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**Association Between Coronary Artery Calcium Score
on Non-Contrast Chest Computed Tomography and All-Cause Mortality
Among Patients with Congestive Heart Failure**

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Abstract

Background: Coronary artery calcium (CAC) score is a robust prognostic tool to predict cardiac events. Although patients with congestive heart failure (CHF) occasionally undergo non-contrast computed tomography (NCCT), the prognostic utility of CAC by NCCT is not widely known. We aimed to determine if CAC measured on NCCT is associated with all-cause mortality (ACM) among patients with CHF.

Methods: We identified 550 patients admitted due to CHF who underwent NCCT. Patients were categorized into three groups according to CAC scores 0, 1-999, and $\geq 1,000$. The multivariate Cox proportional hazards model was used to assess if CAC by NCCT was associated with ACM after adjusting for traditional coronary artery disease (CAD) risk factors, brain natriuretic peptide and left ventricular ejection fraction (LVEF). In a subset of 245 patients with invasive coronary angiography (ICA), the associations between CAC scores and ACM were assessed in the multivariate Cox proportional hazards model. Further, we assessed if CAC increased statin use at discharge.

Results: During a mean follow-up of 3.3 ± 3.1 years, ACM occurred in 168 patients (30.55%). Compared with patients with CAC 0, those with CAC $\geq 1,000$ (HR 1.564, 95%CI 0.969-2.524, $p=0.067$) were more likely to experience ACM, while those with CAC score 1-999 (HR 0.971, 95%CI 0.673-1.399, $p=0.873$) were not. Similarly, a trend toward significance was observed in patients with LVEF $<40\%$ (HR 2.124, 95% CI 0.929-4.856, $p=0.074$). In the sub-analysis, patients with CAC $\geq 1,000$ had increased ACM compared to those with CAC 0, only if ICA $\geq 50\%$ (HR 3.668, 95% CI 1.141–11.797, $p=0.029$). Multivariate logistic regression revealed that statin use at discharge was increased with ICA $\geq 50\%$, but not CAC.

Conclusion: The CAC score measured by NCCT tended to be associated with ACM among CHF patients. Statin use was not increased by CAC on NCCT.

Key words: Coronary artery calcium score, Non-contrast chest computed tomography, Congestive heart failure, Coronary artery disease, Statin use

1. Introduction

Coronary artery calcium (CAC) detected on an electrocardiogram (ECG)-gated coronary computed tomography (CT) is a robust prognostic marker of cardiovascular events and all-cause mortality (ACM). The prognostic impact on CAC has been evident across various population groups (1-4).

Furthermore, CAC is displayed on non-contrast chest CT (NCCT) and acknowledged as an important incidental finding. The Society of Cardiovascular Computed Tomography guidelines announced the clinical recommendations to report CAC detected on NCCT (5), and the CAC incidence on NCCT has thus been increasingly documented in recent reports (6, 7). Although NCCT can be performed for the diagnosis and management of congestive heart failure (HF), the prognostic potential of CAC on NCCT remains unexplored. Therefore, this study aimed to investigate whether CAC on NCCT predicts ACM among patients with congestive HF.

2. Materials and methods

2.1 Patient population

Among the 716 consecutive patients admitted to our hospital due to first onset of congestive HF and who subsequently underwent NCCT scans during the hospitalization between January 2006 and December 2016 (Toho University Omori Medical Center, Tokyo, Japan), the following patients were sequentially excluded: patients who had a history of invasive coronary intervention (n=93), coronary bypass graft surgery (n=38), other cardiac surgery (n=23), and patients with only contrast CT (n=12). Five-hundred and fifty patients were enrolled in the current study. We assessed the clinical

characteristics including age, male sex, coronary risk factors, blood biochemical data, echocardiography data, and drug treatment. Smoking status included both past and current smoking. Family history was defined as having a family member who had suffered cardiovascular death, sudden death, or fatal/non-fatal myocardial infarction. The defined endpoint was the occurrence of ACM. The event data were retrospectively gathered from patients' records.

The Ethics Committee of Toho University Omori Medical Center approved this retrospective observational study (M17261, M20077), and the opt-out form was uploaded to inform patients who do not want their information to be included in this study on the web-site of Toho University Omori Medical Center.

2.2 Chest CT protocol

Non-ECG-gated chest CT was performed using 4, 16, 68, and 128 slice multidetector CT scanner (Aquilion 4 or Aquilion 16 [Canon, Tokyo, Japan] SOMATOM Definition Flash [Siemens, Germany] or Light speed VCT vision [GE healthcare, USA]). The scanning protocol consists of the following parameters: 28 mm × 0.6 mm beam collimation; pitch 1.2; caudocranial scan direction; and smallest field of view including the outer rib margins. No electrocardiographic triggering was performed; no contrast agent was administered. Exposure settings were applied based on body weight: 125 mAs at a tube voltage of 120 kVp. Slice thickness was 3, 5, 7, or 10 mm.

2.3 Coronary artery calcium calculation

Coronary artery calcifications detected on NCCT were utilized for calculating the Agatston score (Figure 1). Using the standard Agatston algorithm (8), the CAC score was analyzed on the AZE software (Canon, Tokyo, Japan). The CAC score was categorized into three groups with CAC 0, 1–999, and $\geq 1,000$.

2.4 Echocardiographic imaging

Echocardiographic images were obtained from the parasternal window for left ventricular function evaluation. Left ventricular ejection fraction (LVEF) was calculated using the Teichholz formula (9). In accordance with the current guidelines, HF with preserved, mid-range, and reduced LVEF were defined by $\geq 50\%$ (Heart failure with preserved ejection fraction [HFpEF]), 40%–50% (Heart failure with mid-range ejection fraction [HFmrEF]), and $< 40\%$ (Heart failure with reduced ejection fraction [HFrEF]), respectively (10).

2.5 Invasive coronary angiography

In a subset of 245 patients, invasive coronary angiography (ICA) was performed for coronary artery disease (CAD) assessment by experienced interventionalists. According to the current guidelines (11), coronary stenosis was defined as a decrease of more than 50% in the arterial diameter as shown by ICA.

2.6 Statistical Analysis

Data are expressed as average \pm standard deviation of continuous variables. Continuous variables from patients in the CAC groups with 0, 1-999, and $\geq 1,000$ were compared using the Mann-Whitney U test, and categorical data were analyzed using the Chi-square

test. We also calculated the multivariable Cox proportional hazards models adjusted for age, male sex, brain natriuretic peptide (BNP), LVEF, and CAC groups. For the survival analysis, the proportion of event-free patients was estimated using the Kaplan-Meier method and compared between each of the three CAC groups by using the log-rank test. In the sub-analyses of patients with HFpEF, HFmrEF, or HFrfEF, ACM was compared between the CAC 0, 1-999, and $\geq 1,000$ groups after adjusting for age, male sex, and BNP, using the Cox proportional models. We also investigated if CAC had an impact on statin use. The prevalence of statin therapy at admission and discharge was compared in the CAC subgroups, HF phenotype, or CAD presence.

In a subset of 245 patients, the multivariable Cox proportional hazards models adjusted for age, male sex, BNP, LVEF, and $\geq 50\%$ stenosis by ICA was also analyzed to assess if CAC was associated with ACM in total, and HF phenotype. The Kaplan-Meier method was estimated in total, and HF phenotype. Similarly, The Kaplan-Meier curves illustrated these sub-analyses. After adjusting for age, male sex, BNP, and LVEF, the ACM risk between CAC 0, 1-999, and $\geq 1,000$ groups was assessed among patients with or without $\geq 50\%$ stenosis by ICA. The multivariate logistic regression model after adjusting for age, male sex, HF phenotype, and $\geq 50\%$ stenosis by ICA was analyzed for CAC association with statin use at discharge.

A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using the StatMate IV software version 4.01 (Advanced Technology for Medicine and Science, Tokyo, Japan) or STATA (Version 14, StataCorp LP, College Station, TX, USA) for Windows.

3. Result

3.1 Baseline clinical characteristics

Patient characteristics are presented in Table 1. The mean patient age was 72.5 ± 13.5 years, and 304 patients (55.3%) were men. Of the 550 patients, 346 (62.9%) showed any CAC on NCCT. We divided the three groups according to CAC scores, namely 0 (n=204, 37.1%), 1-999 (n=288, 52.4%), and $\geq 1,000$ (n=58, 10.5%). Age and the traditional risk factors for CAD including hypertension, dyslipidemia, and diabetes mellitus, as well as HDL cholesterol progressively and significantly increased in the CAC groups 0, 1-999, or $\geq 1,000$ ($p < 0.05$ for all). Among patients with CAC $\geq 1,000$, the majority (53.4%) experienced $\geq 50\%$ stenosis by ICA, followed by those with CAC 1-999 (28.5%), and CAC 0 including only 7.8% patients. Regarding the parameters on echocardiography, the mean LVEF on echocardiography was $47.39 \pm 17.17\%$. HFpEF, HFmrEF, and HFrEF presented in 233 (42.4%), 118 (21.4%), and 199 (36.2%) patients, respectively. The prevalence of HFmrEF and HFrEF did not statistically differ between the three groups; however, the LV end-diastolic dimension and the LV End-systolic dimension progressively and statistically decreased in patients with CAC 0, 1-999, and $\geq 1,000$.

3.2 Clinical outcome

Overall, during a mean follow-up of 3.3 ± 3.1 years, all-cause death occurred in 168 patients. Figures 2, 3, and 4 illustrate the Kaplan-Meier curves for ACM stratified by the CAC groups. The proportion of patients who experienced ACM was significantly highest in the CAC $\geq 1,000$ group than those in the CAC 0 and CAC 1-999 groups in total (Figure 2), patients with HFrEF (Figure 3a), HFmrEF (Figure 3b), and HFpEF (Figure 3c).

Compared to patients with CAC 0, those with CAC $\geq 1,000$ were more likely to experience ACM in the multivariate Cox proportional model, while those with CAC 1-999 were not (Table 2). Similarly, CAC $\geq 1,000$ tended to be associated with higher ACM in the HF_rEF group, while such results were not found in the HF_pEF and HF_{mr}EF groups (Table 3).

In a sub-set of 245 patients with ICA, the Kaplan-Meier curves for ACM illustrated that the patients with ACM were significantly highest in the CAC $\geq 1,000$ group compared to those in the CAC 0 and CAC 1-999 groups in patients with HF_rEF (Figure 4a) and HF_pEF (Figure 4c), but not in those with HF_{mr}EF (Figure 4b). Among patients with HF_rEF, those with CAC $\geq 1,000$ experienced higher ACM than those without any CAC, while those with CAC 1-999 were not (Table 5). Such trends were likely to be observed among patients with HF_pEF, whereas the association with higher ACM was not observed among patients with HF_{mr}EF (Table 5).

Table 6 demonstrates the ACM risk by CAC scores among patients with or without $\geq 50\%$ stenosis by ICA. Although no association between the CAC scores and the ACM was observed among patients having $< 50\%$ stenosis by ICA, CAC $\geq 1,000$ was significantly associated with an increased ACM risk compared with CAC 0 among patients with $\geq 50\%$ stenosis by ICA (Table 6).

Table 7 demonstrates the perseverance of statin therapy at initial admission and discharge. Overall, statin therapy increased 50% at discharge. Similarly, statin was administered at discharge in most of the subgroups, whereas it was not administered among patients with $< 50\%$ stenosis by ICA or HF_pEF. In terms of the CAC groups, although the statin use was increased at discharge in the groups with CAC 1-999 ($p < 0.01$), or $\geq 1,000$ ($p = 0.165$), its prevalence was limited to only one-third of the patients.

Multivariate logistic regression model revealed that $\geq 50\%$ stenosis by ICA was associated with statin use at discharge, while CAC was not (Table 8).

4. Discussion

In the current study, we have demonstrated that the increased CAC detected on NCCT was more likely to be associated with higher ACM among patients presenting with congestive HF, especially patients with HFrEF. The significant association between increased CAC and ACM was observed among patients with $\geq 50\%$ stenosis by ICA. In addition, the NCCT-derived CAC score did not impact the increase in statin use.

Limited investigations on the prognostic values of CAC on NCCT were previously reported in patients with chronic obstructive pulmonary disease (12), suspected lung cancer (13), or community-living adults (14). While it is clinically uncommon to often report the CAC score on NCCT (7), these studies demonstrated that the increased CAC score on NCCT was significantly associated with higher ACM (12-14). Additionally, a previous study revealed that the prognostic value of the CAC scores on NCCT was found to be comparable with CAC on ECG-gated coronary CT (14). Similarly, the significant associations between the increased CAC on NCCT and the higher risk in ACM were observed in the Kaplan-Meier curves among patients with congestive HF, the multivariate Cox proportional models tended to show such associations in the current study. The findings may be due to the explanation that the association between the presence of CAD and increased ACM tended to be more robust among patients with HF. Indeed, $CAC \geq 1,000$ was associated with higher ACM only patients with $\geq 50\%$ stenosis by ICA in the current study.

Although CAC has been well-established as a tool to improve physician behavior and encourage lifestyle modification in patients with CAC (15, 16), the preventive and therapeutic aspects of CAC based on NCCT images have often been neglected (6). In this study, the increased CAC did not affect the treatment decision-making for preventive therapy, such as statin, at discharge, although all patients were treated by cardiologists. Additionally, the prevalence of statin use at discharge was only limited in 25.7% and 44.2% of patients with any CAC in total, and those with $\geq 50\%$ stenosis by ICA, respectively. This trend is consistent with the previous study showing that the prevalence was 35% in a similar population (6). The recent prevention and imaging guidelines have recommended using statin based on the CAC score by ECG-gated non-contrast coronary CT among asymptomatic patients (17, 18). Although cardiac experts tended to recognize CAC incidence on NCCT more frequently than non-cardiac experts or radiologists (6, 7), our study revealed that statin use was mainly driven by the presence of $\geq 50\%$ stenosis by ICA and not by the increased CAC or HF phenotype. It is still challenging to routinely measure CAC scores on NCCT in a clinical setting, which is served as a class IIb recommendation by the current guidelines (5). In the same guidelines, however, it has been stated that CAC should be visually evaluated and reported as none, mild, moderate, or severe as a class I indication (5). Clinical role of CAC measurements for patients with HF will be warranted.

5. Limitations

There are several limitations in the current study. This is a single-center study with a relatively small sample size. Given the retrospective nature of our study, we did not

perform ECG-gated non-contrast coronary CT in conjunction with NCCT to compare the CAC scores between the two CT images. In this regard, such data was not available in the current study, although the high correlation of CAC scores between cardiac and non-cardiac CTs ($r=0.93$, $p<0.001$) (14) or the high interscan variability of CAC ($r=0.94$) (19) were previously reported. Since we retrospectively collected the clinical data in the current study, the identification of the mode of death was not confirmed in the medical records among some of patients. Finally, LVEF was measured with the teichholz equation in the current study, and there were no other measures, such as the Simpson method, that might more accurately represent LVEF.

6. Conclusions

In this study, we have demonstrated that the increased CAC scores on NCCT were likely to be associated with worsening ACM among patients with congestive HF. This trend was more prominent among patients with HFrEF or $\geq 50\%$ stenosis by ICA. In addition, statin use was not influenced by CAC at NCCT.

7. Conflict of interest

The authors declare that they have no conflict of interest.

8. Acknowledgments

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Reference

1. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS (2007) Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol* 49:1860-1870.
2. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA (2008) Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 358:1336-1345.
3. Nakanishi R, Li D, Blaha MJ, Whelton SP, Darabian S, Flores FR, Dailing C, Blumenthal RS, Nasir K, Berman DS, Budoff MJ (2016) All-cause mortality by age and gender based on coronary artery calcium scores. *Eur Heart J Cardiovasc Imaging* 17:1305-1314.
4. Nakanishi R, Li D, Blaha MJ, Whelton SP, Matsumoto S, Alani A, Rezaeian P, Blumenthal RS, Budoff MJ (2015) The relationship between coronary artery calcium score and the long-term mortality among patients with minimal or absent coronary artery risk factors. *Int J Cardiol* 185:275-281.
5. Hecht HS, Cronin P, Blaha MJ, Budoff MJ, Kazerooni EA, Narula J, Yankelevitz D, Abbara S (2017) 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Cardiovasc Comput Tomogr* 11:74-84.

6. Uretsky S, Chokshi N, Kobrinski T, Agarwal SK, Po JR, Awan H, Jagarlamudi A, Gudiwada SP, D'Avino RC, Rozanski A (2015) The interplay of physician awareness and reporting of incidentally found coronary artery calcium on the clinical management of patients who underwent noncontrast chest computed tomography. *Am J Cardiol* 115:1513-1517.
7. Kirsch J, Martinez F, Lopez D, Novaro GM, Asher CR (2017) National trends among radiologists in reporting coronary artery calcium in non-gated chest computed tomography. *Int J Cardiovasc Imaging* 33:251-257.
8. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. (1990) Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 15:827-832.
9. Teichholz LE, Kreulen T, Herman MV, Gorlin R (1976) Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 37:7-11.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 37:2129-2200.

11. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, Legako RD, Leon DF, Murray JA, Nissen SE, Pepine CJ, Watson RM, Ritchie JL, Gibbons RJ, Cheitlin MD, Gardner TJ, Garson A Jr, Russell RO Jr, Ryan TJ, Smith SC Jr (1999) ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 33:1756-1824.
12. Budoff MJ, Lutz SM, Kinney GL, Young KA, Hokanson JE, Barr RG, Steiner R, Nath H, Lopez-Garcia C, Duca LM, Rahmani S, Osawa K, Regan EA, Li D, Casaburi R (2018) Coronary Artery Calcium on Noncontrast Thoracic Computerized Tomography Scans and All-Cause Mortality. *Circulation* 138:2437-2438.
13. Jacobs PC, Gondrie MJ, van der Graaf Y, de Koning HJ, Isgum I, van Ginneken B, Mali WPTM (2012) Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. *AJR Am J Roentgenol* 198:505-511.
14. Hughes-Austin JM, Dominguez A 3rd, Allison MA, Wassel CL, Rifkin DE, Morgan CG, Daniels MR, Ikram U, Knox JB, Wright CM, Criqui MH, Ix JH (2016) Relationship of Coronary Calcium on Standard Chest CT Scans With Mortality. *JACC Cardiovasc Imaging* 9:152-159.
15. Rozanski A, Gransar H, Shaw LJ, Kim J, Miranda-Peats L, Wong ND, Rana JS, Orakzai R, Hayes SW, Friedman JD, Thomson LE, Polk D, Min J, Budoff MJ, Berman DS (2011) Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by

Noninvasive Imaging Research) prospective randomized trial. *J Am Coll Cardiol* 57:1622-1632.

16. Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ (2006) Visualizing coronary calcium is associated with improvements in adherence to statin therapy. *Atherosclerosis* 185:394-399.

17. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J (2019) 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 73:e285-e350.

18. Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, Blankstein R, Narula J, Rumberger J, Shaw LJ (2017) Clinical indications for coronary artery calcium scoring in asymptomatic patients: Expert consensus statement from the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr* 11:157-168.

19. Jacobs PC, Isgum I, Gondrie MJ, Mali WP, van Ginneken B, Prokop M, van der Graaf Y (2010) Coronary artery calcification scoring in low-dose ungated CT screening for lung cancer: interscan agreement. *AJR Am J Roentgenol* 194:1244-1249.

Figure legends

Figure 1. The Sample of the case with coronary artery calcium calculation on non-contrast chest computed tomography

Abbreviations: LMT - left main coronary trunk; LAD - left anterior descending artery; LCX - left circumflex artery; RCA - right coronary artery

Figure 2. Kaplan-Meier curves of freedom from all-cause mortality stratified by CAC with 0, 1-999, and $\geq 1,000$ groups (n=550)

Abbreviations: CAC - coronary artery calcium; ACM - all-cause mortality

Figure 3a. Kaplan-Meier curves of freedom from all-cause mortality stratified by CAC with 0, 1-999, and $\geq 1,000$ groups among patients with HFrEF (n=199)

Abbreviations: HFrEF - heart failure with reduced ejection fraction; CAC - coronary artery calcium; ACM - all-cause mortality

Figure 3b. Kaplan-Meier curves of freedom from all-cause mortality stratified by CAC with 0, 1-999, and $\geq 1,000$ groups among patients with HFmrEF (n=118)

Abbreviations: HFmrEF - heart failure with mid-range ejection fraction; CAC - coronary artery calcium; ACM - all-cause mortality

Figure 3c. Kaplan-Meier curves of freedom from all-cause mortality stratified by CAC with 0, 1-999, and $\geq 1,000$ groups among patients with HFpEF (n=233)

Abbreviations: HFpEF - heart failure with preserved ejection fraction; CAC - coronary artery calcium; ACM - all-cause mortality

Figure 4a. Kaplan-Meier curves of freedom from all-cause mortality stratified by the CAC with 0, 1-999, and $\geq 1,000$ groups among patients with HF_rEF who underwent invasive coronary angiography (n=125)

Abbreviations: HF_rEF - heart failure with reduced ejection fraction; CAC - coronary artery calcium; ACM - all-cause mortality

Figure 4b. Kaplan-Meier curves of freedom from all-cause mortality stratified by the CAC with 0, 1-999, and $\geq 1,000$ groups among patients with HF_{mr}EF who underwent invasive coronary angiography (n=48)

Abbreviations: HF_{mr}EF - heart failure with mid-range ejection fraction; CAC - coronary artery calcium; ACM - all-cause mortality

Figure 4c. Kaplan-Meier curves of freedom from all-cause mortality stratified by the CAC with 0, 1-999, and $\geq 1,000$ groups among patients with HF_pEF who underwent invasive coronary angiography (n=72)

Abbreviations: HF_pEF - heart failure with preserved ejection fraction; CAC - coronary artery calcium; ACM - all-cause mortality

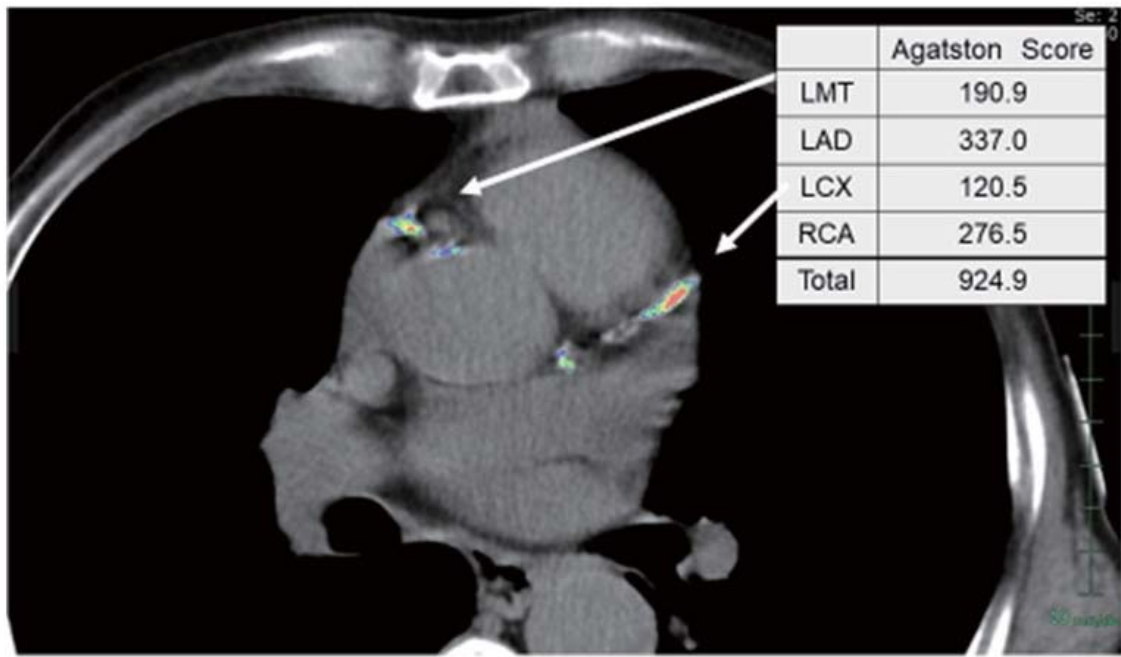


Figure 1

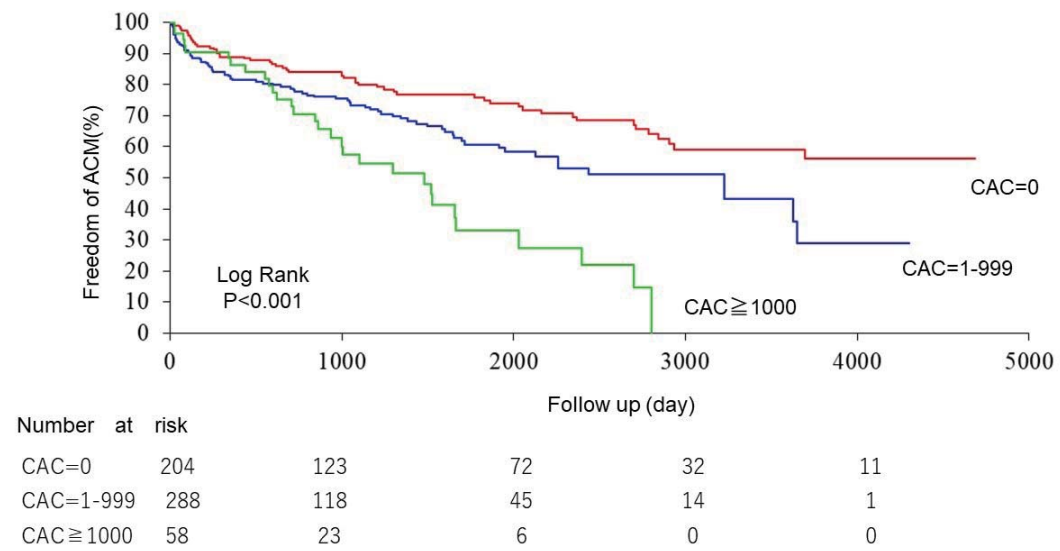
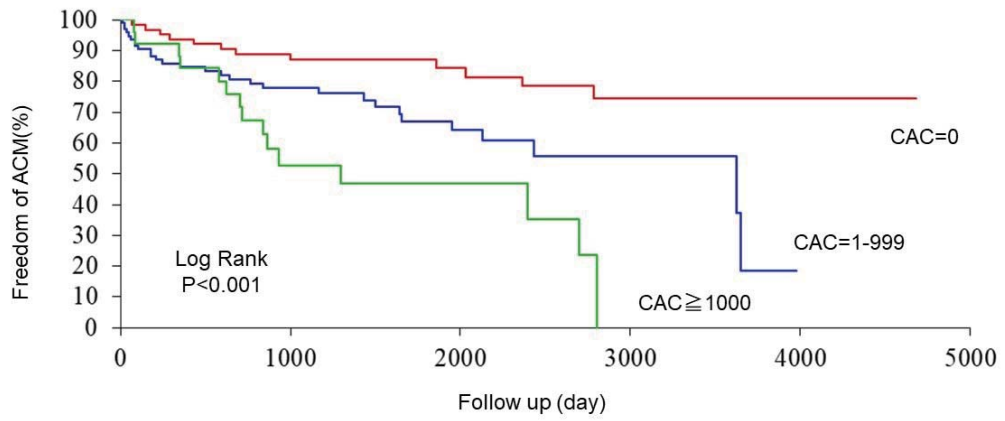
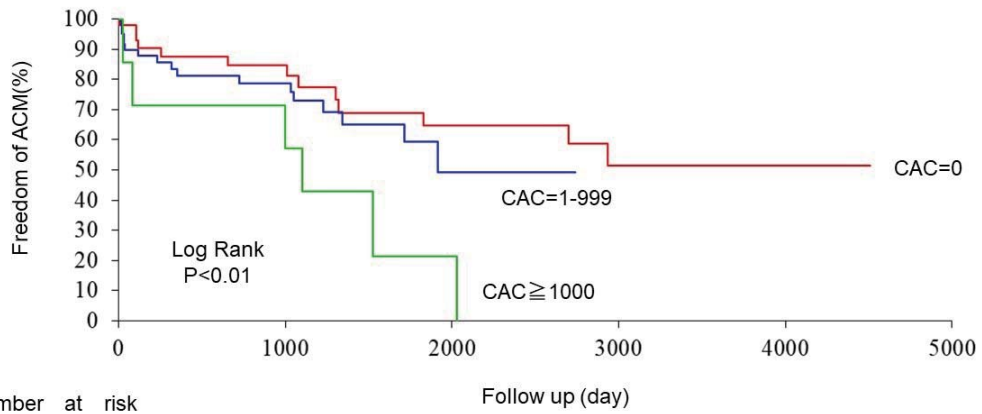


Figure 2



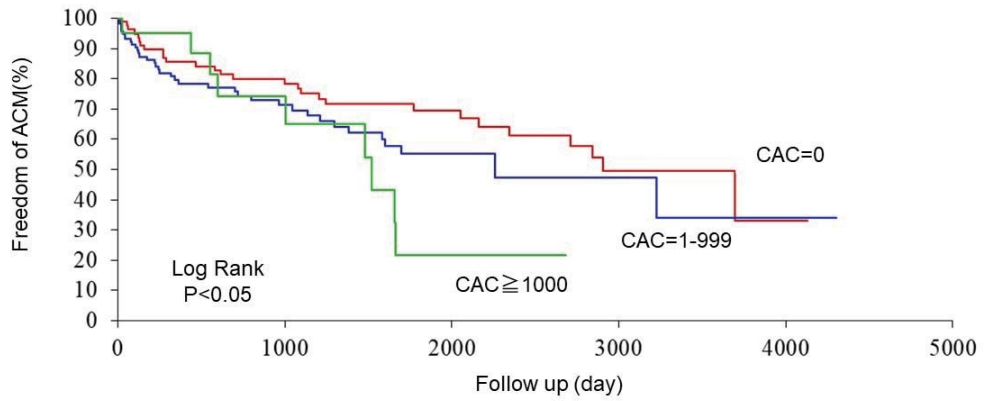
	Number at risk				
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CAC=0	69	49	30	17	9
CAC=1-999	101	47	21	7	0
CAC ≥ 1000	29	10	4	0	0

Figure 3a



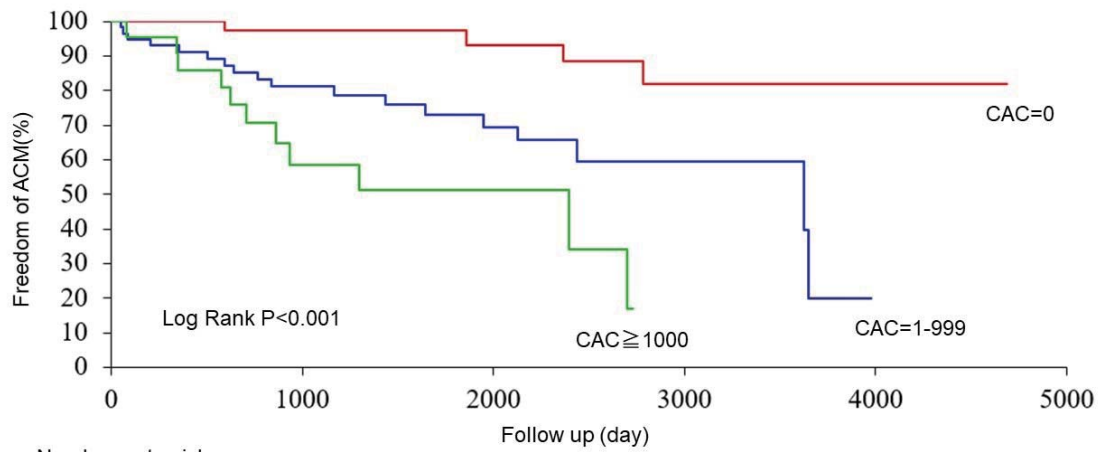
	Number at risk				
	0	1000	2000	3000	4000
CAC=0	47	25	14	7	1
CAC=1-999	64	27	5	0	0
CAC ≥ 1000	7	5	1	0	0

Figure 3b



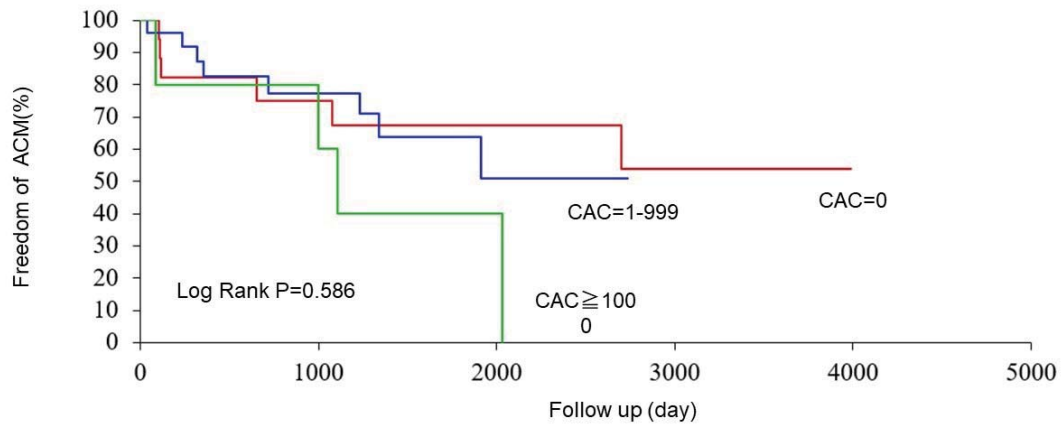
Number at risk	0	1000	2000	3000	4000	5000
CAC=0	88	49	28	8	1	1
CAC=1-999	123	44	19	7	1	1
CAC ≥ 1000	22	8	1	0	0	0

Figure 3c



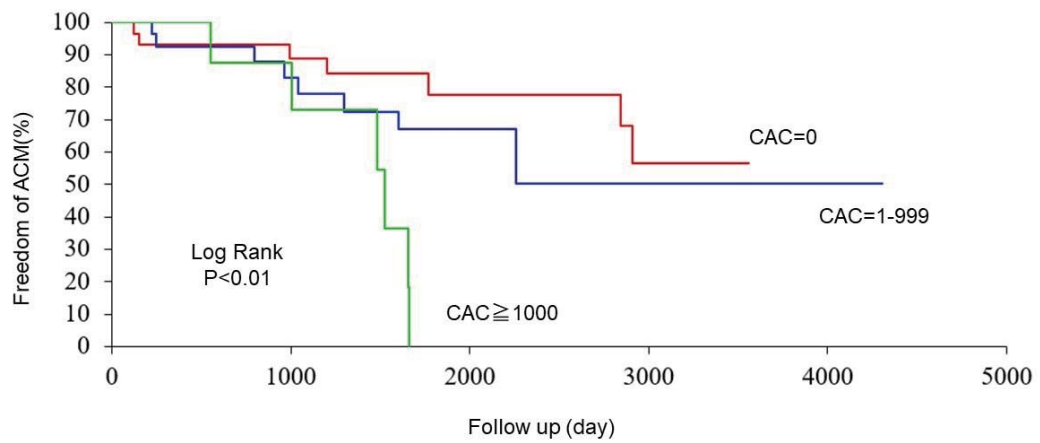
Number at risk	0	1000	2000	3000	4000	5000
CAC=0	45	38	21	12	7	7
CAC=1-999	59	35	19	7	0	0
CAC ≥ 1000	22	9	3	0	0	0

Figure 4a



	Number	at risk			
CAC=0	18	10	6	3	0
CAC=1-999	25	13	4	0	0
CAC ≥ 1000	5	4	1	0	0

Figure 4b



	Number	at risk			
CAC=0	29	21	10	3	0
CAC=1-999	34	17	11	4	1
CAC ≥ 1000	9	6	0	0	0

Figure 4c

Table 1. Baseline characteristics of the patients

	Total	CAC= 0	CAC=1-999	CAC ≥ 1,000	P value
Number of patients	550	204	288	58	
Age (years, mean ± SD)	72.5±13.5	66.1±14.9	76.3±11.2 *	76.1±10.0*	<0.001
Male sex (n, %)	304(55.3)	122(59.8)	150(52.1)	32(55.2)	0.1125
Hypertension (n, %)	348(63.3)	101(49.5)	199(69.1) *	48(82.8) *,**	<0.001
Dyslipidemia (n, %)	99(18)	23(11.3)	58(20.1) *	18(31.0) *	<0.001
Diabetes mellitus (n, %)	169(30.7)	42(20.6)	90(31.3) *	37(63.8) *,**	<0.001
Smoking (n, %)	307(55.8)	113(55.4)	160(55.6)	34(58.6)	0.6425
Family History (n, %)	86(15.6)	43(21.1)	36(12.5) *	7(12.1)	<0.01
CKD(eGFR<60 mL/min/1.73 m ²)	371(67.5)	119(58.3)	207(71.9) *	45(77.6) *	<0.001
Atrial fibrillation (n, %)	238(43.3)	86(42.2)	134(46.5)	18(31.0) **	0.0497
Echocardiography					
LVEF(% ,mean ± SD)	47.4±17.2	47.4±17.3	48.1±17.4	43.5±15.5	0.1997
HFpEF ≥50% (n, %)	233(42.4)	88(43.1)	123(42.7)	22(37.9)	<0.05
HFmrEF 40%–49% (n, %)	118(21.5)	47(23.0)	64(22.2)	7(12.1)	0.6770
HFrEF <40% (n, %)	199(36.2)	69(33.8)	101(35.1)	29(50.0) *,**	0.1318
LV End-diastolic dimension (mm, mean ±SD)	54.1±9.9	55.5±10.1	53.5±9.9 *	52.3±8.3 *	<0.001
LV End-systolic dimension (mm, mean ± SD)	40.9±11.5	42.4±12.2	39.9±11.3*	40.5±9.9*,**	<0.001
Laboratory data					
Hemoglobin(g/dL, mean ± SD)	12.5±2.3	13.2±2.2	12.1±2.3 *	12.1±2.1*	<0.001
Creatinine(mg/dL, mean ± SD)	1.3±1.3	1.1±0.9	1.4±1.2 *	1.7±2.2	0.0776
BNP(pg/mL, mean ± SD)	1067.8±1042.3	897.1±937.4	1127.1±1073.6*	1373.8±1145.7*,**	<0.001
Total cholesterol	168.3±44.7	166.3±48.4	168.9±41.9	171.9±44.9	0.4814
LDL cholesterol	101.8±36.2	100.7±36.5	102.4±35.0	102.4±40.6	0.8141
HDL cholesterol	50.2±15.6	49.0±15.9	50.6±15.7	51.7±13.8	<0.001
Triglyceride	86.4±49.6	89.3±61.4	84.4±40.1	86.3±45.7	0.9662
Medication (n, %)					
B-blocker	74(13.5)	22(10.8)	46(16)	6(10.3)	0.1244
Loop diuretic	135(24.5)	43(21.1)	79(27.4)	13(22.4)	0.1457
Mineralocorticoid receptor antagonist	48(8.7)	20(9.8)	22(7.6)	6(10.3)	0.4236
ACE-I	28(5.1)	10(4.9)	15(5.2)	3(5.2)	0.8788
Angiotensin-II receptor blocker	168(30.5)	45(22.1)	98(34) *	25(43.1) *	<0.001
Aspirin	88(16)	20(9.8)	56(19.4) *	12(20.7) *	<0.01
Invasive coronary angiography	245				
≥50% stenosis by ICA (n, %)	129(52.7)	16(6.5)	82(33.5) *	31(12.7) *,**	<0.001

*P<0.05 compare to CAC=0

**P<0.05 compare to CAC=1-999

Abbreviations: CAC - coronary artery calcium; CKD - chronic kidney disease; ICA - invasive coronary angiography; LVEF - left ventricular ejection fraction; BNP - brain natriuretic peptide; ACE-I - angiotensin converting enzyme-inhibitor; SD - standard deviation; LDL - low density lipoprotein; HDL - high density lipoprotein

Table 2. Multivariate Cox proportional hazards analysis to predict all-cause mortality (n=550)

	HR (95% CI)	P value
Age	1.029 (1.013 - 1.045)	0.000
Male sex	1.304(0.947 - 1.795)	0.104
BNP	1.000159(1.000027 - 1.00029)	0.019
LVEF	1.00138(0.992 - 1.011)	0.784
CAC 0	1 (Ref)	
CAC 1-999	0.971(0.673 - 1.399)	0.873
≥1,000	1.564(0.969 - 2.524)	0.067

Abbreviations: HR - hazard ratio; BNP - brain natriuretic peptide; LVEF - left ventricular ejection fraction; CAC - coronary artery calcium

Table 3. Multivariate Cox proportional hazards analysis to predict all-cause death in patients with HFpEF, HFmrEF, or HFrfEF

	HFpEF (n=233)		HFmrEF (n=118)		HFrfEF (n=199)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.026 (0.999-1.0537)	0.063	1.013 (0.982-1.044)	0.432	1.041 (1.015-1.067)	0.002
Male sex	1.166 (0.726-1.872)	0.525	0.710 (0.344-1.463)	0.353	2.126 (1.170-3.864)	0.013
BNP	1.000052 (0.9997-1.00034)	0.722	1.000422 (1.000193-1.000651)	0.000	1.000105 (0.9999-1.000309)	0.314
CAC 0	1 (Ref)		1 (Ref)		1 (Ref)	
CAC 1-999	0.927 (0.553-1.554)	0.774	0.726 (0.325-1.621)	0.435	1.143 (0.549-2.381)	0.720
≥1,000	1.156 (0.519-2.574)	0.723	1.895 (0.706-5.084)	0.205	2.124 (0.929-4.856)	0.074

Abbreviations: HFpEF- heart failure with preserved ejection fraction; HFmrEF - heart failure with mid-range ejection fraction; HFrfEF - heart failure with reduced ejection fraction; HR - hazard ratio; BNP - brain natriuretic peptide; CAC - coronary artery calcium

Table 4. Multivariate Cox proportional hazards analysis to predict all-cause mortality in patients who underwent invasive coronary angiography (n=245)

	HR (95% CI)	P value
Age	1.051 (1.024–1.079)	<0.01
Male sex	1.081 (0.644–1.816)	0.77
BNP	1.000 (1.000–1.0004)	0.02
LVEF<50%	1.001 (0.984–1.018)	0.94
≥50% stenosis by ICA	1.764 (1.008–3.085)	0.047
CAC 0	1 (Ref)	
CAC 1-999	1.265 (1.079–2.393)	0.47
≥1,000	2.196 (1.011–4.768)	0.047

Abbreviations: HR - hazard ratio; BNP - brain natriuretic peptide; LVEF - left ventricular ejection fraction; ICA - invasive coronary angiography; CAC - coronary artery calcium

Table 5. Multivariate Cox proportional hazards analysis to predict all-cause death in patients with HFpEF, HFmrEF, or HFrEF, who underwent invasive coronary angiography

	HFpEF (n=72)		HFmrEF (n=48)		HFrEF (n=125)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.024 (0.968–1.084)	0.408	1.110 (1.036–1.189)	0.003	1.055 (1.016–1.096)	0.006
Male sex	1.180 (0.412–3.378)	0.758	1.381 (0.478–3.993)	0.551	0.962 (0.432–2.145)	0.925
BNP	1.000 (1.000–1.001)	0.650	1.000 (0.9998–1.001)	0.136	1.000 (0.99997–1.0004)	0.084
≥50% stenosis by ICA	1.796 (0.665–4.851)	0.248	2.086 (0.660–6.595)	0.211	1.694 (0.681–4.214)	0.257
CAC 0	1 (Ref)		1 (Ref)		1 (Ref)	
CAC 1-999	1.173 (0.410–3.359)	0.766	0.229 (0.057–0.917)	0.037	3.109 (0.928–10.413)	0.066
≥1,000	3.378 (0.870–13.117)	0.079	0.369 (0.056–2.449)	0.302	4.521 (1.137–17.976)	0.032

Abbreviations: HFpEF- heart failure with preserved ejection fraction; HFmrEF - heart failure with mid-range ejection fraction; HFrEF - heart failure with reduced ejection fraction; HR - hazard ratio; BNP - brain natriuretic peptide; ICA - invasive coronary angiography; CAC - coronary artery calcium

Table 6. Results of multivariate Cox proportional hazards analysis to predict all-cause death in patients with $\geq 50\%$ stenosis or $< 50\%$ stenosis by ICA who underwent invasive coronary angiography

	$\geq 50\%$ stenosis by ICA (n=129)		$< 50\%$ stenosis by ICA (n=116)	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.048 (1.014–1.083)	0.005	1.064 (1.014–1.115)	0.011
Male sex	0.873 (0.449–1.697)	0.688	1.661 (0.668–4.132)	0.275
BNP	1.000 (0.9999–1.000)	0.283	1.001 (1.000–1.001)	0.002
LVEF $<50\%$	0.991 (0.968-1.015)	0.462	1.015 (0.989–1.042)	0.266
CAC 0	1 (Ref)		1 (Ref)	
CAC 1-999	2.091 (0.705–6.201)	0.183	0.880 (0.356–2.179)	0.783
$\geq 1,000$	3.668 (1.141–11.797)	0.029	1.416 (0.292–6.859)	0.666

Abbreviations as in Table 2

Table 7. Statin use at initial admission and discharge.

	Baseline	At discharge	P value
Total (n=550)	75 (13.6)	119 (21.6)	<0.001
The presence of CAC (n, %)	62 (17.9)	89 (25.7)	<0.05
CAC 0 (n, %)	13 (6.4)	30 (14.7)	<0.01
CAC 1-999 (n, %)	51 (17.7)	73 (25.3)	<0.05
CAC ≥ 1,000 (n, %)	11 (19.0)	16 (27.6)	0.330
HFpEF (n, %)	40 (17.2)	47 (20.2)	0.434
HFmrEF (n, %)	15 (12.7)	29 (24.6)	<0.05
HFrEF(n, %)	20 (10.1)	43 (21.6)	<0.01
Invasive coronary angiography (n=245)	32(13.1)	68(27.8)	<0.001
≥50% stenosis by ICA (n, %)	23 (17.8)	57 (44.2)	0.001
<50% stenosis by ICA (n, %)	9 (7.8)	11 (9.5)	0.640

Abbreviations as in Table 1

Table 8. Multivariate logistic regression model to predict statin use at discharge. (n=245)

	Odds Ratio (95% CI)	P value
Age	0.985 (0.955–1.015)	0.321
Male sex	1.523 (0.744–3.130)	0.249
≥50% stenosis by ICA	10.966 (4.535–26.517)	<0.001
HFpEF	1 (Ref)	
HFmrEF	0.931 (0.369–2.346)	0.879
HFrEF	0.562 (0.259–1.220)	0.145
CAC 0	1 (Ref)	
CAC 1-999	0.822 (0.329–2.053)	0.674
CAC ≥1,000	0.626 (0.193–2.025)	0.434

Abbreviations as in Table 1