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Multifocal cardiovascular calcification in patients with established cardiovascular disease; prevalence, risk factors, and relation with recurrent cardiovascular disease

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ABSTRACT

Aims: The aim is to investigate (multifocal) cardiovascular calcification in patients with established cardiovascular disease (CVD), regarding prevalence, risk factors, and relation with recurrent CVD or vascular interventions. Coronary artery calcification (CAC), thoracic aortic calcification (TAC) (including ascending aorta, aortic arch, descending aorta), mitral annular calcification (MAC), and aortic valve calcification (AVC) are studied.

Methods: The study concerned 568 patients with established CVD enrolled in the ORACLE cohort. All patients underwent computed tomography. Prevalence of site-specific and multifocal calcification was determined. Ordinal regression analyses were performed to quantify associations of risk factors with cardiovascular calcification, and Cox regression analyses to determine the relation between calcium scores and recurrent CVD or vascular interventions.

Results: Calcification was multifocal in 76% (N = 380) of patients with calcification. Age (per SD) was associated with calcification at all locations (lowest OR 2.17; 99%CI 1.54–3.11 for ascending aorta calcification). Diabetes mellitus and systolic blood pressure were associated with TAC, whereas male sex was a determinant of CAC. TAC and CAC were related to the combined endpoint CVD or vascular intervention (N = 68). In a model with all calcium scores combined, only CAC was related to the combined outcome (HR 1.39; 95%CI 1.15–1.68).

Conclusion: Cardiovascular calcification is generally multifocal in patients with established CVD. Differences in associations between risk factors and calcification at various anatomical locations stress the divergence in pathophysiological pathways. CAC is most strongly related to recurrent CVD or vascular interventions independent of traditional risk factors, and independent of heart valve and thoracic aorta calcification.

1. Introduction

Cardiovascular calcification is a complicated and multifaceted process [1]. Risk factors and relation with incident cardiovascular disease have been studied in population based studies or apparently healthy people [2–7]. However, etiology of cardiovascular calcification is not yet completely understood and the relation between calcification and recurrent cardiovascular events in

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patients with established cardiovascular disease (CVD) specifically is unknown.

Pathophysiology of calcium deposition is an active process and varies between tissues. Calcification of the mitral valve occurs primarily in the mitral annulus (mitral annulus calcification (MAC)), the fibrous base of the mitral valve [8], whereas aortic valve calcification (AVC) mainly affects the cusps [9]. In the vasculature, deposition of calcium in either the tunica media or tunica intima of the arterial wall are discrete forms of calcification; intimal calcification is generally related to atherosclerotic risk factors including hyperlipidemia and smoking [1], whereas medial calcification is mainly influenced by diabetes mellitus and renal dysfunction [10]. Similar pathways exist in valvular and vascular calcification, including differentiation of resident cell population to osteoblast-like bone producing cells, and the loss of calcification inhibitors [1,8,9,11], eventually leading to ectopic bone formation [1,8,9]. However, the impact of risk factors on initiation and progression of cardiovascular calcification differs [8–12], potentially leading to calcification in one location but not in another. Comparing associations of risk factors with calcification in multiple anatomical locations directly could provide insight in varying impact.

Regardless of pathophysiology, cardiovascular calcification; coronary artery calcification (CAC) as well as thoracic aorta calcification (TAC), is related to a higher risk of cardiovascular mortality in the general population [13] and incident cardiovascular disease in apparently healthy people [5,14–16], independent of general cardiovascular risk factors.

The aim of the present study is to investigate (multifocal) cardiovascular calcification in patients with established vascular disease, with regard to (I) the prevalence of CAC, TAC (including ascending aorta, aortic arch, and descending aorta), MAC, and AVC, (II) the associations of predetermined cardiovascular risk factors with calcification of these anatomical locations in a direct comparison, and (III) the relation between cardiovascular calcification and recurrent cardiovascular disease and vascular interventions.

2. Methods

Study population

Patients originated from the ORACLE study (Clinicaltrials.gov Identifier NCT01932671), embedded in the UCC-SMART cohort. The UCC-SMART cohort is an ongoing prospective cohort study including 18–79 year-old patients referred to the University Medical Center in Utrecht (the Netherlands) with clinically manifest atherosclerotic vascular disease or marked risk factors. Study design and rationale have been described in detail previously [17]. Patients enrolled in the UCC-SMART cohort from August 2012, without contra-indications for contrast enhanced computed tomography, were invited to participate in the ORACLE study, consisting of non-contrast enhanced cardiac computed tomography (CT) and CT-angiography (CTA) visualizing the aortic arch to the circle of Willis. Contra-indications were reduced renal function (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2), previous severe allergic reaction to contrast, previous exposure to radiation for scientific purposes or any other known contra-indication for CT-scanning. Information about the determinants and potential confounders was collected at baseline, following the UCC-SMART protocol, entailing thorough investigation of medical history, laboratory, physical and radiological examinations. Kidney function was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [18]. The study is in accordance with the 1964 Helsinki declaration, was approved by the institutional review board of the Utrecht University Medical Center, and all patients gave written informed consent. For the current study, 568 patients with established cardiovascular disease enrolled in the ORACLE study were included.

CT-scan protocol and image analysis

Images were acquired using a 256-slice MDCT-scanner (iCT, Philips Healthcare, the Netherlands) on the same day as the baseline measurements. Non-contrast enhanced cardiac CT-scan, as well as coronary CT angiography images were acquired. Upon completion of the coronary CTA, a second acquisition with a new contrast injection was performed to visualize the vascular system from the aortic arch to the circle of Willis. Detailed information on the CT-scan protocol is summarized in Supplemental Methods. Calcification scoring was performed manually by an observer trained by an experienced radiologist and blinded for patient characteristics. Calcification of heart valves, coronary arteries, and ascending and descending aorta was scored on the non-contrast enhanced cardiac CT visualizing heart base to the pulmonary artery bifurcation. The aortic arch was scored on the contrast enhanced scan, as it was not included in the non-contrast cardiac scan. Due to the different scan settings for the contrast enhanced scan, calcium scores of aortic arch could not be added up to calcium scores of ascending and descending aorta and were therefore analyzed separately. Calcifications on valves and in the thoracic aorta were quantified using a "pseudo-mass" score, calculated by multiplying the mean calcium HU value by the region of interest (ROI) volume for every lesion, and summing up the scores of all the lesions. CAC was quantified using the Agatston method [19]. Detailed information on image analysis is summarized in Supplemental Methods. Supplemental figure S1 shows examples of calcification scoring for each location.

Incident cardiovascular disease or vascular interventions

Participants received biannual questionnaires during follow-up, gathering information on occurrence of recurrent CVD, bleeding events, incident diabetes, end stage renal disease, and hospitalizations for vascular interventions. Additional information was gained by collecting hospital or general practitioner's data. An endpoint committee of three physicians independently adjudicated all cardiovascular disease events and conflicting classifications were discussed. Experienced research nurses classified all vascular interventions. Cardiovascular disease was defined as non-fatal myocardial infarction, non-fatal stroke or vascular death. Cardiovascular interventions were percutaneous interventions or revascularization surgery, including carotid endarterectomy (CEA), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), major amputations, and peripheral artery stenting, angioplasty or bypass (Supplemental Table S1 for outcome definitions).

Data preparation

Continuous risk factors were truncated to the 99th percentile to correct for outliers. Missing data was singly imputed for waist circumference (1.1%), LDL-c (0.2%), kidney function (0.2%), triglycerides (0.2%), hsCRP (1.2%), number of pack-years (0.2%), and HDL-c (0.2%) using bootstrapping and predictive mean matching based on multivariable regression with independent variable and outcome data. Calcium scores were categorized (Supplemental Table S1). Categories for coronary artery calcification were based on clinical cut-off values: 0, 1–99, 100–399, and 400 or higher [20]. Since no clinical cut-off values were available for the other locations, calcium scores of ascending aorta, descending aorta, aortic arch, and aortic valve were divided into three categories: 0 if no calcification was present (calcium scores < 1 were considered no calcification), 1 and 2 for calcium scores $\geq$ 1 and lower or higher than the 50th percentile. Mitral annulus calcium scores were dichotomized (0 = no calcification and 1 = calcification), due to the low prevalence. Presence of multifocal calcification was summarized in the 'calcium sum score'. The sum score was calculated

by adding up presence of calcification in the six locations, resulting in a minimum of 0 (no calcification in any of the locations), and a maximum of 6 (presence of calcification in all 6 structures) for every patient individually.

Data analyses

Prevalence and risk factors of cardiovascular calcification

Frequencies of the calcium sum score were calculated and plotted in histograms accordingly, for all patients combined, and after stratification by sex, age higher or lower than 60 years (mean age of the study population), and presence of diabetes mellitus. A cross table was created showing prevalence of calcification in groups of patients with CAC, MAC, AVC, and TAC. Potential risk factors for calcification were predetermined and included age, sex, diabetes mellitus, number of pack-years of smoking, waist circumference, systolic blood pressure, pulse pressure, LDL-c, HDL-c, triglycerides, hsCRP, and kidney function. To explore the association of these risk factors with the presence and extent of cardiovascular calcification per location separately, regression analyses were performed. Due to the excess of zero scores (no calcification), ordinal regression by means of the proportional odds model was performed [21], and logistic regression for MAC, with the ordered categories as outcome (Supplemental Table S1). The proportional odds model results in a single odds ratio representing the association of a risk factor with the presence and extent of calcification per location. For continuous risk factors, odds ratios were given per one SD higher of that risk factor. To account for multiple testing, 99% confidence intervals (CI) were calculated around the estimates. Potential confounding was addressed by adjusting for age and sex, and additionally for systolic blood pressure, LDL-c, pack-years of smoking, kidney function, and diabetes mellitus, if not the determinant of interest. Models exploring the association between triglycerides and calcification were additionally adjusted for HDL-c. As more men entered the cohort with existing coronary heart disease (CHD), and more women with cerebrovascular disease, association of sex and calcification was assessed in strata of previous vascular disease; coronary heart disease (N = 408) and cerebrovascular disease (N = 165).

Relation between cardiovascular calcification and recurrent cardiovascular disease

To assess the relation between cardiovascular calcification at the different locations and incident CVD or the combined endpoint of CVD or vascular intervention, Cox proportional hazards regression analyses were performed. Calcium scores of the different locations, CAC, AVC, MAC, and TAC (ascending aorta, aortic arch, and descending aorta separately) were implemented as continuous determinants, as individual variables in separate models, and as individual variables in one model combined. Hazard ratios were given per one SD higher calcium score. Additionally, the relation between the calcium sum score and incident CVD was assessed. Traditional atherosclerotic risk factors; age, sex, systolic blood pressure, LDL-c, pack-years of smoking, kidney function, and diabetes mellitus were included in the models for the combined outcome. Due to the limited number of recurrent CVD specifically (N = 15), only univariable analysis was performed for this outcome.

Model assumptions of the proportional odds, logistic regression, and Cox regression models were assessed (detailed description in supplemental methods) and no violations were observed. Data analyses were performed in R statistical software (version 3.5.1).

3. Results

Baseline characteristics

In total 568 patients, 126 women and 442 men, underwent CT imaging (Table 1). The majority of the patients were previously diagnosed with coronary heart disease (72%). Most of the patients were treated with lipid lowering medication (85%), blood pressure lowering agents (81%), and/or anti-platelet medication (88%).

Table 1
Baseline characteristics of the study population.

Total number of patients	568
Men (%)	442 (78%)
Age (years)*	58 ± 10
Cerebrovascular disease, n (%)	165 (29%)
Coronary heart disease, n (%)	408 (72%)
Peripheral vascular disease, n (%)	29 (5%)
Diabetes Mellitus, n (%)	65 (11%)
Metabolic syndrome, n (%)	274 (48%)
Number of pack-years*	9 (0–24)
Physical examination and laboratory measurements	
Body Mass Index (kg/m^2)*	27 ± 4
Waist circumference (cm)*	96 ± 12
Systolic blood pressure (mmHg)*	129 ± 15
Diastolic blood pressure (mmHg)*	78 ± 9
Pulse pressure (mmHg)*	51 ± 11
Common carotid intima-media thickness (cm)*	0.8 ± 0.2
Triglycerides (mmol/L)*	1.3 (1.0–1.8)
LDL-cholesterol (mmol/L)*	2.3 (1.9–2.9)
HDL-cholesterol (mmol/L)*	1.2 (1.0–1.4)
Hs-CRP (mg/L)*	1.4 (0.7–3.3)
eGFR (CKD-EPI, mL /min/1.73 m^2)*	89 ± 12
Medication	
Lipid lowering medication, n (%)	483 (85%)
Blood pressure lowering agents, n (%)	458 (81%)
Anti-platelet therapy, n (%)	500 (88%)
Anti-coagulants (vitamin K-antagonists), n (%)	37 (7%)

* Data are mean (±standard deviation) or median (interquartile range).

Prevalence of (multifocal) arterial and heart valve calcifications

55 (10%) patients had no calcifications in any of the anatomical locations, whereas 25 (4%) of the patients had calcium depositions in all anatomical locations (coronary arteries, mitral and aortic valve, and thoracic aorta simultaneously) (Supplemental Table S1). CAC was most common, with a prevalence of 83%. Distributions of the calcium sum score are shown in supplemental Figure S2A. Stratification by sex resulted in similar distributions of the calcium sum score in men and women, whereas stratification by age or diabetes mellitus showed higher calcium sum scores in patients with higher age, and patients with diabetes mellitus (Supplemental Figure S2B,C,D). Of the patients with calcification, in 76% (N = 380) calcification was multifocal. Patients with MAC were most likely to have calcification in other locations simultaneously, whereas patients with CAC were least likely to have calcification in other locations (Table 2).

Association between risk factors and calcification

For all of the investigated anatomical locations (coronary arteries, ascending and descending aorta, aortic arch, and heart valves), a higher age (per one SD) was associated with presence and greater extent of calcification (lowest OR 2.17; 99%CI 1.54–3.11 for ascending aorta calcification) (Fig. 1). Except for age, no association was observed between any of the other risk factors and MAC or AVC. Number of pack-years was a determinant of CAC and TAC (OR 1.26; 99%CI 1.02–1.57 for CAC, OR 1.43; 99%CI 1.13–1.81 for ascending aorta calcification, OR 1.81; 99%CI 1.42–2.32 for aortic arch, and OR 1.59; 99%CI 1.25–2.04 for descending aorta calcification). Male sex was associated with CAC (OR 2.66; 99%CI 1.57–4.55). The association with male sex was no longer observed after stratification for type of CVD at baseline. Diabetes mellitus was strongly associated with aortic arch calcification (OR 2.21; 99%CI 1.08–4.58) and descending aorta calcification (OR 3.04; 99%CI 1.43–6.56). Associations with diabetes mellitus and calcification of coronary arteries and heart valves were slightly weaker and not statistically significant. Associations with systolic blood

Table 2
Prevalence of calcification per anatomical location, in groups of patients with CAC, MAC, AVC, and TAC.

Total N = 568	Coronary artery calcification N = 474	Mitral annulus calcification N = 72	Aortic valve calcification N = 276	Thoracic aorta calcification N = 364
Coronary artery calcification N = 474	474 (100%)	67 (93%)	260 (95%)	335 (92%)
Mitral annulus calcification N = 72	67 (14%)	72 (100%)	59 (21%)	66 (18%)
Aortic valve calcification N = 276	260 (56%)	59 (82%)	276 (100%)	231 (64%)
Thoracic aorta calcification N = 364	335 (71%)	66 (92%)	231 (84%)	364 (100%)
No calcification in other locations	96 (20%)	1 (1%)	6 (2%)	18 (5%)

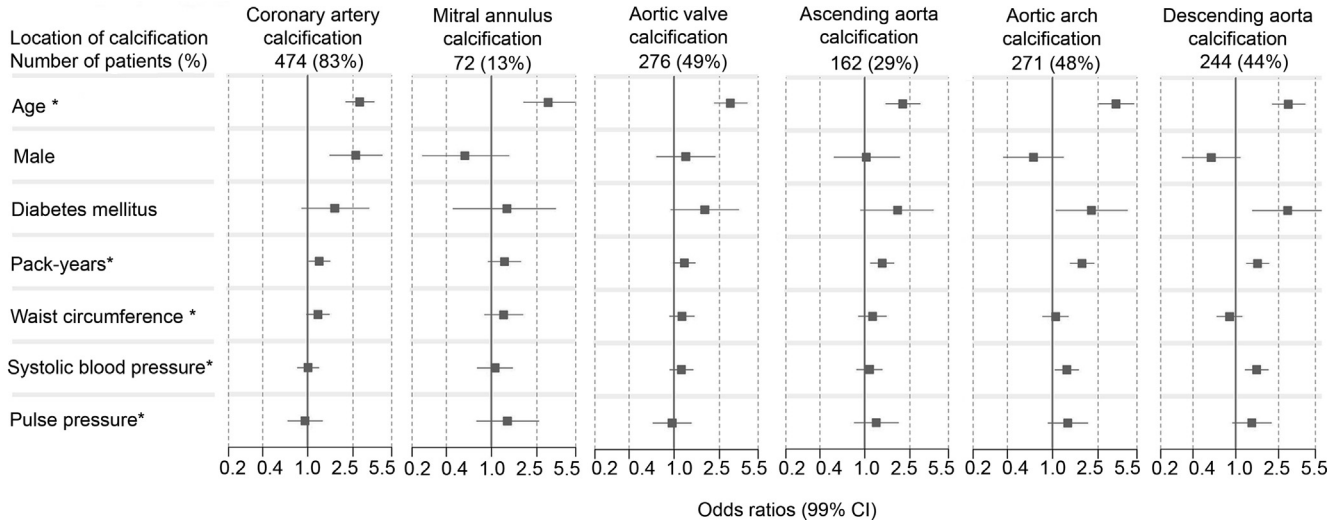

Fig. 1. Associations of risk factors with presence and extent of calcification per anatomical location. Results from ordinal regression and logistic regression for mitral annulus calcification are shown. Models are adjusted for age, sex, pack-years of smoking, systolic blood pressure, LDL cholesterol, kidney function, and diabetes mellitus (if not the determinant of interest). * For continuous variables, odds ratios per one SD are given.

pressure were observed in descending aorta (OR 1.56; 99%CI 1.22–2.01) and aortic arch calcification (OR 1.34; 99%CI 1.05–1.70). No associations were observed with LDL-c, HDL-c, triglycerides, hsCRP, and kidney function (Supplemental Table S3).

Relation between cardiovascular calcification and incident cardiovascular disease and interventions

During a median follow-up time of 2.74 years (IQR 1.55–3.96) 15 recurrent cardiovascular events were observed, of which 6 non-fatal strokes, 7 non-fatal myocardial infarctions, and 2 vascular deaths. Total number of events in the combined endpoint was 68 (5 non-fatal strokes, 6 non-fatal myocardial infarctions, 2 carotid artery interventions, 42 cardiac interventions, 11 peripheral artery interventions, and 2 vascular deaths).

TAC and CAC were related to incident CVD in univariable analysis (highest HR for CAC of 1.51; 95%CI 1.14–1.99) (Supplemental table S4). TAC and CAC were also related to the combined endpoint incident CVD or vascular intervention (Table 3). CAC showed the strongest relation with the combined endpoint (HR 1.35; 95%CI 1.15–1.58). Furthermore, in a model with calcium scores of all the different locations combined, the relation between CAC and the combined endpoint was the only to remain statistically significant (HR 1.39; 95%CI 1.15–1.68 respectively).

Table 3
Relation between cardiovascular calcification and combined endpoint of incident cardiovascular disease or vascular intervention (N = 68).

	Calcium scores in separate models HR (95% CI)	All calcium scores combined in one model HR (95% CI)
Coronary artery calcification	**1.35 (1.15–1.58)**	**1.39 (1.15–1.68)**
Mitral annulus calcification	1.09 (0.90–1.31)	0.79 (0.35–1.80)
Aortic valve calcification	0.91 (0.69–1.19)	1.01 (0.79–1.29)
Ascending aorta calcification	**1.19 (1.06–1.34)**	1.21 (0.96–1.53)
Aortic arch calcification	**1.16 (1.03–1.31)**	1.10 (0.70–1.73)
Descending aorta calcification	**1.15 (1.03–1.28)**	0.87 (0.56–1.37)
Calcium sum score	1.18 (0.84–1.67)	–

All models include age, sex, LDL cholesterol, pack-years of smoking, diabetes mellitus, kidney function, and systolic blood pressure. HR per 1SD higher calcium score are given. HR = hazard ratio. CI = confidence interval.

4. Discussion

Cardiovascular calcification of the coronary arteries, thoracic aorta and heart valves was common (90%) and generally multifocal in patients with established cardiovascular disease. Although cardiovascular calcification was generally multifocal, only a small percentage of patients (4%) showed calcium depositions in all of the locations simultaneously, and 10% had no calcification. Male sex was associated with CAC, whereas diabetes and systolic blood pressure were most strongly associated with TAC. Relation

between calcium scores and incident CVD or vascular intervention was most pronounced for CAC.

Even though cardiovascular calcification is a systemic process, only 4% of the patients had calcifications in all studied anatomical locations, supporting hypotheses of divergence in pathophysiological processes [12]. For valvular calcification, no associations were observed with cardiovascular risk factors other than age, in contrast with arterial calcification. These results suggest that atherosclerotic processes, despite some contribution [6–9], are less prominent in the initiation and progression of valvular calcification, and other pathophysiological pathways might be more influential. Growing evidence supports the role of increased mechanical stress as an important initiator of valvular calcification, by causing endothelial injury as well as accelerated degeneration of collagen and elastin fibers [8,9]. Vascular calcification can be characterized as intimal and medial calcification [10]. In the current study, systolic blood pressure and diabetes were most strongly associated with thoracic aorta calcification, in contrast with coronary artery calcification. Since systolic blood pressure and diabetes mellitus are both predominantly linked to media calcification [10], these results suggest involvement of the tunica media layer in TAC. For blood pressure, the association is presumably two directional; hypertension might induce endothelial damage in the thoracic aorta, influencing atherosclerosis and intimal calcification [22], but more importantly, medial calcification could cause vascular stiffness and a subsequent rise in blood pressure [22]. Hyperglycemia in diabetes stimulates transformation of vascular smooth muscle cells to osteoblast-like cells via multiple pathways, including enhanced expression of osteoblast transcription factors [10,23].

There is debate about whether calcium scores represent a reflection of total plaque burden and that calcification is simply a consequence ('scar tissue') of the atherosclerotic process, or that calcification is causally related to cardiovascular disease [1,11]. For intimal calcification, calcification of plaques might even serve as a stabilizer, preventing acute atherosclerotic events [1]. Regardless of which of these hypotheses is correct, the relation between calcification and incident cardiovascular disease is important for clinical practice. Similar to primary prevention [14,24–26], in the current study coronary artery calcification and thoracic aorta calcification are related to incident CVD or vascular intervention independent of atherosclerotic risk factors. The relation between coronary artery calcification and incident cardiovascular outcomes was most prominent, suggesting that CAC is the strongest predictor of recurrent CVD, and that if CAC is used in risk prediction, calcium scores of other locations might be redundant.

Patient with established cardiovascular disease are considered very high risk by guidelines [27], however, the distribution of predicted 10-year risk of recurrent CVD is widespread [28] and a risk prediction models are available for these patients [29,30]. Although these patients will all require blood pressure and lipid management, accurate risk stratification could aid in clinical decision making regarding more aggressive risk factor treatment by expensive novel drugs, or lifestyle intervention programs [28,30]. Additionally, patients could be more accurately informed about their prognosis and risk of recurrence [30]. Future studies are needed to investigate the potential added prognostic value of CAC and extra-coronary calcification in the prediction of recurrent cardiovascular disease. Calcification can also be assessed by ultrasound [31], and relation with cardiovascular events was observed in primary prevention patients [32,33]. It could be hypothesized that, even though ultrasound gives a semi-quantative score, ultrasound could also be appropriate to assess calcification for risk prediction in patients with established CVD.

This study had several strengths. First, calcification was measured in thoracic arteries, including the aortic arch, and in both heart valves in a specific study population of patients with established cardiovascular disease. Second, follow-up information was available in this prospective cohort study. Potential limitations of the study included the cross-sectional nature with regard to the risk factor analyses. Long-term effects of a determinant on the presence and extent of calcification could not be examined, and causal relations between the investigated risk factors and calcification could not be ascertained. Furthermore, the majority of the included patients with previous clinically manifest CVD used preventive medication, and baseline cholesterol levels and CRP might not reflect previous exposure, resulting in an underestimation of the association. Additionally, as patients were included based on sufficient kidney function due to contrast administration, no conclusions can be formulated regarding associations between low kidney function and cardiovascular calcification. Despite the large sample size of patients with a high prevalence of multifocal calcification, the prevalence and extent of calcification varied between the anatomical locations, leading to varying precision of the estimates. Especially the lower prevalence of aortic valve and mitral annular calcification might have led to more uncertainty compared to the other anatomical locations. Lastly, number of recurrent CVD events was relatively low (N = 15). It could be hypothesized that the relation between calcium scores and CVD is different for incident stroke (N = 5) and myocardial infarction (N = 6) separately, however, too few events were observed for reliable analysis.

To conclude, cardiovascular calcification is generally multifocal in patients with established CVD. Differences in associations between risk factors and calcification at various anatomical locations stress the divergence in pathophysiological pathways. CAC is most strongly related to incident CVD or vascular intervention independent of traditional risk factors, and independent of heart valve and thoracic aorta calcification.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100499.

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