

Prognostic Values of Coronary Artery Calcium Score and ^{123}I -BMIPP SPECT In Patients With Non-Ischemic Heart Failure With Preserved Ejection Fraction

Hideobu Hashimoto (✉ hideobu.hashimoto@med.toho-u.ac.jp)

Toho University Faculty of Medicine <https://orcid.org/0000-0003-2656-3445>

Rine Nakanishi

Toho University Faculty of Medicine

Sunao Mizumura

Toho University Faculty of Medicine

Yukiko Hashimoto

Toho University Faculty of Medicine

Yuriko Okamura

Toho University Faculty of Medicine

Kyoko Ota

Toho University Faculty of Medicine

Junichi Yamazaki

Toho University Faculty of Medicine

Takanori Ikeda

Toho University Faculty of Medicine

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Abstract

Purpose

This study aimed to determine whether coronary artery calcium score (CACS) can be a prognostic indicator for the development of major adverse cardiac events (MACEs) and compare the value of CACS with that of the ^{123}I -betamethyl-p-iodophenyl-pentadecanoic acid (^{123}I -BMIPP) defect score (BDS) in patients with non-ischemic heart failure with preserved ejection fraction (NIHFpEF).

Methods

Among 643 consecutive patients hospitalized due to acute heart failure, 108 ($74 \pm 13\text{y}$) were identified to have NIHFpEF on non-contrast regular chest computed tomography and ^{123}I -BMIPP single-photon emission computed tomography (SPECT). We evaluated whether CACS and BDS were associated with MACEs using multivariate Cox models.

Results

Thirty-two MACEs developed at a mean follow-up period of 2.4 years. Higher CACS (hazard ratio [HR] 2.27, 95% confidence interval [CI] 1.10–4.67) and higher BDS (HR 22.14, 95% CI 7.95–61.60) were significantly associated with the development of MACEs. Patients showing higher CACS and BDS carried a significantly higher risk for developing MACE (HR 23.65, 95% CI 10.33–54.13, $p < 0.001$).

Conclusion

CACS, as well as BDS, could serve as potential prognostic indicators in patients with NIHFpEF.

Introduction

One in nine people die of heart failure (HF), and half the patients diagnosed as having HF die within 5 years [1]. Approximately half the patients with HF have preserved ejection fraction (HFpEF) [2]. Although considerable research efforts and funds have been devoted to improve mortality and reduce hospitalization, there has been no evidence-based treatment developed, to date, in patients with HFpEF [3].

The coronary artery calcium score (CACS), calculated using non-contrast regular chest computed tomography (CT), has recently been recognized as a prognostic marker for the assessment of cardiovascular event risk among asymptomatic patients [4]. The most common cause of HFpEF is diastolic HF, and the primary cause of diastolic HF is hypertensive heart disease [5]. Experimental and clinical data have demonstrated serological and morphometric evidence of increased myocardial fibrosis

in patients with hypertensive heart disease [6, 7]. Therefore, HFpEF could be related to the progression of arteriosclerosis. However, the prognostic utility of CACS in patients with non-ischemic HFpEF (NIHFpEF) has not been well examined. On the other hand, ^{123}I -betamethyl-p-iodophenyl-pentadecanoic acid single-photon emission computed tomography (^{123}I -BMIPP SPECT) plays an important role in the assessment of cardiovascular event risk in patients with coronary artery disease [8]. Although, in the clinical setting, the relationship between ^{123}I -BMIPP defect score (BDS) and CACS of the patients with NIHFpEF, and clinical importance of them were unclear. Our previous study showed that ^{123}I -BMIPP SPECT could be a useful modality for identifying high-risk patients with NIHFpEF [9]. In the present study, we aimed to investigate whether CACS is associated with the occurrence of major cardiac events (MACEs) and to compare the prognostic value of CACS with that of BDS in patients with NIHFpEF.

Methods

Patient population

Among 643 consecutive patients who were admitted to our hospital for congestive HF and underwent non-contrast regular chest CT to evaluate the presence of complication of pneumonia or quantity of pulmonary congestion and pleural effusion, ^{123}I -BMIPP SPECT imaging to evaluate the presence of ischemic myocardial injury, echocardiography, and coronary artery angiography within 60 days between January 2010 and January 2014. We finally enrolled 108 patients with no obstructive coronary artery disease (<50% stenosis) on coronary artery angiography and had preserved ejection fraction ($\geq 50\%$) on echocardiography (Fig. 1). The patients' clinical characteristics, including age, sex, coronary risk factors, blood biochemical data, echocardiography data, and medications were assessed. The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived (M20136). This study was performed in accordance with the ethical standards of the Declaration of Helsinki.

Invasive coronary angiography

Invasive coronary angiography was performed for all participants. According to the American College of Cardiology/American Heart Association guidelines [10], quantitative coronary angiography was performed by experienced interventionalists. Coronary stenosis was defined as >50% diameter stenosis on invasive coronary angiography.

Echocardiographic imaging

Echocardiography from the parasternal window was performed to evaluate left ventricular function (Vivid E9 device, GE Vingmed, Horten, Norway). The Teichholz formula was used to calculate the left ventricular ejection fraction (LVEF) [11]. A LVEF >50% was defined as a preserved EF.

Non-contrast non-cardiac chest CT

Baseline CT scans were conducted with a 64-slice multidetector CT scanner (SOMATOM Definition Flash, Siemens, Munich, Germany). The scanning protocol consisted of the following parameters were applied: 28mm × 0.6 mm beam collimation, pitch 1.2, caudocranial scan direction, and smallest field of view to include the outer rib margins. No electrocardiographic triggering was performed, and no contrast agent was administered. Exposure settings were applied based on body weight: 125mAs at a tube voltage of 120 kVp.

All scans were reconstructed as 5.0 mm thick slices with an increment of 5.0 mm. Coronary artery calcium measurements were performed on a workstation (SYNAPSE VINCENT; FUJIFILM Medical Co., Ltd, Tokyo, Japan), and CACS was calculated using the Agatston scoring method [12].

¹²³I-BMIPP imaging

¹²³I-BMIPP (111MBq) was injected with the patients at rest. Twenty minutes later, ¹²³I-BMIPP SPECT was performed over 360° in 72 steps of 37.5 s each in a 64 × 64 matrix, using a triple-head gamma camera (Prism IRIX; Philips, Amsterdam, Netherlands) equipped with low-energy general-purpose collimators. A Butterworth filter (order 8.0, cutoff value 0.25-0.30 cycle/pixel) and filtered back projection were used to process and reconstruct the images, respectively.

BDS was calculated according to a previously reported method [9], using an automated program for myocardial SPECT (Heart Risk View-S software; Nihon Medi-Physics Co Ltd, Tokyo, Japan). A hybrid 2-part sampling method [13], i.e., an algorithm for generating a polar map, was used to generate count profiles from a 3-dimensional sampling scheme of short-axis slices by operating in a 3-dimensional space and using short axis images. Then, polar maps were generated from ¹²³I-BMIPP SPECT data divided into 17 segments to calculate the mean count in each segment, as recommended by the American Society of Nuclear Cardiology guidelines [14]. The mean counts in these segments were compared with references from the ¹²³I-BMIPP database for Japanese patients which was developed by the Japanese Society of Nuclear Medicine working group [15]. The mean % uptake in each segment was derived and converted to scores using a five-point grading system (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, absent). The BDS value in each segment was summed to obtain the total defect score in each patient.

Assessment of clinical outcomes

The endpoints were the development of MACEs (HF-related death, acute myocardial infarction, lethal ventricular arrhythmias, and other cardiac disorders), cardiovascular events (acute myocardial infarction and unstable angina), and severe HF requiring hospitalization. The diagnosis of acute myocardial infarction and unstable angina was based on standard laboratory findings, electrocardiograms, or examination criteria. Dyspnea, associated with pulmonary edema or congestion on chest radiograph, that required hospitalization was defined as HF exacerbation. The first event was included in the counting of clinical outcomes during the follow-up period. The event data were retrospectively gathered from the patients' records, including in-hospital or out-of-hospital reports.

Statistical analysis

Data are expressed as average \pm standard deviation of continuous variables. Continuous variables in patients with and without events were compared using the Mann-Whitney U test, and categorical data were analyzed using the chi-square test. To evaluate the clinical importance of CACS and BDS, all patients were divided into two groups based on their CACS values and BDS values. Each cutoff value was determined using the area under the curve (AUC) from a receiver operating characteristic (ROC) analysis based on MACE occurrences. The proportion of event-free patients was estimated using the Kaplan-Meier method and compared between each of the high and low CACS and BDS groups by using the log-rank test. Variables with a significance level of P-value < 0.05 in the univariate COX regression analysis were included in multivariate Cox regression models to determine whether the future occurrence of MACEs was associated with the parameters of echocardiographic imaging, CACS, or BDS. A P-value of < 0.05 was considered statistically significant. All statistical analyses were performed using StatMate V software version 5.01 (Advanced Technology for Medicine and Science, Tokyo, Japan).

Results

The patients' characteristics, including coronary risk factors, New York Heart Association (NYHA) class, etiology of HF, B-type natriuretic peptide (BNP), LVEF calculated using echocardiography, CACS calculated using non-contrast non-cardiac chest CT, and BDS calculated using ^{123}I -BMIPP SPECT are presented in Table 1. The mean age of the 108 patients was 74 ± 13 years, and 63 (58%) of them were men. Tachycardia-induced cardiomyopathy was the most common complication ($n = 22$, 20%). The other complications were valvular heart disease ($n = 20$), hypertensive heart disease ($n = 19$), atrioventricular block ($n = 10$), sick sinus syndrome ($n = 7$), dilated cardiomyopathy ($n = 5$), hypertrophic cardiomyopathy ($n = 5$), myocarditis ($n = 3$), pulmonary hypertension ($n = 3$), infective endocarditis ($n = 2$), and pulmonary thromboembolism ($n = 2$), respectively.

Table 1
Patients characteristics of all participants with or without MACEs

	Total (n = 108, %)	MACE (n = 32, %)	No MACE (n = 76, %)	P value
Age (years)	74 ± 13	76 ± 11	73 ± 14	0.455
Male	63 (58)	18 (56)	45 (59)	0.831
Obesity (BMI > 25kg/m ²)	20 (19)	6 (19)	14 (18)	0.786
Diabetes mellitus	27 (25)	7 (22)	20 (26)	0.626
Hypertension	76 (70)	25 (78)	51 (67)	0.356
Dyslipidemia	36 (33)	12 (38)	24 (32)	0.655
Current smoking	63 (58)	19 (59)	44 (58)	0.831
CKD (eGFR < 60mL/min/1.73m ²)	59 (55)	20 (63)	39 (51)	0.290
NYHA I/II/III/IV	24/27/30/27	5/7/9/11	19/20/21/16	0.184
BNP	710 ± 716	938 ± 929	613 ± 586	0.045
Complications				
Tachycardia-induced cardiomyopathy	22 (20)	5 (16)	17 (22)	0.433
Valvular heart disease	20 (19)	9 (28)	11 (14)	0.104
Hypertensive heart disease	19 (18)	7 (22)	12 (16)	0.580
Dilated cardiomyopathy	5 (5)	2 (6)	3 (4)	0.616
Hypertrophic cardiomyopathy	5 (5)	0 (0)	5 (7)	0.316
Echocardiography				
LVEF (%)	64.9 ± 9.5	63.5 ± 8.4	65.5 ± 9.9	0.451
LAD (cm)	4.0 ± 0.1	4.5 ± 1.1	3.9 ± 0.9	0.010
LVEDVI (ml/m ²)	83.3 ± 32.0	91.8 ± 27.5	79.7 ± 33.2	0.039
LVMI (g/m ²)	122.2 ± 40.1	130.5 ± 32.2	118.7 ± 42.7	0.047

MACEs = major adverse cardiac events; BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; BNP = B-type natriuretic peptide; LVEF = left ventricular ejection fraction; LAD = left atrium dimension; LVEDVI = left ventricular end-diastolic volume index; LVMI = left ventricular wall mass index; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CT = computed tomography; CACS = coronary artery calcium score; ¹²³I-BMIPP SPECT = ¹²³I-betamethyl-p-iodophenyl-pentadecanoic acid single-photon emission computed tomography; BDS = ¹²³I-BMIPP defect score.

	Total (n = 108, %)	MACE (n = 32, %)	No MACE (n = 76, %)	P value
Medications				
β-blockers	62 (61)	20 (63)	42 (55)	0.487
Calcium blockers	46 (43)	14 (44)	32 (42)	0.875
ACEI, ARB	67 (62)	19 (59)	48 (63)	0.711
Antiplatelet drugs	20 (19)	9 (28)	11 (14)	0.095
Anticoagulation drugs	36 (33)	13 (41)	23 (30)	0.297
Statins	25 (23)	5 (16)	20 (26)	0.229
Non gated chest CT				
CACS	300.3 ± 649.4	406.8 ± 776.0	255.5 ± 594.2	0.004
¹²³ I-BMIPP SPECT				
BDS	3.5 ± 3.3	5.9 ± 3.3	2.4 ± 2.8	< 0.001
<p>MACEs = major adverse cardiac events; BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; BNP = B-type natriuretic peptide; LVEF = left ventricular ejection fraction; LAD = left atrium dimension; LVEDVI = left ventricular end-diastolic volume index; LVMI = left ventricular wall mass index; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CT = computed tomography; CACS = coronary artery calcium score; ¹²³I-BMIPP SPECT = ¹²³I-betamethyl-p-iodophenyl-pentadecanoic acid single-photon emission computed tomography; BDS = ¹²³I-BMIPP defect score.</p>				

Overall, 32 patients (30%) experienced MACEs during 2.4 ± 1.6 years of median follow-up. Cardiac deaths occurred in four patients (acute myocardial infarction in two patients, deterioration of HF in two patients), non-fatal acute myocardial infarction in one patient, and severe HF requiring hospitalization in 27 patients, respectively. Table 1 shows that BNP, left atrial dimension (LAD), left ventricular end-diastolic volume index (LVEDVI), left ventricular mass index (LVMI), CACS, and BDS were significantly higher in patients with MACEs. From the ROC analysis, the cutoff value for high BDS was 4 (AUC = 0.87), the cutoff value for high CACS was 68 (AUC = 0.69). Then, we determined the score of 100 was the cutoff value of CACS, since the score of 100 was commonly used for the risk stratification of coronary heart disease [16]. Of the 32 incidents of events, 17 cases occurred in the high CACS group. The proportion of patients who experienced MACEs was significantly higher in the high CACS group than in the low CACS group (Fig. 2). Of the 32 incidents of events, 26 cases occurred in the high BDS group. The proportion of patients who experienced MACEs was significantly higher in the high BDS group than in the low BDS group (Fig. 3). The Kaplan-Meier curves for MACEs in the combined groups of CACS and BDS are shown in Fig. 4. The proportion of patients who experienced MACEs was significantly higher in the high CACS and high BDS group than in the low CACS and low BDS group (7% vs. 78%, $P < 0.001$). In univariate analysis using categorical variables, BNP, CACS, and BDS were found to be the significant factors for MACEs (Table 2).

CACS and BDS were determined to be the significant prognostic factors of MACEs in each multivariate analysis model after adjusting for age, sex, and BNP (Table 3, models 1–3). In the multivariate Cox proportional model, the MACEs risk was significantly the highest in the high CACS and high BDS group (Table 3, model 4).

Table 2
Univariate Cox regression analysis for occurrence of MACEs

Univariate analysis		
	HR (CI)	P value
Age (≥ 75)	1.160 (0.579–2.325)	0.675
Male	0.990 (0.491–1.993)	0.977
BNP (≥ 600)	2.179 (1.061–4.475)	0.034
LAD ($> 4\text{cm}$)	1.752 (0.855–3.590)	0.126
LVEDVI (> 75)	1.351 (0.660–2.764)	0.410
LVMI (> 120)	1.939 (0.956–3.934)	0.066
CACS (≥ 100)	2.463 (1.222–4.966)	0.012
BDS (≥ 4)	17.995 (6.662–48.606)	< 0.001
HR = hazard ratio; CI = confidence interval; other abbreviations as Table 1.		

Table 3
Multivariate Cox regression analysis for occurrence of MACEs

Multivariate analysis		
	HR (CI)	P value
Model 1: echocardiographic imaging		
LAD (> 4cm)	1.752 (0.854–3.596)	0.126
LVEDVI (> 75)	1.407 (0.678–2.923)	0.360
LVMi (> 120)	1.980 (0.972–4.032)	0.060
Model 2: ¹²³I-BMIPP scintigraphy		
BDS (≥ 4)	22.135 (7.954–61.596)	< 0.001
Model 3: Non gated chest CT scan		
CACS (≥ 100)	2.271 (1.104–4.672)	0.026
Model 4		
Low CACS, Low BDS group	1 (ref)	-
High CACS, Low BDS group	2.644 (0.572–12.228)	0.389
Low CACS, High BDS group	12.078 (4.555–32.024)	< 0.001
High CACS, High BDS group	23.646 (10.330–54.128)	< 0.001
Abbreviations as in Table 1, 2. Model 1–3 adjusted for age, sex and BNP.		

Case presentations

Figure 5 shows a typical patient in the high CACS and high BDS group. This 72-year-old man had HF due to hypertensive heart disease (NYHA: class II, Nohria-Stevenson classification: wet and warm). He had a history of hypertension, diabetes mellitus, and hyperlipidemia. He also had a smoking habit. He underwent non-contrast non-cardiac chest CT for HF evaluation, and ¹²³I-BMIPP SPECT, coronary artery angiography, and echocardiography owing to a suspicion of coronary heart disease. He had no coronary artery disease on coronary artery angiography, and his LVEF was 56% on echocardiography. His CACS was 1150.4, and his BDS was 7. In this case, the patient was admitted to the hospital because of HF deterioration at 210 days after non-contrast non-cardiac chest CT.

Discussion

The findings of the present study demonstrated that CACS calculated using non-contrast regular chest CT was associated with an increase in MACEs and ¹²³I-BMIPP SPECT findings, and that the evaluation of

CACS in addition to BDS had a predictive value for the identification of future MACEs in patients with NIHFpEF.

HFpEF

As patients with HFpEF are in a high-risk situation, it is essential that future cardiac risk be predicted using non-invasive imaging modalities. Echocardiography [17] and cardiac magnetic resonance imaging [18] have been shown to be useful in determining the outcomes of patients with HFpEF. In general, left ventricular diastolic dysfunction is recognized as a major pathophysiological abnormality [19].

Mechanisms underlying the development of HFpEF include endothelial dysfunction, myocardial hypertrophy, and myocardial fibrosis [20]. Endothelial dysfunction is reported to play an important role in the initial stage of atherosclerosis development [21, 22]. Atherosclerosis has been shown to be involved in the development of hypertension, accumulation of extracellular matrix material, and fibrosis within myocardial tissue [23]. More specifically, endothelial dysfunction initially causes atherosclerosis, leading to the development of hypertension, increase of extracellular matrix material, and fibrosis within myocardial tissue, which in turn results in left ventricular diastolic dysfunction. The present study demonstrated the potential of CACS to reflect the status of atherosclerosis, similar to a previous study which showed that BDS has the potential for reflecting the amount of extracellular matrix material and fibrosis within the myocardial tissue [9].

Non-contrast non-cardiac chest CT

The prognostic value of CACS calculated using cardiac CT has been evident across various population groups [24, 25]. Previous reports have shown that CACS by using non-contrast non-cardiac chest CT is a valid modality for determining CACS with an accuracy of up to 90%, compared with dedicated cardiac CT [26]. Hughes-Austin JM et al. reported that the CACS calculated using non-contrast non-cardiac chest CT is highly correlated with the CACS calculated using cardiac CT, and that the two scores are similarly associated with the mortality risk [27]. While the prognostic potential of CACS calculated using non-contrast non-cardiac chest CT in patients with HFpEF remains unexplored, this is the first study on the relationship between the prognostic value of CACS calculated using non-contrast non-cardiac chest CT and NIHFpEF. Our findings suggest that the evaluation of atherosclerosis could predict the grade of LV diastolic dysfunction and that could be able to predict the prognosis of HFpEF excepting for predicting of ischemic heart disease.

Prognostic value of CACS in addition to BDS in patients with NIHFpEF

In the current study, NIHFpEF patients in the high CACS and high BDS group showed the most significant association with cardiac events based on multivariate analysis. On the Basis of the mechanism of LV diastolic dysfunction development from endothelial dysfunction, BDS reflects early prognosis compared with CACS. The results shown in Fig. 2, 3, and 4 do not contradict this mechanism.

In the present study, high CACS and high BDS were associated with poor prognosis of cardiac events. The results suggest that BDS evaluation in addition to CACS evaluation enables early risk stratification in patients with NIHFpEF.

Study limitations

There are several limitations to this study. First, it had a relatively small sample size, which precluded the statistical reliability of the study. However, our results showed higher CACS and BDS to be significantly associated with the development of MACEs. Second, this study did not provide data on echocardiographic parameters, such as E/e' , which may have an important implication for determining diastolic function. Instead, other diastolic parameters, such as LVEDVI and LVMI, were calculated as substitutes for diastolic parameters. Finally, this study was limited by the retrospective nature of the data obtained from non-contrast regular chest CT, ^{123}I -BMIPP SPECT, echocardiography, and coronary artery angiography, as well as the outcomes of patients with NIHFpEF. Therefore, the timing of the imaging studies varied from patient to patient, and patient outcomes, which were reviewed based on the medical records, might have been incomplete. Further prospective studies with a larger number of participants are warranted to confirm the prognostic values of CACS and BDS in patients with NIHFpEF.

Conclusion

In this study, CACS demonstrated a high prognostic value for MACEs in patients with NIHFpEF. The evaluation of CACS in addition of BDS could have a predictive value for the identification of future MACEs in patients with NIHFpEF.

Declarations

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived (M20136).

Consent to participate and publish

Comprehensive agreement was obtained from all patients in the form of an opt-out on the institution's web-site.

Data and/or code availability

The data that support the findings of this study are available from the corresponding author.

Author contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by Hidenobu Hashimoto, Rine Nakanishi, Yukiko Hashimoto, Yuriko Okamura and Kyoko Ota. Hidenobu Hashimoto performed the statistical analyses and drafted the manuscript. Sunao Mizumura, Junichi Yamazaki and Takanori Ikeda reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Figures

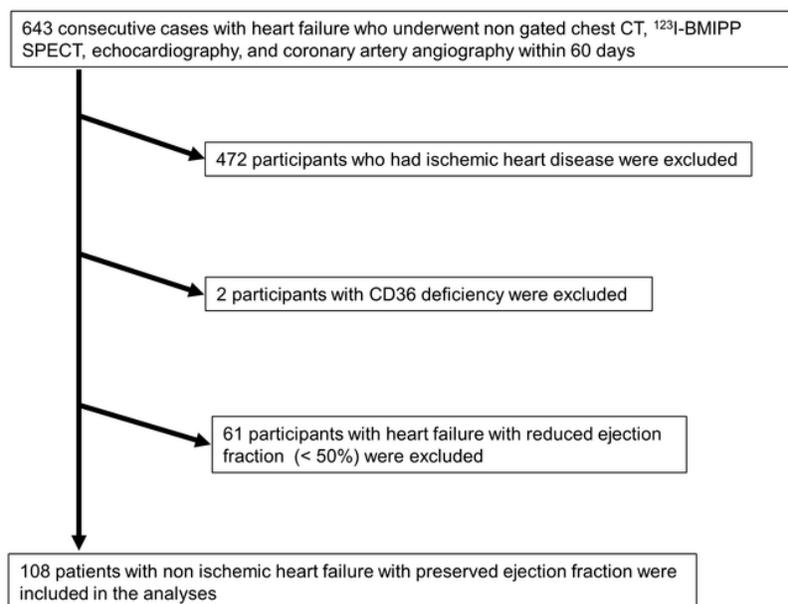


Fig. 1

Figure 1

Flow chart of patient inclusion and exclusion criteria in the study 123I-BMIPP = 123I-betamethyl-p-iodophenyl-pentadecanoic acid; SPECT = single-photon emission computed tomography; CT = computed tomography

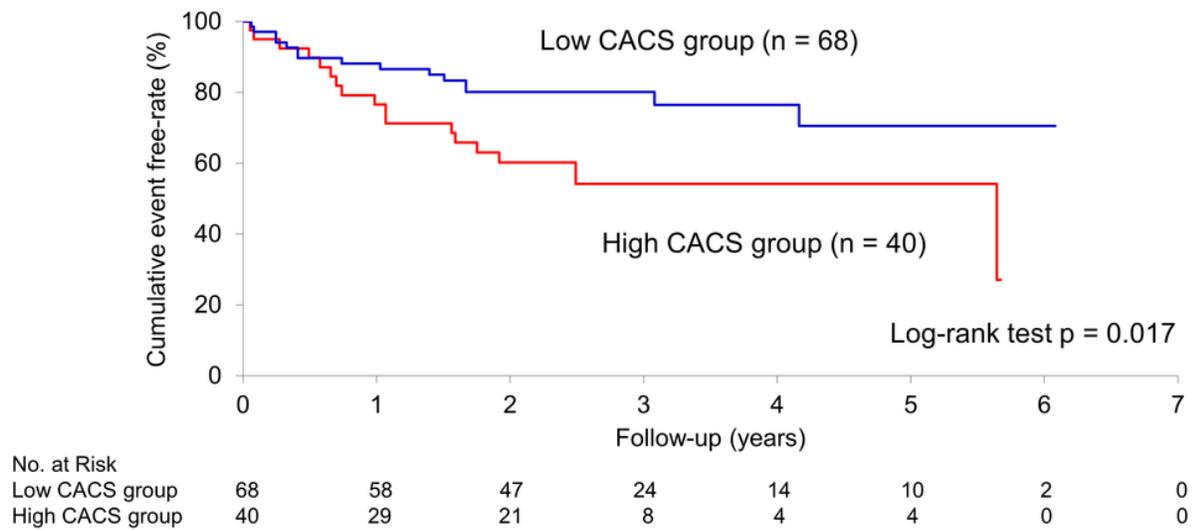


Fig. 2

Figure 2

Kaplan-Meier curve in reference to MACEs stratified by CACS value The y-axis represents the cumulative event-free rate; the rate in the low CACS group was significantly higher than that in the high CACS group (log-rank test, P = 0.017) CACS = coronary artery calcium score

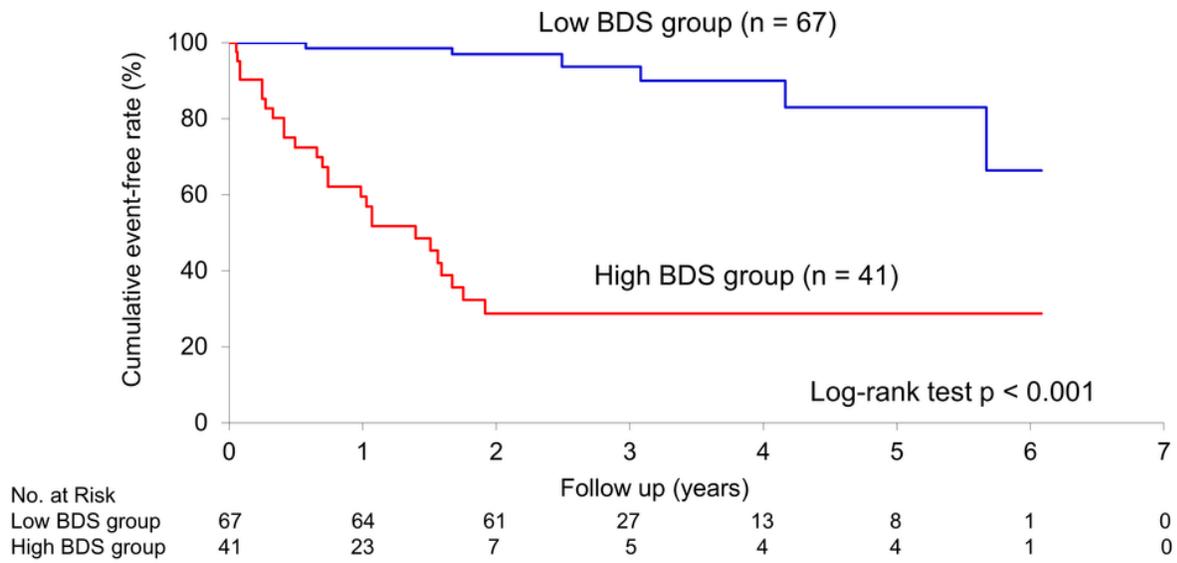


Fig. 3

Figure 3

Kaplan-Meier curve in reference to MACEs stratified by BDS value The y-axis represents the cumulative event-free rate; the rate in the low BDS group was significantly higher than that in the high group (log-rank test, $P < 0.001$) BDS = 123I-BMIPP defect score

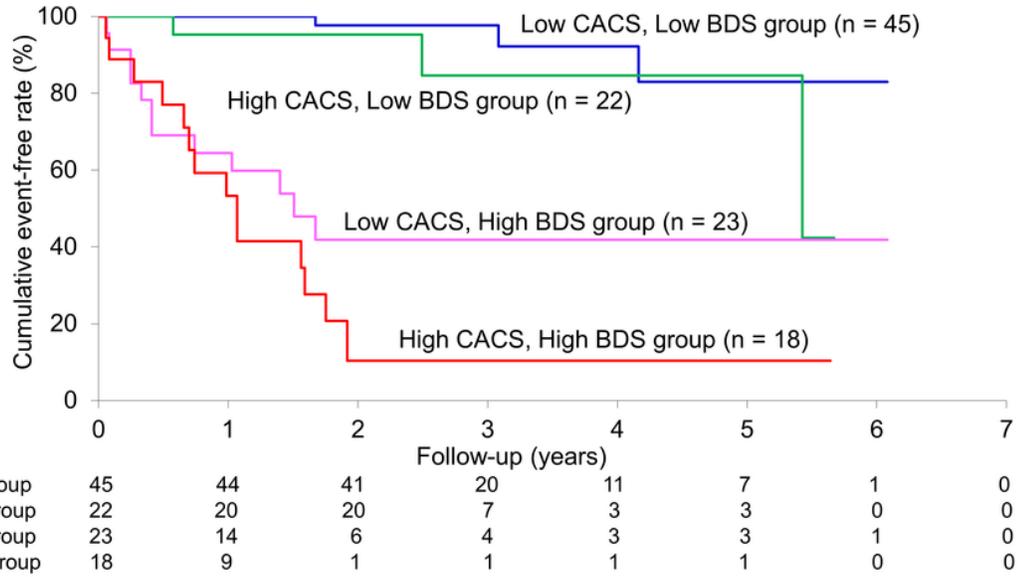


Fig. 4

Figure 4

Kaplan-Meier curve in reference to MACEs stratified by combination of CACS and BDS values. The y-axis represents the cumulative event-free rate; the rate in the low CACS and low BDS group was significantly the highest in the low CACS and low BDS group ($P < 0.001$). Abbreviations as in Figure 2 and 3.

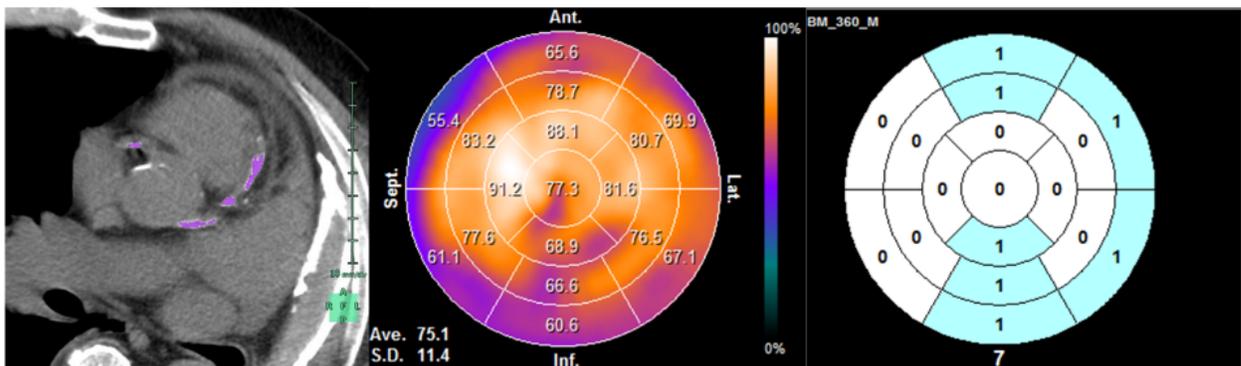


Fig. 5

Figure 5

Non-contrast non-cardiac chest CT image, polar map and heart risk map of ¹²³I-BMIPP SPECT images of a patient in the higher CACS and higher BDS group. The CACS was 1150.4 and BDS was 7. This patient was admitted to hospital due to deterioration of HF 210 days after the examination.