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ORIGINAL ARTICLE

Coronary angiography in patients with acute heart failure: from the KCHF registry

Yuta Seko[1†], Takefumi Kishimori[2†], Takao Kato[1*], Takeshi Morimoto[3], Hidenori Yaku[1], Yasutaka Inuzuka[2], Yodo Tamaki[4], Neiko Ozasa[1], Masayuki Shiba[1], Erika Yamamoto[1], Yusuke Yoshikawa[1], Yugo Yamashita[1], Takeshi Kitai[5], Ryoji Taniguchi[6], Moritake Iguchi[7], Kazuya Nagao[8], Takafumi Kawai[9], Akihiro Komasa[10], Ryusuke Nishikawa[11], Yuichi Kawase[12], Takashi Morinaga[13], Mamoru Toyofuku[14], Yutaka Furukawa[15], Kenji Ando[13], Kazushige Kadota[12], Yukihito Sato[6], Koichiro Kuwahara[16], Takeshi Kimura[1] and for the KCHF Study Investigators

[1]*Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan;* [2]*Department of Cardiovascular Medicine, Shiga General Hospital, Moriyama, Japan;* [3]*Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan;* [4]*Division of Cardiology, Tenri Hospital, Tenri, Japan;* [5]*Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan;* [6]*Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan;* [7]*Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan;* [8]*Department of Cardiology, Osaka Red Cross Hospital, Osaka, Japan;* [9]*Department of Cardiology, Kishiwada City Hospital, Kishiwada, Japan;* [10]*Department of Cardiology, Kansai Electric Power Hospital, Osaka, Japan;* [11]*Department of Cardiology, Shizuoka General Hospital, Shizuoka, Japan;* [12]*Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan;* [13]*Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan;* [14]*Department of Cardiology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan;* [15]*Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; and* [16]*Department of Cardiovascular Medicine, Shinshu University Graduate School of Medicine, Matsumoto, Japan*

Abstract

Aims Little is known about the characteristics and outcomes of patients who undergo coronary angiography during heart failure (HF) hospitalization, as well as those with coronary stenosis, and those who underwent coronary revascularization.

Methods and results We analysed 2163 patients who were hospitalized for HF without acute coronary syndrome or prior HF hospitalization. We compared patient characteristics and 1 year clinical outcomes according to (i) patients with versus without coronary angiography, (ii) patients with versus without coronary stenosis, and (iii) patients with versus without coronary revascularization. The primary outcome measure was the composite of all-cause death or HF hospitalization. Coronary angiography was performed in 37.0% of patients. In the multivariable logistic regression analysis, factors independently associated with coronary angiography were age $<$ 80 years [adjusted odds ratio (OR) = 1.76, 95% confidence interval (CI) = 1.41–2.20, $P < 0.001$], men (adjusted OR = 1.28, 95% CI = 1.03–1.59, $P = 0.02$), diabetes (adjusted OR = 1.27, 95% CI = 1.02–1.60, $P = 0.04$), no atrial fibrillation or flutter (adjusted OR = 1.45, 95% CI = 1.17–1.82, $P < 0.001$), no prior device implantation (adjusted OR = 1.81, 95% CI = 1.13–2.91, $P = 0.01$), current smoking (adjusted OR = 1.40, 95% CI = 1.05–1.87, $P = 0.02$), no cognitive dysfunction (adjusted OR = 1.90, 95% CI = 1.34–2.69, $P < 0.001$), ambulatory status (adjusted OR = 2.89, 95% CI = 2.03–4.10, $P < 0.001$), HF with reduced ejection fraction (adjusted OR = 1.55, 95% CI = 1.24–1.93, $P < 0.001$), estimated glomerular filtration rate $\geq$ 30 mL/min/1.73 m^2 (adjusted OR = 1.93, 95% CI = 1.45–2.58, $P < 0.001$), no anaemia (adjusted OR = 1.27, 95% CI = 1.02–1.59, $P = 0.04$), and no prescription of β-blockers prior to admission (adjusted OR = 1.32, 95% CI = 1.03–1.68, $P = 0.03$). Patients who underwent coronary angiography had a lower risk of the primary outcome [adjusted hazard ratio (HR) = 0.70, 95% CI = 0.58–0.85, $P < 0.001$]. Among the patients who underwent coronary angiography, those with coronary stenosis (38.9%) did not have lower risk of the primary outcome measure than those without coronary stenosis (adjusted HR = 0.93, 95% CI = 0.65–1.32, $P = 0.68$). Among the patients with coronary stenosis, those with coronary revascularization (54.3%) did not have higher risk of the primary outcome measure than those without coronary revascularization (adjusted HR = 1.36, 95% CI = 0.84–2.21, $P = 0.22$).

Conclusions In patients with acute HF, patients who underwent coronary angiography had a lower risk of clinical outcomes and were significantly different from those who did not undergo coronary angiography.

Keywords Acute heart failure; Coronary angiography; Outcome

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*Correspondence to: Takao Kato, MD, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. Tel: +81-75-751-4254; Fax: +81-75-751-3289. Email: tkato75@kuhp.kyoto-u.ac.jp
†These authors equally contributed to this study.

Introduction

Diagnosis and treatment of the underlying heart disease is the first step for the management of heart failure (HF).[1] In the setting of acute heart failure (AHF) hospitalization, especially in the case of first-time hospitalization, identifying the underlying heart disease such as hypertensive heart disease, valvular heart disease, cardiomyopathy, and ischaemic heart disease is important to provide disease-specific treatment, although the urgent therapy for haemodynamic abnormalities is of course mandatory.[2] Coronary artery disease (CAD) is reported to represent the most common underlying disease in HF[3,4] through the necrosis and fibrosis of the infarcted area, the remodelling of non-infarct area, and hibernation of myocardium under chronic ischaemia. Coronary angiography is the 'gold standard', though invasive, technique for the assessment of the presence, extent, and severity of CAD, and for the decision making on the revascularization therapy together with physiological assessment of myocardial ischaemia.[5]

According to the current guidelines, coronary angiography should be considered for patients with HF in the following situations[6–8]: (1) when symptoms worsen without a clear cause in patients with HF, no angina, and known CAD and (2) in HF caused by systolic dysfunction in association with angina or regional wall-motion abnormalities and/or scintigraphic evidence of reversible myocardial ischaemia when revascularization is being considered. Previous studies demonstrated that the coronary angiography in patients with AHF and worsening symptoms and/or signs of HF was associated with a subsequent reduced risk of death and HF hospitalization,[9,10] through optimization of HF treatment including coronary revascularization. However, these studies had a major limitation, because the group without coronary angiography actually included those patients with multiple times of hospitalization who had already known CAD as an aetiology of HF, and those whose general conditions did not allow invasive coronary angiography[9,10] after multiple times of hospitalization. There is no data regarding patients with de novo HF hospitalization who performed coronary angiography during hospitalization. There also is a scarcity of data on the timing of coronary angiography, coronary angiographic findings, and the subsequent coronary revascularization in patients with HF. Therefore, the aims of the present study in patients with AHF are as follows: (i) to investigate the characteristics and associated factors for coronary angiography, coronary angiographic findings, and prevalence of coronary revascularization and (ii) to assess the clinical outcomes of those patients with versus without coronary angiography, with versus without coronary stenosis, and with versus without coronary revascularization.

Methods

Study design

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicentre cohort study that enrolled consecutive patients hospitalized for AHF for the first time between 1 October 2014 and 31 March 2016 across 19 secondary and tertiary hospitals throughout Japan. The overall design of the study has been previously described in detail.[11,12] Briefly, we enrolled consecutive patients with AHF, as defined by the modified Framingham criteria, who were admitted to the participating centres and who underwent HF-specific treatment involving intravenous drugs administered within 24 h of hospital presentation. Among the 4056 patients who were enrolled in the KCHF registry, we excluded 271 patients who died during the index hospitalization (Supporting Information, *Table S1*), 206 patients with acute coronary syndrome (ACS), 1292 patients with prior HF hospitalization, 67 patients without data regarding prior HF hospitalization, and 57 patients who were lost to follow-up. The current study population consisted of 2163 patients with de novo HF hospitalization and without ACS (*Figure 1*).

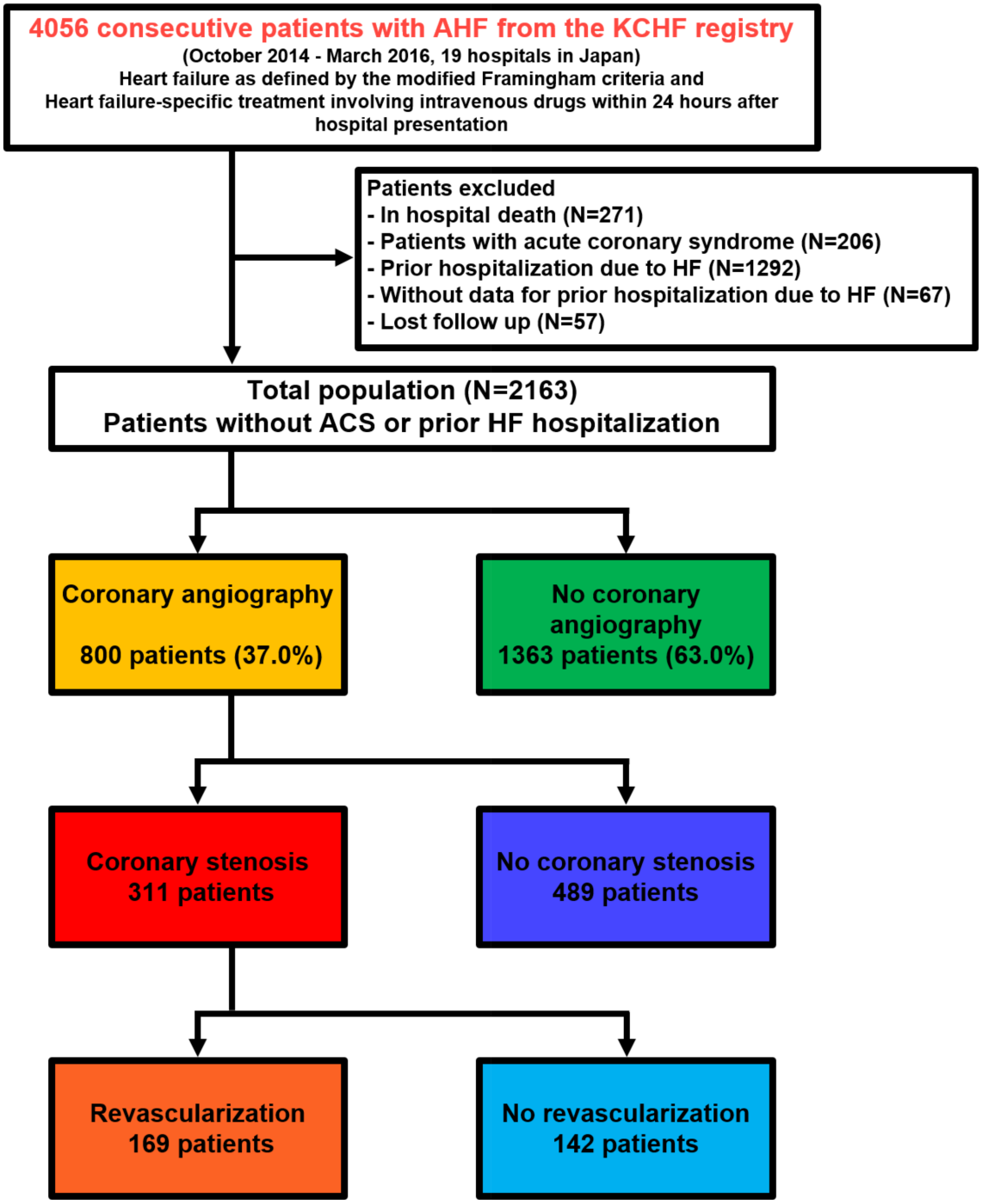
Ethics

The investigation conformed to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethics committee in Kyoto University Hospital (local identifier: E2311) and each participating hospital. A waiver of written informed consent was granted by the institutional review boards of Kyoto University and each participating centre, as the study met the conditions outlined in the Japanese ethical guidelines for medical and health research involving human subjects.[13] We disclosed the details of the present study to the public as an opt-out method and informed the patients of their right to refuse enrolment.

Data collection and definitions

The attending physicians or research assistants at each participating hospital collected data on patient demographics,

Figure 1 Study flowchart and study population. AHF, acute heart failure; HF, heart failure; KCHF, Kyoto Congestive Heart Failure.



medical histories, underlying heart disease, signs, symptoms, medications, laboratory tests, chest radiographs on admission and at discharge, electrocardiography, and echocardiography during the index hospitalization. The timing of echocardiography varied among the patients, but we adopted the data at the earliest echocardiographic examination during the index hospitalization. Moreover, we collected data on coronary angiography during the index hospitalization. We did not collect data on coronary computer tomography angiography (CTA). One-year clinical follow-up data with an allowance of 1 month were collected in October 2017. The attending physicians or research assistants at each

participating hospital collected data regarding clinical events that occurred during follow-up from the hospital charts or by contacting patients, their relatives, or their referring physicians with their consent.

Coronary stenosis was defined as >50% diameter stenosis by visual estimation. Coronary revascularization was defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Aetiology of HF was defined as the most likely cause of structural or functional cardiac disorders, of which only one category was chosen.[12] Aetiology was classified as (i) CAD; (ii) hypertensive heart disease; (iii) cardiomyopathy; (iv) valvular heart disease; or (v) other heart disease. CAD was defined as previous myocardial infarction, or prior PCI/CABG. Primary cardiomyopathy was classified as hypertrophic cardiomyopathy, dilated cardiomyopathy, and dilated phase of hypertrophic cardiomyopathy. Valvular heart disease was classified as moderate–severe aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation (excluding functional mitral regurgitation), tricuspid regurgitation, and prosthetic valve dysfunction. As the valvular heart disease, we chose only one category that seemed to be the most closely related to AHF. Other heart disease included other cardiomyopathy, arrhythmia (bradycardia or tachycardia), congenital heart disease, and constrictive pericarditis.[12] Anaemia was defined using the World Health Organization criteria (haemoglobin < 12.0 g/dL in women and <13.0 g/dL in men). Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 at admission.[14] B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) was measured at admission in each participating institution using commercially available immunochemical assays. HF was classified based on left ventricular ejection fraction (LVEF) as heart failure with preserved LVEF (HFpEF) with LVEF ≥ 50%, heart failure with mildly reduce LVEF (HFmrEF) with LVEF 40–49%, and heart failure with reduced LVEF (HFrEF) with LVEF < 40%.[8]

The primary outcome measure in the present study was the composite of all-cause death or HF hospitalization. The secondary outcome measures were all-cause death and HF hospitalization, respectively. HF hospitalization was defined as hospitalization due to worsening of HF requiring intravenous drug therapy.[11,12] A clinical event committee adjudicated all the endpoint events.[11,12]

Statistical analysis

Categorical variables were presented as numbers and percentages and were compared using the χ^2 test or Fisher's exact test. Continuous variables were expressed as means and standard deviations or medians with interquartile ranges (IQRs) and were compared using Student's *t*-test or Wilcoxon rank sum test based on their distributions. To explore the factors associated with coronary angiography, we developed a multivariable logistic regression model. The model used clinical and laboratory categorical variables at admission and medications at admission with *P*-value < 0.05 as entry criteria from *Table 1*. We assessed multicollinearity by the variance inflation factor (VIF)[15] and verified these variables with VIF < 10. The results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We compared baseline characteristics and 1 year clinical outcomes according to (i) patients with versus without coronary angiography, (ii) patients with versus without coronary stenosis, and (iii) patients with versus without coronary revascularization. We regarded the date of discharge from the index hospitalization as 'time zero' for clinical follow-up. The cumulative incidences of clinical events that occurred during 1 year period after discharge were estimated using the Kaplan–Meier method with intergroup differences assessed by the log-rank test. Multivariable Cox proportional hazard models were developed for the primary and secondary outcome measures by adjusting the potential confounders. The results were expressed as hazard ratios (HRs) and 95% CIs. We included the following 18 clinically relevant risk-adjusting variables according to their clinical relevance to the clinical outcomes and based on the previous studies[16]: age ≥ 80 years, sex, body mass index (BMI) ≤ 22 kg/m^2, LVEF < 40% on echocardiography, hypertension, diabetes, atrial fibrillation or flutter, previous myocardial infarction, previous stroke, ambulatory status, systolic blood pressure < 90 mmHg, heart rate < 60 b.p.m., eGFR < 30 mL/min/1.73 m^2, serum albumin < 3.0 g/dL, serum sodium < 135 mEq/L, anaemia, and prescription of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) at discharge, and prescription of β-blockers at discharge. Continuous variables were dichotomized using clinically meaningful reference values or median values. All the statistical analyses were conducted by two physicians (Y.S. and T.K.) and a statistician (T.M.) using JMP Version 15 (SAS Institute Inc., Cary, NC, USA) and EZR.[17] All the reported *P*-values were two-tailed, and the level of statistical significance was set at $P < 0.05$.

Results

Characteristics of the study population

From the 2163 patients in de novo hospitalization without ACS included in this study, 800 patients (37.0%) underwent coronary angiography (*Figure 1*). The mean age was 77.2 ± 12.4 years and 45.0% of patients were women. The mean LVEF was 47.4 ± 16.1%.

Characteristics of the patients with or without coronary angiography are shown in *Table 1*. Patients who underwent coronary angiography were younger, more likely to be men, had higher BMI, heart rate, BNP, eGFR, serum albumin, and

Table 1 Patient characteristics

Variables	Entire study population (N = 2163)	Coronary angiography (N = 800)	No coronary angiography (N = 1363)	P-value	Total N of patients analysed
Clinical characteristic					
Age, years	77.2 ± 12.4	72.3 ± 12.2	80.1 ± 11.5	<0.001	2163
Age ≥ 80 years[a]	1087 (50.3)	259 (32.4)	828 (60.7)	<0.001	2163
Women[a]	973 (45.0)	276 (34.5)	697 (51.1)	<0.001	2163
BMI, kg/m^2	23.0 ± 4.5	23.6 ± 4.5	22.6 ± 4.5	<0.001	2046
BMI ≤ 22 kg/m^{2a}	914 (44.7)	301 (38.5)	613 (48.5)	<0.001	2046
Aetiology				<0.001	2163
Coronary artery disease	555 (25.7)	276 (34.5)	279 (20.5)		
Hypertensive heart disease	647 (29.9)	187 (23.4)	460 (33.7)		
Valvular heart disease	445 (20.6)	133 (16.6)	312 (22.9)		
Cardiomyopathy	323 (14.9)	159 (19.9)	164 (12.0)		
Other heart disease	193 (8.9)	45 (5.6)	148 (10.9)		
Medical history					
Hypertension[a]	1590 (73.5)	571 (71.4)	1019 (74.8)	0.08	2163
Diabetes[a]	729 (33.7)	309 (38.6)	420 (30.8)	<0.001	2163
Dyslipidaemia	765 (35.4)	316 (39.5)	449 (32.9)	0.002	2163
Atrial fibrillation or flutter[a]	818 (37.8)	236 (29.5)	582 (42.7)	<0.001	2163
Previous myocardial infarction[a]	369 (17.1)	157 (19.6)	212 (15.6)	0.02	2163
Previous PCI or CABG	403 (18.6)	147 (18.4)	256 (18.8)	0.81	2163
Prior device implantation				<0.001	2163
Pacemaker	107 (4.9)	18 (2.3)	89 (6.5)		
ICD	19 (0.9)	7 (0.9)	12 (0.9)		
CRTP/CRTD	11 (0.5)	3 (0.4)	8 (0.6)		
Previous stroke[a]	330 (15.3)	97 (12.1)	233 (17.1)	0.002	2163
Current smoking	289 (13.6)	166 (21.1)	123 (9.2)	<0.001	2126
Chronic kidney disease	791 (36.6)	227 (28.4)	564 (41.4)	<0.001	2163
COPD	181 (8.4)	57 (7.1)	124 (9.1)	0.11	2163
Malignancy	312 (14.4)	110 (13.8)	202 (14.8)	0.49	2163
Cognitive dysfunction	371 (17.2)	57 (7.1)	314 (23.0)	<0.001	2163
Daily life activities				<0.001	2148
Ambulatory[a]	1748 (81.4)	748 (93.9)	1000 (74.0)		
Use of wheelchair	316 (14.7)	44 (5.5)	272 (20.1)		
Bedridden	84 (3.9)	5 (0.6)	79 (5.8)		
Vital signs at presentation					
Heart rate, b.p.m.	98.1 ± 29.0	101.8 ± 26.6	95.9 ± 30.1	<0.001	2151
<60 b.p.m.[a]	170 (7.9)	38 (4.8)	132 (9.7)	<0.001	2151
Systolic BP, mmHg	152.3 ± 34.8	152.2 ± 35.4	152.4 ± 34.4	0.90	2159
<90 mmHg[a]	35 (1.6)	15 (1.9)	20 (1.5)	0.46	2161
Rhythms at presentation				<0.001	2163
Sinus rhythm	1227 (56.7)	517 (64.6)	710 (52.1)		
Atrial fibrillation or flutter	799 (36.9)	249 (31.1)	550 (40.4)		
Others	137 (6.3)	34 (4.3)	103 (7.6)		
NYHA class III or IV	1875 (87.1)	693 (87.1)	1182 (87.1)	0.98	2153
Echocardiography					
LVEF, %	47.4 ± 16.1	42.6 ± 15.7	50.3 ± 15.6	<0.001	2120
LVEF classification				<0.001	2157
HFrEF (LVEF < 40%)[a]	747 (34.6)	374 (46.8)	373 (27.5)		
HFmrEF (LVEF 40–49%)	408 (18.9)	180 (22.5)	228 (16.8)		
HFpEF (LVEF ≥ 50%)	1002 (46.5)	246 (30.8)	756 (55.7)		
Laboratory findings on admission					
BNP, pg/mL	689 (379–1217)	733 (421–1319)	653 (360–1168)	0.003	1937
NT-proBNP, pg/mL	4956 (2677–10 283)	4319 (2660–8416)	6226 (2772–11 685)	0.053	199
Troponin I, ng/mL	0.052 (0.023–0.176)	0.055 (0.024–0.183)	0.050 (0.022–0.168)	0.30	920
Troponin T, ng/mL	0.040 (0.024–0.090)	0.037 (0.021–0.094)	0.042 (0.026–0.088)	0.51	459
Serum creatinine, mg/dL	1.01 (0.77–1.41)	0.99 (0.77–1.29)	1.03 (0.77–1.53)	0.002	2160
eGFR, mL/min/1.73 m^{2a}	50.3 ± 24.2	54.4 ± 23.1	47.9 ± 24.6	<0.001	2160
<30 mL/min/1.73 m^2	439 (20.3)	105 (13.1)	334 (24.6)	<0.001	2160
Albumin, g/L	34.8 ± 4.9	35.5 ± 4.9	34.4 ± 4.9	<0.001	2104
<30 g/L[a]	287 (13.6)	89 (11.5)	198 (14.9)	0.03	2104
Sodium, mEq/L	139.3 ± 4.1	139.4 ± 3.8	139.3 ± 4.3	0.83	2155
<135 mEq/L[a]	234 (10.9)	79 (9.9)	155 (11.4)	0.27	2155
Haemoglobin, g/dL	11.7 ± 2.4	12.4 ± 2.5	11.3 ± 2.3	<0.001	2158
Anaemia[a]	1354 (62.7)	415(51.9)	939 (69.1)	<0.001	2158
Medication prior to admission					

(*Continues*)

Table 1 (continued)

Variables	Entire study population (*N* = 2163)	Coronary angiography (*N* = 800)	No coronary angiography (*N* = 1363)	*P*-value	Total *N* of patients analysed
ACEI/ARBs	902 (41.7)	325 (40.6)	577 (42.3)	0.44	2163
β-Blockers	628 (29.0)	205 (25.6)	423 (31.0)	0.008	2163
MRAs	242 (11.2)	72 (9.0)	170 (12.5)	0.01	2163
Loop diuretics	715 (33.1)	210 (26.3)	505 (37.1)	<0.001	2163
Aspirin	572 (26.4)	199 (24.9)	373 (27.4)	0.20	2163
P2Y12 receptor blockers	217 (10.0)	68 (8.5)	149 (10.9)	0.07	2163
Medication at discharge					
ACEI/ARBs[a]	1271 (58.8)	551 (68.9)	720 (52.8)	<0.001	2163
β-Blockers[a]	1406 (65.0)	617 (77.1)	789 (57.9)	<0.001	2163
MRAs	1024 (47.3)	417 (52.1)	607 (44.5)	<0.001	2163
Loop diuretics	1715 (79.3)	617 (77.1)	1098 (80.6)	0.06	2163
Aspirin	709 (32.8)	352 (44.0)	357 (26.2)	<0.001	2163
P2Y12 receptor blockers	353 (16.3)	202 (25.3)	151 (11.1)	<0.001	2163
Length of hospital stay (days)	16 (11–23)	17 (12–25)	15 (11–22)	<0.001	2162

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
Values are number (%) or mean ± standard deviation, or median (interquartile range). *P*-values were calculated using the χ^2 test or Fisher's exact test for categorical variables, and the Student's *t*-test or Wilcoxon rank sum test for continuous variables.
Aetiology was defined as the most likely cause of structural or functional cardiac disorders, of which only one category was chosen. Aetiology was classified as (i) coronary artery disease; (ii) hypertensive heart disease; (iii) cardiomyopathy; (iv) valvular heart disease; or (v) other heart disease. Coronary artery disease was defined as previous myocardial infarction, or prior PCI/CABG. Acute coronary syndrome was excluded in the present study. Primary cardiomyopathy was classified as hypertrophic cardiomyopathy, dilated cardiomyopathy, and dilated phase of hypertrophic cardiomyopathy. Valvular heart disease was classified as moderate–severe aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation (excluding functional mitral regurgitation), tricuspid regurgitation, and prosthetic valve dysfunction. As the valvular heart disease, we chose only one category that seemed to be the most closely related to acute HF. Other heart disease included other cardiomyopathy, arrhythmia (bradycardia or tachycardia), congenital heart disease, and constrictive pericarditis.
[a]Risk-adjusting variables selected for the Cox proportional hazard models.

haemoglobin, had higher prevalence of aetiology associated with CAD, diabetes, dyslipidaemia, and previous myocardial infarction, while they had lower prevalence of atrial fibrillation or flutter, prior device implantation, previous stroke, and CKD, and had lower LVEF. Patients who underwent coronary angiography were less frequently treated with β-blockers, mineralocorticoid receptor antagonist (MRA), and loop diuretics at admission, but more frequently treated with ACEI/ARBs, β-blockers, MRA, aspirin, and P2Y12 receptor blockers at discharge. Patients who underwent coronary angiography had longer hospital stay (*Table 1*).

By the multivariable logistic regression analysis, the factors independently associated with coronary angiography were age < 80 years (adjusted OR = 1.76, 95% CI = 1.41–2.20, $P < 0.001$), men (adjusted OR = 1.28, 95% CI = 1.03–1.59, $P = 0.02$), diabetes (adjusted OR = 1.27, 95% CI = 1.02–1.60, $P = 0.04$), no atrial fibrillation or flutter (adjusted OR = 1.45, 95% CI = 1.17–1.82, $P < 0.001$), no prior device implantation (adjusted OR = 1.81, 95% CI = 1.13–2.91, $P = 0.01$), current smoking (adjusted OR = 1.40, 95% CI = 1.05–1.87, $P = 0.02$), no cognitive dysfunction (adjusted OR = 1.90, 95% CI = 1.34–2.69, $P < 0.001$), ambulatory (adjusted OR = 2.89, 95% CI = 2.03–4.10, $P < 0.001$), HFrEF (adjusted OR = 1.55, 95% CI = 1.24–1.93, $P < 0.001$), eGFR ≥ 30 mL/min/1.73 m^2 (adjusted OR = 1.93, 95% CI = 1.45–2.58, $P < 0.001$), no anaemia (adjusted OR = 1.27, 95% CI = 1.02–1.59, $P = 0.04$), and no prescription of β-blockers prior to admission (adjusted OR = 1.32, 95% CI = 1.03–1.68, $P = 0.03$) (*Table 2*).

Coronary angiographic findings

Coronary stenosis was found in 38.9% (*N* = 311) of 800 patients who underwent coronary angiography. Characteristics of patients with and without coronary stenosis are presented in Supporting Information, *Table S2*. Patients with coronary stenosis were older, had higher prevalence of aetiology associated with CAD, hypertension, diabetes, dyslipidaemia, previous myocardial infarction, previous PCI or CABG, previous stroke, and CKD, and had higher systolic blood pressure, BNP, troponin I, troponin T, eGFR, and had lower serum albumin, and haemoglobin. Patients with coronary stenosis were more frequently treated with ACEI/ARBs at admission. Patients with coronary stenosis were more frequently treated with aspirin and P2Y12 receptor blockers at both admission and discharge. Patients with coronary stenosis had longer hospital stay (Supporting Information, *Table S2*).

Table 2 Factors associated with coronary angiography by logistic regression analysis

Variables	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Variance inflation factor
Age < 80 years	3.23 (2.69–3.88)	<0.001	1.76 (1.41–2.20)	<0.001	1.17
Men	1.99 (1.66–2.38)	<0.001	1.28 (1.03–1.59)	0.02	1.12
BMI > 22 kg/m^2	1.50 (1.25–1.80)	<0.001	1.09 (0.88–1.35)	0.41	1.09
Diabetes	1.41 (1.18–1.70)	<0.001	1.27 (1.02–1.60)	0.04	1.17
Dyslipidaemia	1.33 (1.11–1.59)	0.002	1.19 (0.95–1.49)	0.12	1.15
No atrial fibrillation or flutter	1.78 (1.48–2.15)	<0.001	1.45 (1.17–1.82)	<0.001	1.10
Previous myocardial infarction	1.33 (1.06–1.66)	0.02	1.11 (0.83–1.47)	0.48	1.19
No prior device implantation	2.40 (1.57–3.67)	<0.001	1.81 (1.13–2.91)	0.01	1.05
No previous stroke	1.49 (1.16–1.93)	0.002	1.16 (0.86–1.57)	0.33	1.04
Current smoking	2.64 (2.05–3.40)	<0.001	1.40 (1.05–1.87)	0.02	1.09
No cognitive dysfunction	3.90 (2.90–5.25)	<0.001	1.90 (1.34–2.69)	<0.001	1.10
Ambulatory	5.36 (3.92–7.33)	<0.001	2.89 (2.03–4.10)	<0.001	1.08
Heart rate ≥ 60 b.p.m.	2.15 (1.48–3.12)	<0.001	1.48 (0.97–2.25)	0.07	1.03
HFrEF (LVEF < 40%)	2.32 (1.93–2.78)	<0.001	1.55 (1.24–1.93)	<0.001	1.14
eGFR ≥ 30 mL/min/1.73 m^2	2.15 (1.70–2.74)	<0.001	1.93 (1.45–2.58)	<0.001	1.11
Albumin ≥ 30 g/L	1.36 (1.04–1.77)	0.03	1.04 (0.76–1.42)	0.82	1.07
No anaemia	2.08 (1.74–2.49)	<0.001	1.27 (1.02–1.59)	0.04	1.19
No prescription of β-blockers prior to admission	1.31 (1.07–1.59)	0.008	1.32 (1.03–1.68)	0.03	1.18
No prescription of MRAs prior to admission	1.44 (1.08–1.93)	0.01	0.99 (0.69–1.43)	0.98	1.20
No prescription of loop diuretics prior to admission	1.65 (1.36–2.00)	<0.001	1.10 (0.85–1.41)	0.47	1.31

BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA; mineralocorticoid receptor antagonist; OR, odds ratio.

Coronary revascularization during hospitalization

Of 311 patients with coronary stenosis, 169 patients (54.3%) underwent coronary revascularization therapy (PCI: 150 patients, CABG: 18 patients, PCI and CABG: 1 patient). Characteristics of patients with and without revascularization are presented in Supporting Information, *Table S3*. Patients who underwent revascularization had higher prevalence of aetiology associated with CAD, had lower prevalence of hypertension and previous PCI or CABG, and had lower systolic blood pressure. Patients who underwent revascularization were less frequently treated with β-blockers and aspirin at admission, but more frequently treated with aspirin and P2Y12 receptor blockers at discharge. Patients who underwent revascularization had longer hospital stay (Supporting Information, *Table S3*). Details of angiographic findings are presented in Supporting Information, *Table S4* and *Figure S1*. Patients who underwent revascularization were more likely to have stenosis of left anterior descending coronary artery (Supporting Information, *Table S4*). The median interval from admission to the day of PCI was 13 (IQR: 8–18) days (Supporting Information, *Figure S2*).

Outcomes: coronary angiography versus no coronary angiography

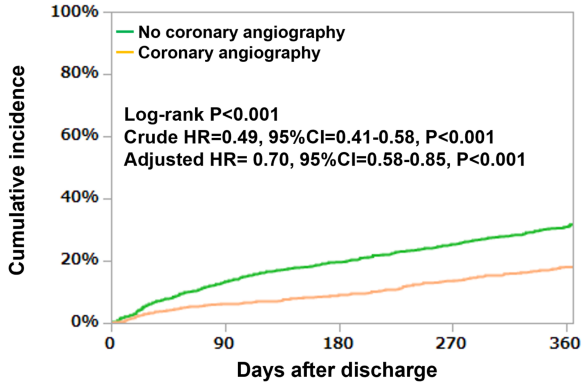
The median follow-up duration was 475 (IQR: 364–642) days with 95.1% follow-up rate during a 1 year period. The cumulative 1 year incidence of the primary outcome measure (composite of all-cause death or HF hospitalization) was significantly lower in patients who underwent coronary angiography than in those who did not undergo coronary angiography (18.0% vs. 31.6%, $P < 0.001$) [*Figure 2(A)*]. The cumulative 1 year incidence of all-cause death or HF hospitalization was also significantly lower in patients who underwent coronary angiography than in those who did not undergo coronary angiography (7.9% vs. 18.3%, $P < 0.001$; 12.1% vs. 19.5%, $P < 0.001$) [*Figure 2(B)* and *2(C)*]. After adjusting for confounders, the lower risk of patients who underwent coronary angiography relative to those who did not undergo coronary angiography remained significant for the primary outcome measure (adjusted HR = 0.70, 95% CI = 0.58–0.85, $P < 0.001$), all-cause death (adjusted HR = 0.66, 95% CI = 0.51–0.86, $P = 0.002$), and HF hospitalization (adjusted HR = 0.70, 95% CI = 0.55–0.90, $P = 0.005$) [*Figure 2(A)–2(C)*].

Outcomes: coronary stenosis versus no coronary stenosis

The cumulative 1 year incidences of the primary outcome measure, all-cause death, and HF hospitalization were not significantly different between the two groups of patients with and without coronary stenosis (20.7% vs. 16.2%, $P = 0.06$; 10.4% vs. 6.3%, $P = 0.06$; 13.3% vs. 11.4%, $P = 0.21$, respectively) [*Figure 3(A)–3(C)*]. After adjusting for confounders, the risk of patients with coronary stenosis relative to those without coronary stenosis remained insignificant for the primary outcome measure (adjusted HR = 0.93, 95% CI = 0.65–1.32, $P = 0.68$), all-cause death (adjusted HR = 0.93, 95% CI = 0.56–1.54, $P = 0.77$), and HF hospitaliza-

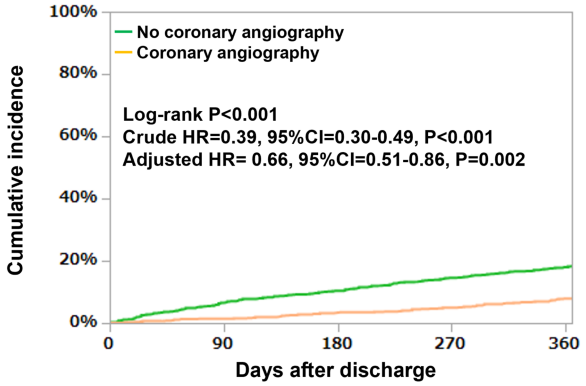
Figure 2 Kaplan–Meier curves for the primary and secondary outcome measures: coronary angiography versus no coronary angiography. (A) Composite of all-cause death or HF hospitalization, (B) all-cause death, and (C) HF hospitalization. CI, confidence interval; HF, heart failure; HR, hazard ratio.

(A)



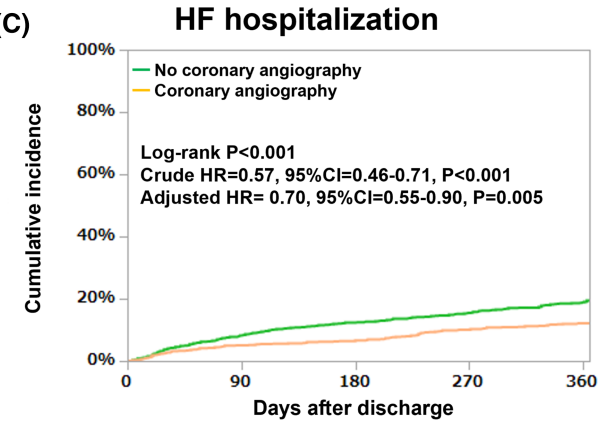
Interval (days)	0	30	180	365
No coronary angiography				
N of patients with at least 1 event		82	264	419
N of patients at risk	1363	1272	1062	825
Cumulative incidence		6.0%	19.6%	31.6%
Coronary angiography				
N of patients with at least 1 event		25	72	142
N of patients at risk	800	774	722	558
Cumulative incidence		3.1%	9.0%	18.0%

(B)



Interval (days)	0	30	180	365
No coronary angiography				
N of patients with event		38	139	242
N of patients at risk	1363	1316	1180	978
Cumulative incidence		2.8%	10.4%	18.3%
Coronary angiography				
N of patients with event		5	28	62
N of patients at risk	800	794	765	632
Cumulative incidence		0.6%	3.5%	7.9%

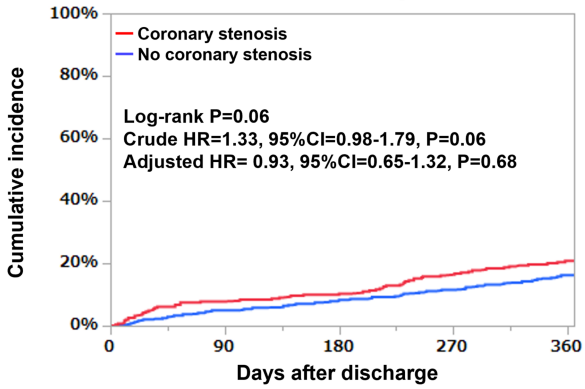
(C)



Interval (days)	0	30	180	365
No coronary angiography				
N of patients with at least 1 event		51	161	241
N of patients at risk	1363	1272	1062	825
Cumulative incidence		3.8%	12.5%	19.5%
Coronary angiography				
N of patients with at least 1 event		21	52	94
N of patients at risk	800	774	722	558
Cumulative incidence		2.6%	6.6%	12.1%

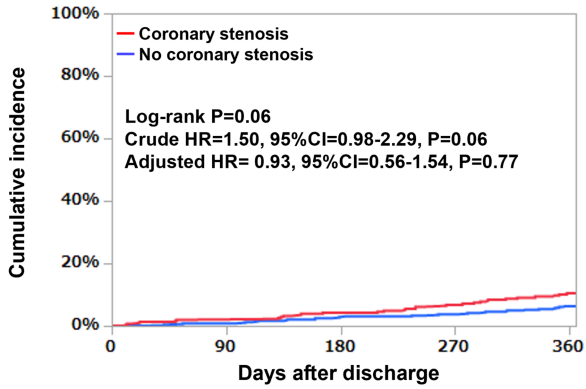
Figure 3 Kaplan–Meier curves for the primary and secondary outcome measures: coronary stenosis versus no coronary stenosis. (A) Composite of all-cause death or HF hospitalization, (B) all-cause death, and (C) HF hospitalization. CI, confidence interval; HF, heart failure; HR, hazard ratio.

(A)



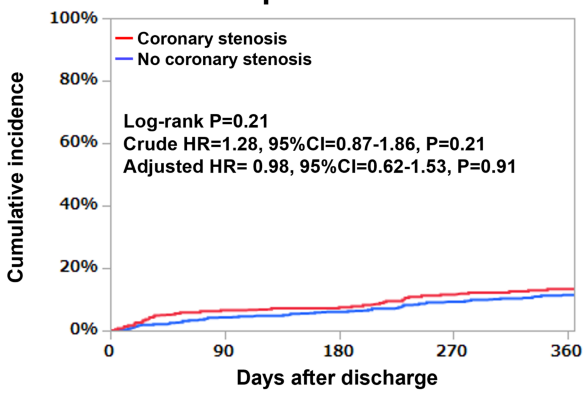
Interval (days)	0	30	180	365
Coronary stenosis				
N of patients with at least 1 event		15	32	64
N of patients at risk	311	296	278	212
Cumulative incidence		4.8%	10.3%	20.7%
No coronary stenosis				
N of patients with at least 1 event		10	40	78
N of patients at risk	489	478	444	346
Cumulative incidence		2.0%	8.2%	16.2%

(B)



Interval (days)	0	30	180	365
Coronary stenosis				
N of patients with event		4	13	32
N of patients at risk	311	307	297	241
Cumulative incidence		1.3%	4.2%	10.4%
No coronary stenosis				
N of patients with event		1	15	30
N of patients at risk	489	487	468	391
Cumulative incidence		0.2%	3.1%	6.3%

(C)



Interval (days)	0	30	180	365
Coronary stenosis				
N of patients with at least 1 event		12	23	40
N of patients at risk	311	296	278	212
Cumulative incidence		3.9%	7.5%	13.3%
No coronary stenosis				
N of patients with at least 1 event		9	29	54
N of patients at risk	489	478	444	346
Cumulative incidence		1.8%	6.0%	11.4%

tion (adjusted HR = 0.98, 95% CI = 0.62–1.53, *P* = 0.91) [*Figure 3(A)–3(C)*].

Outcomes: coronary revascularization versus no revascularization

The cumulative 1 year incidences of the primary outcome measure, all-cause death, and HF hospitalization were not significantly different between the two groups of patients with and without coronary revascularization (24.4% vs. 16.3%, *P* = 0.16; 11.4% vs. 9.2%, *P* = 0.91; 15.1% vs. 11.0%, *P* = 0.13, respectively) [*Figure 4(A)–4(C)*]. After adjusting for confounders, the risk of patients with coronary revascularization relative to those without coronary revascularization remained insignificant for the primary outcome measure (adjusted HR = 1.36, 95% CI = 0.84–2.21, *P* = 0.22), all-cause death (adjusted HR = 0.99, 95% CI = 0.50–1.96, *P* = 0.98), and HF hospitalization (adjusted HR = 1.57, 95% CI = 0.84–2.92, *P* = 0.15) [*Figure 4(A)–4(C)*].

Discussion

The main findings of the present study are as follows: (i) among patients with de novo HF hospitalization, 37.0% of patients underwent coronary angiography; (ii) the factors independently associated with coronary angiography were age $<$ 80 years, men, diabetes, current smoking, ambulatory status, HFrEF, eGFR $\geq$ 30 mL/min/1.73 m^2, no atrial fibrillation or flutter, no prior device implantation, no cognitive dysfunction, no anaemia, and no prescription of β-blockers prior to admission; and (iii) the lower adjusted risk of patients who underwent coronary angiography relative to those who did not undergo coronary angiography remained significant for the composite of all-cause death or HF hospitalization, all-cause death, and HF hospitalization.

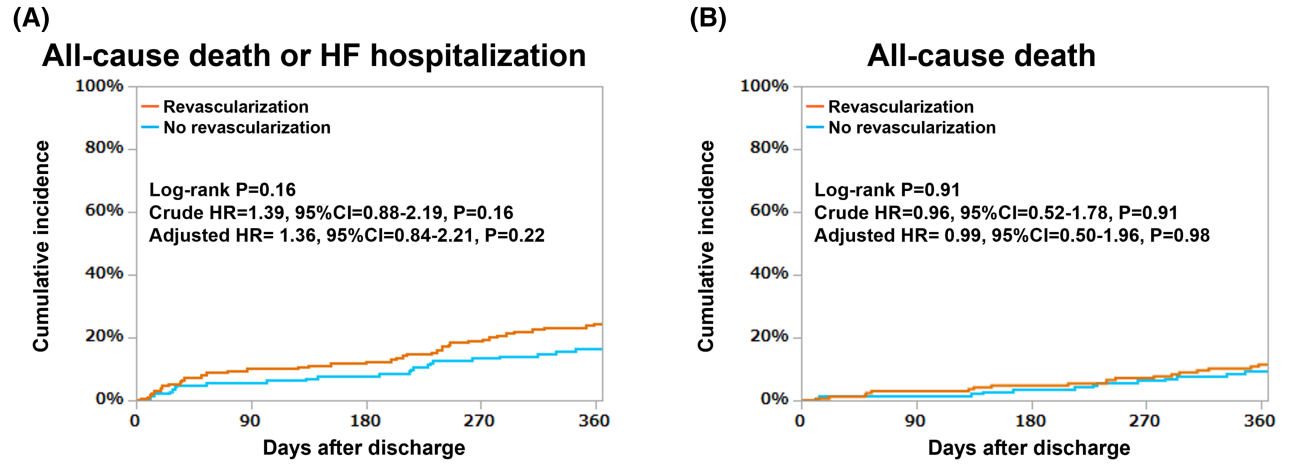
Previous studies reported that around 10% of the patients with worsening HF underwent coronary angiography.[9,10] Flaherty *et al*. reported 18.6% of patients with de novo HF underwent in-hospital angiography.[9] In our study, the prevalence of coronary angiography was numerically higher than in those studies. Clinical practices for HF and the length of hospital stay may be quite different in the different regions. In Japan, the higher coronary angiography rate may be related to the longer hospital stay and the lower threshold for coronary angiography than in other countries.[18]

Coronary artery disease has been reported to represent the most common aetiology of HF.[3] Coronary angiography is recommended as a method for detecting the ischaemic aetiology in patients with HF despite of its invasiveness[8] or for excluding CAD for the subsequent surgical procedures. We determined the aetiology of HF not only by findings of coronary angiography but also by echocardiographic findings, magnetic resonance imaging findings, nuclear cardiologic findings, and clinical course. If left ventricular dysfunction was not expected based on the findings of coronary angiography, it was not classified as an ischaemic aetiology. The association with β-blocker use prior to hospitalization and coronary angiography may be the case in patients with suspected cardiomyopathy. Men and diabetes were major risk factors for atherosclerosis and by be the driving force to coronary angiography in the present study.[19,20] Advanced age, renal dysfunction, and anaemia were associated with lower rates of undergoing coronary angiography in the present study. Elderly patients had more likely to have HFpEF and renal dysfunction and a high risk for contrast-induced nephropathy.[10,21–23] Due to the invasiveness of coronary angiography, patients with non-ambulatory status and cognitive dysfunction might be less likely to undergo coronary angiography. Patients with cardiac devices and atrial fibrillation or flutter might be already investigated for coronary disease at the timing of device implantation or treatment of arrhythmia and require less investigation.

In the current study, undergoing coronary angiography was associated with reduced risk of worse clinical outcomes, consistent with the previous studies.[9,10] Coronary angiography itself is a diagnostic tool; thus, it does not improve outcomes. It provides information regarding the extent or severity of CAD and provides an opportunity for treatment (e.g. coronary revascularization and optimal medical therapy) that will likely have an influence on the prognosis.[24] Coronary angiography was associated with an increased use of antiplatelets, β-blockers, and ACEI/ARBs in our study in consistent with the study by Flaherty *et al*.[9] Masoudi *et al*. reported that aspirin prescription was associated with a significantly lower risk of mortality in patients with CAD and HF hospitalization.[25] We consider that coronary angiography results in optimal medical therapy for HF in the patients both with CAD and without CAD. Lopes *et al*. reported that coronary revascularization was associated with better clinical outcomes in patients with CAD and HF with left ventricular dysfunction.[26] Coronary revascularization may optimize the treatment of patients with both CAD and AHF. Further research, particularly clinical trials, would be warranted to evaluate the clinical benefit of coronary revascularization to patients with CAD and AHF.

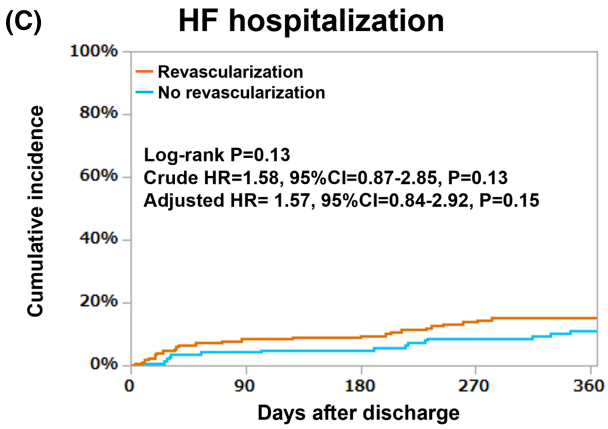
The presence of coronary stenosis is not associated with worse prognosis, and this finding contrasted with previous studies.[10,27] There may be two speculative reasons: optimal medical therapies and revascularization for CAD. Optimal medical therapies for CAD may reduce the impact of coronary stenosis on mortality and HF rehospitalization.[25,28] Optimal coronary revascularization also may reduce the impact of coronary stenosis on mortality and HF rehospitalization.[29,30] There was a difference in high in-hospital revascularization rate (54% in our study) in patients with coronary stenosis

Figure 4 Kaplan–Meier curves for the primary and secondary outcome measures: coronary revascularization versus no revascularization. (A) Composite of all-cause death or HF hospitalization, (B) all-cause death, and (C) HF hospitalization. CI, confidence interval; HF, heart failure; HR, hazard ratio.



Interval (days)	0	30	180	365
Revascularization				
N of patients with at least 1 event		9	21	41
N of patients at risk	169	160	148	109
Cumulative incidence		5.3%	12.4%	24.4%
No revascularization				
N of patients with at least 1 event		6	11	23
N of patients at risk	142	136	130	103
Cumulative incidence		4.2%	7.8%	16.3%

Interval (days)	0	30	180	365
Revascularization				
N of patients with event		2	8	19
N of patients at risk	169	167	161	129
Cumulative incidence		1.2%	4.7%	11.4%
No revascularization				
N of patients with event		2	5	13
N of patients at risk	142	140	136	112
Cumulative incidence		1.4%	3.5%	9.2%



Interval (days)	0	30	180	365
Revascularization				
N of patients with at least 1 event		8	16	25
N of patients at risk	169	160	148	109
Cumulative incidence		4.8%	9.6%	15.1%
No revascularization				
N of patients with at least 1 event		4	7	15
N of patients at risk	142	136	130	103
Cumulative incidence		2.8%	5.0%	11.0%

than previous study (<30%),[9] although the appropriateness and completeness of the revascularization were not assessed in the present study.

Although coronary revascularization was associated with better clinical outcomes in patients with CAD and HF with left ventricular dysfunction,[26,31] there are no reports regarding the association with coronary revascularization and post-discharge outcomes during hospitalization for AHF. The timing of PCI was almost 2 weeks after admission and probably under stable conditions in the present study. Our data did not show the favourable association with coronary revascularization of outcomes in patients with coronary stenosis and AHF. Patients who underwent revascularization were more likely to have stenosis in left anterior descending coronary artery, left main coronary artery, and multi-vessel disease, while we did not collect the data on plaque morphology and composition, and the details of the way in which patients have been revascularized (complete/not complete/number of vessels treated). Advance age and the high rate of HFpEF in our present study population were remarkable characteristics compared with the previous studies. These multiple factors may hamper the effect of coronary revascularization in the present study. The pre-specified criteria for coronary angiography and revascularization were not determined because the study was conducted in an observational fashion; further studies are needed to evaluate the clinical benefit of coronary angiography and revascularization during hospitalization in patients with AHF and CAD under pre-specified criteria for the diagnostic tests and subsequent coronary treatment. Despite of these limitations, our study illustrated the characteristics and outcomes in patients who underwent coronary angiography and coronary revascularization during HF hospitalization in the real world in Japan.

Limitations

The present study had several limitations. First, the observational nature of the study design could have introduced residual confounding factors. Second, it is impossible to account for the effect of selection biases that may have determined who underwent angiography as well as treatment biases that may have influenced who received pharmacological therapies for CAD and HF. Third, results from coronary intervention outcomes (e.g. stent placement and CABG referral) are not available in the dataset. Fourth, we can only hypothesize on the reasons that led clinicians to perform a coronary angiogram because this information is also not available. Fifth, we did not collect data about coronary CTA, coronary plaque morphology and composition, speckle-tracking global longitudinal strain, or cardiac magnetic resonance imaging, which would have influenced the decision to perform coronary angiography and coronary revascularization. Finally, the data from the KCHF registry come from Japan centres only and may not be representative of HF patients in other regions of the world.

Conclusions

In patients with AHF, patients who underwent coronary angiography had a lower risk of clinical outcomes and were significantly different from those who did not undergo coronary angiography.

Conflict of interest

None declared.

Funding

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient characteristics in patients who died during hospitalization.
Table S2. Patient characteristics: coronary stenosis vs. no coronary stenosis.
Table S3. Patient characteristics: revascularization vs. no revascularization.
Table S4. Coronary angiographic findings.
Figure S1. Coronary angiographic findings.
Figure S2. Interval from admission to the day of PCI.

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