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Original article

# An increase in the coronary calcification score is associated with an increased risk of heart failure in patients without a history of coronary artery disease

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ABSTRACT

*Background:* The presence of coronary artery calcification (CAC) and its severity predict future cardiovascular events and is used for risk stratification. However, the association of CAC with heart failure (HF) in patients without a history of coronary artery disease (CAD) remains unclear. This study aimed to determine the correlations of CAC with N-terminal pro-B-type natriuretic peptide (NT-proBNP) and HF events in patients without a history of CAD or HF.

*Methods:* From June 2010 to June 2013, a total of 487 patients without a history of CAD and HF were enrolled. All of the patients underwent plane multi-detector computed tomography. They were divided into four categories according to CAC scores: ≤10, 11–100, 101–400, and ≥401.

*Results:* The proportion of patients with high NT-proBNP levels increased with CAC categories ($p < 0.0001$). The CAC score was associated with NT-proBNP levels ≥400 pg/ml, with an odds ratio of 2.901 (95% confidence interval: 1.368–6.151, $p = 0.0055$) for CAC scores ≥401 compared with CAC scores of 0–10 after adjustment for confounding factors. During the follow-up period of 497 ± 315 days, nine patients were admitted for HF. Kaplan–Meier analysis showed that patients with CAC scores ≥401 had a lower rate of freedom from admission for HF with cumulative incidences of 0.4%, 1%, 2%, and 8% for CAC scores of 0–10, 11–100, 101–400, and ≥401, respectively ($p < 0.0001$). Increasing CAC scores were associated with an increase in incidence of admission for HF, with a hazard ratio of 10.371 for CAC scores ≥401 (95% CI: 1.062–101.309, $p = 0.0443$) compared with CAC scores of 0–10 after adjustment for risk factors.

*Conclusion:* Severe CAC is an independent determinant of high NT-proBNP levels and a predictor of admission for HF in a population without a history of CAD or HF.



## Introduction

Heart failure (HF) is associated with reduced life expectancy and ever increasing costs. Therefore, HF is one of the most important health concerns in the industrialized world [1]. Although the survival rate of patients with HF has improved over the past few decades, its prevalence and incidence have been steadily increasing. Early prediction of patients at high risk for HF is important for preventing the progression of HF. Traditional risk assessment for coronary artery disease (CAD) using coronary risk factors has been refined with the selective use of coronary artery calcium (CAC). This is possible because CAC is pathognomonic of atherosclerosis [2], and a histological study showed its close correlation with the atherosclerotic plaque burden [3,4]. The severity of CAC can be easily quantified by electron beam computed tomography (CT) or multi-detector CT (MDCT). CAC is currently a useful marker of subclinical CAD and an independent predictor of cardiovascular events [5]. CAD is a risk factor for HF, but information on the association of CAC scores with HF is still lacking. In a population-based study, Kalsch et al. demonstrated

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that CAC was higher in patients with HF than in those without HF [6]. Leening et al. showed that the extent of CAC has a clear association with the risk for development of HF in elderly patients [7].

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), both of which are increased in relation to cardiac stretch, are associated with the severity and prognosis of left ventricular (LV) dysfunction and HF [8]. NT-proBNP has been shown to independently predict all-cause mortality and cardiovascular events. NT-proBNP has emerged as a useful biomarker for guiding diagnosis, prognosis, and management in patients with cardiovascular disease and HF [9]. Recently, the Japanese Heart Failure Society statement indicated that close examinations by specialized physicians are needed in patients with NT-proBNP levels ≥400 pg/ml (Japanese Heart Failure Society statement 2013) [10]. In this study, we investigated the correlation of CAC with NT-proBNP levels in patients without a history of CAD or HF. Additionally, we followed HF events after measurement of CAC to establish the effect of CAC on the development of HF events.

## Methods

### *Selection of patients*

From June 2010 to June 2013, a total of 692 patients who visited our hospital and were suspected of having CAD were examined. Among them, we excluded 103 patients who were <40 years old and those with congestive heart failure, acute coronary syndrome, a history of HF, or a history of CAD defined as prior myocardial infarction (MI) or coronary intervention (percutaneous coronary intervention and coronary artery bypass grafting). The other 589 patients underwent MDCT just for measurement of CAC. Of these, 254 patients with positive exercise test results, or symptoms that were likely to be related to myocardial ischemia, or CAC scores ≥401 were recommended for further examinations, including stress single-photon emission computed tomography (SPECT) or an invasive coronary angiogram, because of suspected CAD. Ten patients who rejected further examinations were excluded. A total of 244 patients underwent stress SPECT or coronary angiogram, and 80 patients with findings of myocardial ischemia in stress SPECT or who had significant coronary artery stenosis in a coronary angiogram were excluded from this study. Another 164 patients who had no significant coronary artery stenosis in a coronary angiogram ($n$ = 98), or had no findings of myocardial ischemia in stress SPECT ($n$ = 66) were enrolled in the analysis. Patients with an estimated glomerular filtration rate (eGFR) of <15 ml/min/1.73 $m^2$, severe valvular heart disease, an advanced stage of malignancy, or dysthyroidism ($n$ = 12) were also excluded. Finally, a total of 487 patients were included in the analysis.

### *Study protocol*

All of the patients underwent blood sampling, including measurement of NT-proBNP levels, measurement of CAC scores, and an echocardiographic examination. NT-proBNP levels were measured using the commercially available Elecsys proBNP sandwich immunoassay using an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The study protocol was approved by the appropriate institutional review board of the hospital and all of the participants provided written informed consent.

### *Measurement of the CAC score*

CAC in epicardial coronary arteries was assessed. CT scanning of the coronary artery was performed using a 64-slice multidetector system (Aquilion 64, Toshiba, Tokyo, Japan). Images were acquired in 3.0-mm slices throughout coronary artery regions using a prospectively electrocardiogram-triggered scan acquisition at 75% of the RR intervals. CAC scores were calculated using an automated computer system (Ziostation System 1000, Ziosoft, Tokyo, Japan) by the Agatston method [11].

### *Analysis of echocardiographic data*

Standard imaging was performed in the left lateral decubitus position using a commercially available system. Left atrial diameter, end-diastolic interventricular septal and posterior wall thicknesses, and end-diastolic and end-systolic LV internal dimensions were determined according to the recommendations of the American Society of Echocardiography [12]. LV mass was calculated from LV linear dimensions and was expressed as a ratio to body surface area (LVMI). LV hypertrophy was defined by LVMI thresholds of 115 g/$m^2$ for men and 95 g/$m^2$ for women [12]. LV end-diastolic and end-systolic volumes were measured from an apical four-chamber view and were indexed to body surface area. The LV ejection fraction (LVEF) was calculated according to the modified Simpson's rule. Mitral inflow was assessed by pulsed-wave Doppler echocardiography from the apical four-chamber view. On the basis of the mitral inflow profile, E- and A-wave velocities, deceleration time of the E-wave, and the E/A ratio were determined. Tissue Doppler imaging of the mitral annulus was performed from the apical four-chamber view. A sample volume was placed sequentially at the septal mitral annulus, and early diastolic velocity ($e'$) was measured. The ratio of mitral velocity to early diastolic velocity of the medial mitral annulus ($E/e'$), which is a marker of LV diastolic filling pressure, was calculated.

### *Measurement of brachial-ankle pulse wave velocity*

Brachial-ankle pulse wave velocity (baPWV) was measured using an automatic waveform analyzer (BP-203RPEII; Omron Colin, Tokyo, Japan) just before an echocardiogram. Subjects were examined in the supine position after 5 min of bed rest.

### *Follow-up study*

The incidence of HF events, defined as admission due to HF, was followed after measurement of CAC scores. HF was defined by modified Framingham criteria as follows: satisfaction of ≥two major criteria (paroxysmal nocturnal dyspnea, orthopnea, rales, jugular venous distension, third heart sound, and radiological signs of pulmonary congestion and/or cardiomegaly) or of one major criterion together with ≥two minor criteria (effort dyspnea, peripheral edema, hepatomegaly, and pleural effusion). Diagnosis of HF was made by a cardiologist or an internist.

### *Statistical analysis*

Patients were divided into four categories based on CAC scores: ≤10, 11–100, 101–400, and ≥401 [5]. Comparison of continuous variables among groups was performed by one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Categorical data were compared by chi-square analysis. Patients were also classified into four groups according to NT-proBNP levels as described in the Japanese Heart Failure Society statement 2013: <125 pg/ml, ≥125 and <400 pg/ml, ≥400 and <900 pg/ml, and ≥900 pg/ml [10]. Univariate and multivariate logistic regression analyses were performed to determine which of the following factors were associated with NT-proBNP levels ≥400 pg/ml: age, sex, and the prevalence of hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease (CKD), which was defined as an eGFR <60 ml/min/1.73 $m^2$, LV systolic dysfunction, which