC vs. 33.3% in 1st subgroup of VC with calcium volume below the median VC volume vs. 55.5% in 2nd subgroup of VC with calcium volume above the median VC volume, p<0.001). C. coronary-event-free survival was significantly worse for the patients with VC (coronary-event rate: 11% in no VC vs. 38.8% in VC, p<0.001). D. survival was significantly worse for the patients with VC (survival rate: 99.1% in no VC vs. 92.3% in VC, p=0.002). VC= valve calcium, vs.=versus

DISCUSSION

The current study sought to investigate the prognostic value of aortic and mitral VC quantified on contrast CCTA in symptomatic patients with suspected CAD. The main findings are: 1) Increased age and CAC score were independently associated with VC. 2) Patients with VC had more events in comparison to those without; and those with higher VC volume, had even more events. 3) VC volume was independently associated with the study endpoint. Furthermore, the current study showed that quantification of VC volume on contrast CCTA was associated with all-cause mortality and cardiovascular events in symptomatic patients with clinical suspicion of CAD.

Non-contrast multi-detector computed tomography (MDCT) is a well-established method for identifying aortic and/or mitral VC.[5-8,15-18] In addition to identifying VC, a few studies focused on quantification of aortic VC.[5,15,19-21] Recently, aortic VC has been identified and quantified on contrast enhanced MDCT in patients with severe aortic valve stenosis undergoing transcatheter aortic valve implantation (TAVI).[3,4] Contrast-enhanced CT allows also accurate discrimination between calcium of the circumflex coronary artery and the mitral annulus, permitting more accurate evaluation of the mitral VC volume.[22]

Echocardiography is an imaging modality that is widely used for identifying aortic and/or mitral VC.[22-27] However, echocardiography can provide semi-quantification of VC and cannot provide absolute quantification of the VC volume.[22] Moreover, with echocardiography the discrimination between calcium and dense fibrosis is difficult, leading to an overestimation of VC in comparison to the reference standard MDCT.[16,19] Cardiac magnetic resonance imaging is an excellent modality for differentiating between mitral annulus VC and caseous calcification, but has not been used for VC assessment in large cohorts of patients.[28]

Aortic and mitral VC are known to be an expression of generalized atherosclerosis as demonstrated by several studies proving strong clinical association of cardiovascular risk factors with the presence of VC on MDCT.[15-17,21,29,30] Advanced age is the risk factor that has been recognized by all studies conducted so far as an independent predictor of VC in the asymptomatic population.[16,17,21,29,30] The other risk factors associated with mitral and/or aortic VC in the asymptomatic population were hypertension, type 2 diabetes, smoking, dyslipidemia and obesity.[16,17,21,29,30] Moreover, quantitative assessment of aortic VC, demonstrated higher VC volumes in hypertensive, diabetic and dyslipidemic patients.[15] The Agatston CAC score, as an expression of the atherosclerotic plaque burden, has been associated with VC, but only recently it was demonstrated to be an independent predictor of mitral VC. [5,17,21,29]

The current study quantified both aortic and mitral VC on contrast CCTA and showed that VC volume was significantly higher in patients with hypertension and in those with Agatston CAC score >100 (table 2). Furthermore, advanced age and Agatston CAC score were independently associated with aortic and mitral VC (table 3) which is in concordance with previous studies,

although the present study focused on symptomatic patients.[16,17,21,29,30]

In addition to the association with clinical risk factors, the prognostic value of VC has been widely studied. Wong et al. studied aortic VC and thoracic aorta calcium on non-contrast cardiac electron beam computed tomography (EBCT) and MDCT in self-referred or physician-referred patients without known CAD and demonstrated the incremental value of VC over the Agatston CAC score for predicting the 10-year risk of CAD estimated by the Framingham risk score.[29] In a similar way, Gondrie et al. studied aortic and mitral VC on chest MDCT in the population of the PROgnostic Value of incidental Information in Diagnostic Imaging (PROVIDI) study and observed that patients with VC had a higher incidence of CAD, heart failure, peripheral artery disease, aortic aneurysm or cerebrovascular disease.[7] The prognostic value of VC on mortality has been studied in the primary prevention Multi-Ethnic Study of Atherosclerosis (MESA) population by Blaha et al.[6] In this study aortic VC on non-contrast cardiac EBCT was an independent predictor of all-cause mortality even after adjusting for the classical cardiovascular risk factors and Agatston CAC score.[6] Analyzing the same MESA study population, Owens et al. concluded that aortic VC detected on non-contrast cardiac MDCT was independently associated with cardiovascular and coronary events and that the risk of cardiac death increased in parallel to increasing VC severity, even after adjusting for the Agatston CAC score.[5]

In contrast to previous studies that assessed the association between aortic VC (assessed with non-contrast MDCT) and mortality, the current study focused on the association of aortic and mitral VC with all-cause mortality quantifying VC on contrast cardiac MDCT. Moreover, our study focused on the quantification of VC in a symptomatic population. Since symptomatic patients are increasingly undergoing contrast CCTA, additional prognostic information can be extracted by quantifying the VC.[1,2,5-7]

Some limitations have to be acknowledged. In the current study, CCTAs were not performed primarily for VC quantification, but for the assessment of CAD. As a result, VC assessment was performed retrospectively. Moreover, CCTA can overestimate coronary artery stenosis leading to referral for invasive coronary angiography and subsequent revascularization. In addition, C-reactive protein was not available for all patients included in the study and its association to VC was not studied. Finally, the cause of death was not systematically available.

Aortic and mitral VC identified on clinically indicated contrast CCTA in symptomatic patients with suspected CAD is associated with worse survival and more coronary events. The volume of VC can be used as an additional and independent predictor of cardiac events.

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