IJC Heart & Vessels 2 (2014) 15–20

Contents lists available at ScienceDirect

IJC Heart & Vessels

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vessels

# Association between heart calcification assessed by echocardiography and future cardiovascular disease mortality and morbidity

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ARTICLE INFO

*Article history:*
Received 2 November 2013
Accepted 18 November 2013
Available online 26 November 2013

*Keywords:*
Aortic valve calcification
Cardiovascular disease
Echocardiography
Mitral annular calcification
Morbidity/mortality

ABSTRACT

*Background:* Echocardiography can detect calcium deposits in heart valves and aortic root, but the relationship of echocardiographic heart calcification such as aortic valve calcification (AVC), mitral annular calcification (MAC), and aortic root calcification (ARC) with future cardiovascular disease (CVD) mortality and morbidity is not fully elucidated.

*Methods:* We analyzed data from 943 patients with suspected coronary heart disease (mean age, 65.7 years; 36% female). Echocardiographic total heart calcification (THC) score was determined by summing up the AVC, MAC, and ARC variables; THC-0 (N = 397), THC-1 (N = 236), THC-2 (N = 224), and THC-3 (N = 86). Subjects were followed for mean 2.9 years to assess the risk of death from CVD causes. Cardiovascular morbidity was defined as new episodes of non-fatal myocardial infarction, congestive heart failure, stroke, and surgical treatment of vascular disease.

*Results:* There were 43 CVD deaths and a total of 160 CVD events. Kaplan–Meier curves showed a graded CVD mortality and morbidity across increasing THC score values. With full adjustment, Cox regression hazard ratios (95% confidence intervals) for CVD mortality and morbidity, using no calcification as reference, for THC-1, THC-2, and THC-3 were 2.21 (1.31–3.74), 2.59 (1.53–4.39) and 4.14 (2.30–7.47), respectively. When THC score was added to models with CVD risk factors, C-statistics were significantly larger for CVD mortality ($p = 0.048$) and for CVD mortality and morbidity ($p = 0.004$).

*Conclusions:* THC score, the sum of the amounts of AVC, MAC, and ARC present as estimated by echocardiography, has an independent and incremental prognostic value in a high-risk population.



## 1. Introduction

Calcium deposits in heart valves, such as aortic valve calcification (AVC) and mitral annular calcification (MAC), have been considered incidental echocardiographic findings with no clinical significance unless they cause significant blood flow obstruction. However, recent data have shown that both AVC and MAC are active and highly regulated processes with histological similarities to atherosclerosis [1]. Several community-based cohort studies have suggested a strong association of AVC and MAC with traditional cardiovascular disease (CVD) risk factors [2,3], and these valvular calcifications are strongly associated with an increased risk of CVD events and death in the general population [4–6]. Similarly, as part of thoracic aortic calcification, the presence of aortic root calcification (ARC) has been independently associated with an increased risk of CVD mortality [7]. Coronary artery calcium is a marker of subclinical coronary atherosclerosis and is an established predictor of future coronary heart disease (CHD) events independent of traditional CVD risk factors [8]. However, information on an association between calcified atherosclerosis in the coronary artery, heart valves, and aortic root is currently limited [9,10], and no large observational studies have examined the relationship of echocardiographic AVC, MAC and ARC with future CVD mortality and morbidity. The aims of this study were to evaluate the associations of AVC, MAC, and ARC with calcified coronary atherosclerosis, and to test the ability of total heart calcification (THC) score determined by echocardiography for the prediction of future CVD mortality and morbidity in a sample of individuals with suspected CHD referred for clinically indicated echocardiography and computed tomography (CT).

## 2. Methods

### 2.1. Study population

The study was performed as an observational longitudinal study of chronic complication in patients with suspected CHD attending the cardiovascular outpatient clinic at Hiroshima University Hospital. We analyzed the data from outpatients suspected to have CHD who attended our clinic and underwent coronary CT angiography during

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http://dx.doi.org/10.1016/j.ijchv.2013.11.007
2214-7632 

the years 2005–2011. Of these, we selected all patients with suspected CHD who had undergone a first echocardiography and CT examination no more than 1 month apart for clinical reasons (chest symptoms, N = 343; asymptomatic with ischemic findings, N = 129; and asymptomatic with multiple CVD risk factors, N = 471) at our institution. Patients with known CHD by previous invasive coronary angiography, prior coronary stenting and/or bypass surgery, advanced malignancies, and with follow-up periods shorter than 1 year were excluded. On the basis of these criteria, 943 patients (603 men and 340 women; mean age, 65.7 ± 11.2 years) suspected to have CHD were identified and included in the final analysis. The study was approved by the hospital's ethics committee, and written informed consent was obtained from all patients.

### 2.2. Risk factor assessment

Overnight fasting blood samples were collected and serum levels of total cholesterol, low-density cholesterol, high-density cholesterol, and triglyceride and hemoglobin A1C level were measured. Hypertension was defined as blood pressure greater than 140/90 mm Hg or current use of hypertensive medication for this condition. Diabetes mellitus was defined as having a fasting plasma glucose level greater than 126 mg/dL or current use of hypoglycemic medication. Dyslipidemia was defined as having a fasting serum total cholesterol level greater than 200 mg/dL or current use of a lipid-lowering medication. Cigarette smoking was considered present if a subject had smoked at least one cigarette per day in the last year. A family history of early CHD was considered present if a patient's immediate family had had non-fatal myocardial infarction, coronary revascularization, or a fatal cardiovascular event before the age of 55. Glomerular filtration rate (eGFR) was estimated from the four-variable Modification of Diet in Renal Disease study equation.

### 2.3. Echocardiography and CT imaging

Complete echocardiographic studies of all patients were performed at our institution with a commercially available system (Vivid 7, GE Healthcare, Milwaukee, WI; or iE33, Philips Medical Systems, Andover, MA) by four experienced sonographers who were blinded to the clinical and CT information. Apical 4- and 2-chamber views were acquired for calculation of left ventricular ejection fraction and left atrial volume using the modified Simpson's formula [11]. Left ventricular mass was calculated using the area–length method and indexed to body surface area. AVC was defined as focal or diffused calcification and thickening of the aortic leaflets/annulus with or without restriction of leaflet motion using the criteria of Otto et al. [6] (Fig. 1A). MAC was defined by increased echogenicity located at the junction of the atrioventricular groove and posterior mitral leaflet on the parasternal long-axis, short-axis, or apical 4-chamber view [12] (Fig. 1B). ARC was defined as a focal area of increased echogenicity and thickening in the aortic root on the parasternal long-axis view [13] (Fig. 1C). In accord with a previous study, we calculated a THC score that was graded from 0 to a maximum of 3 according to the number of anatomic sites involved; namely, at the aortic valve, the mitral annulus, and/or the aortic root [13].

CT examinations were performed using a 64-multidetector CT scanner (LightSpeed VCT, GE Healthcare). Prospective electrocardiogram-triggered scans were performed from the root of aorta to the apex of the heart with the following parameters: axial scan; gantry rotation times, 350 ms; X-ray exposure times, 233 ms; tube voltage, 120 kV; tube currents, 140 mA; center of imaging window, 75% of R-R. Thirty-five to 40 contiguous images of 2.5-mm thickness were obtained. Coronary artery calcium score was calculated based on the Agatston method with dedicated software (Smartscore, version 3.5, GE Healthcare) [14]. In addition, we used non-contrast CT datasets to score AVC, MAC, and ARC with the same software.

### 2.4. Study outcomes

Subjects were followed for a mean duration of 2.9 years (range 1.0–7.4 years). Patient information was obtained from medical records or telephone interviews with patients or their families. Ascertainment of CVD events was conducted by persons who were unaware of the baseline data and echocardiographic results. The primary outcome for the present study was the occurrence of incident CVD events [6], including death from CVD causes and CVD morbidity defined as new episodes of non-fatal myocardial infarction, unstable angina pectoris, congestive heart failure, stroke, and surgical treatment of vascular or valvular disease. Coronary revascularization was not included in CVD events.

### 2.5. Statistical analysis

Continuous variables are presented as mean ± SD or median (interquartile range). Group comparisons of continuous variables were performed by 1-way analysis of variance with post-hoc analysis using the Tukey's method. Multivariate logistic analyses included valvular and aortic root calcification and were adjusted for age, gender, eGFR, body mass index, and the traditional CVD risk factors. Event rates were estimated by Kaplan–Meier curves and compared by log-rank tests stratified by the presence of AVC, MAC, and ARC or THC scores. The Cox proportional hazard model was used to calculate univariate and multivariate hazard ratios (HRs) for the occurrence of incident CVD mortality and morbidity. The independent predictive values of the presence of AVC, MAC, and ARC or THC score were assessed in the following hierarchical models: model 1, unadjusted; model 2, adjusted for age and gender; model 3, model 2 plus eGFR and the traditional CVD risk factors; and model 4, model 2 plus left ventricular ejection fraction < 50%, left atrial volume, and left ventricular mass index determined by echocardiography. In addition, we used natural log-transformed AVC, MAC, ARC, and coronary artery calcium scores for the analyses in which the quantity of calcium was used. Receiver operating characteristic analyses were conducted from logistic regression models and the probability values were compared between different models using the method described by DeLong et al. [15]. All statistical analyses were performed using SPSS software (version 16.0: SPSS Inc., Chicago, IL). A probability value of $<0.05$ was considered significant.

## 3. Results

### 3.1. Baseline characteristics

There were 441 subjects (46.8%) with AVC, 145 (15.4%) with MAC, and 344 (36.5%) with ARC. Overall, 397 patients (42.1%) were free of any calcification at the valve and aortic root levels (*i.e.*, THC-0), 236 patients (25.0%) had isolated AVC, isolated MAC, or isolated ARC (*i.e.*, THC-1), and 224 patients (23.8%) had the combined presence of calcium deposits in any two areas (*i.e.*, THC-2). The remaining 86 patients (9.1%) had the combined presence of calcium deposits in all three areas (*i.e.*, THC-3). Table 1 summarizes baseline clinical characteristics, echocardiographic measurements, and CT findings stratified by THC scores. Left ventricular ejection fraction was preserved in all groups, but the THC-3 group had larger left atrial volume and higher left ventricular mass, indicating impairment of diastolic function.

### 3.2. Relationship between coronary artery calcium and AVC, MAC, and ARC

As shown in Table 1, coronary artery calcium score escalated in proportion with THC scores (all $p < 0.001$ by ANOVA). Overall, the age- and gender-adjusted Pearson's correlation coefficient between AVC and coronary artery calcium score was 0.33 ($p < 0.001$). Similarly, the amount of MAC and ARC was fairly correlated with coronary artery calcium score ($r = 0.18$, $p < 0.001$; $r = 0.42$, $p < 0.001$, respectively). With adjustment for age, gender, CVD risk factors, and the presence of calcium

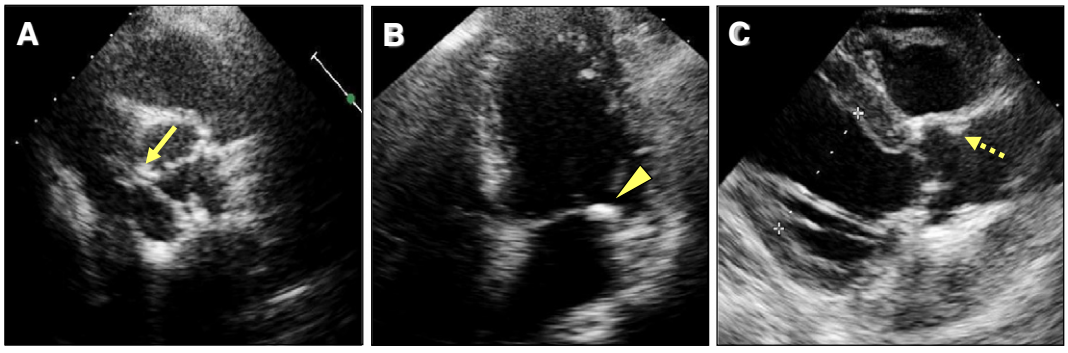


**Fig. 1.** Examples of determining the THC score. Two-dimensional echocardiographic images show aortic valve calcification (A, solid arrow), mitral annular calcification (B, arrowhead), and aortic root calcification (C, broken arrow). THC score was determined by summing these extracoronary calcifications. It was calculated to be 3.