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ORIGINAL ARTICLE
Acute Heart Failure

Starting Neurohormonal Antagonists in Patients With Acute Heart Failure With Mid-Range and Preserved Ejection Fraction

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Background: The clinical benefits of neurohormonal antagonists for patients with heart failure (HF) with mid-range and preserved ejection fraction (HFmrEF and HFpEF) are uncertain.

Methods and Results: This study analyzed 858 consecutive patients with HFmrEF (EF: 40–49%) or HFpEF (EF ≥50%), who were hospitalized for acute HF, and who were discharged alive, and were not taking angiotensin-converting enzyme inhibitors (ACE)-I/angiotensin II receptor blockers (ARB) or β-blockers at admission. The study population was classified into 4 groups according to the status of prescription of ACE-I/ARB and β-blocker at discharge: no neurohormonal antagonist (n=342, 39.9%), ACE-I/ARB only (n=128, 14.9%), β-blocker only (n=189, 22.0%), and both ACE-I/ARB and β-blocker (n=199, 23.2%) groups. The primary outcome measure was a composite of all-cause death or HF hospitalization. The cumulative 1-year incidence of the primary outcome measure was 41.2% in the no neurohormonal antagonist group, 34.0% in the ACE-I/ARB only group, 28.6% in the β-blocker only group, and 16.4% in the both ACE-I/ARB and β-blocker group (P<0.001). Compared with the no neurohormonal antagonist group, both the ACE-I/ARB and β-blocker groups were associated with a significantly lower risk for a composite of all-cause death or HF hospitalization (HR: 0.46, 95% CI: 0.28–0.76, P=0.002).

Conclusions: In hospitalized patients with HFmrEF and HFpEF, starting both ACE-I/ARB and a β-blocker was associated with a reduced risk of the composite of all-cause death or HF hospitalization compared with patients not starting on an ACE-I/ARB or β-blocker.

Key Words: Acute heart failure; Heart failure with mid-range ejection fraction; Heart failure with preserved ejection fraction; Neurohormonal antagonist

Neurohormonal antagonists, such as angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), and β-blockers, have been shown to reduce mortality and hospitalization rates and to improve symptoms in patients affected by heart failure (HF) with reduced left ventricular ejection fraction (EF) (HFrEF).[1,2] Therefore, ACE-I or ARB and

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β-blocker are recommended for patients with HFrEF (EF <40%) in the current guidelines.[3] In contrast, ACE-I, ARB and β-blockers failed to demonstrate beneficial outcomes in patients with stable HF with an EF ≥40% in randomized trials.[4–6] However, large observational studies and meta-analyses in patients with an EF ≥40% have suggested that ACE-I or ARB and β-blockers might reduce mortality in these patients.[7,8] A recent study also suggested that ACE-I or ARB and β-blockers were associated with a reduced risk of mortality in HF patients with mid-range EF (HFmrEF, EF 40–49%).[9] This inconsistency about the effect of ACE-I, ARB and β-blockers might be partly explained by the differences in patient characteristics between the randomized trials with broad exclusion criteria and the observational studies having fewer exclusion criteria in real clinical practice.

Despite these existing evidences, there are still scarcity of data regarding the prognostic effect of starting neurohormonal antagonists in patients with HFmrEF and HF with preserved EF (HFpEF, EF ≥50%), particularly in patients hospitalized for acute HF (AHF).[10] Therefore, we aimed to investigate the effects of starting ACE-I/ARB and β-blockers during AHF hospitalization on post-discharge clinical outcomes in patients with HFmrEF and HFpEF in a large Japanese real-world database of patients with AHF.

Methods

Study Design, Setting, and Population

The Kyoto Congestive Heart Failure registry (KCHF) is a physician-initiated, prospective, observational, multicenter cohort study, which enrolled consecutive patients hospitalized for AHF for the first time between October 1, 2014, and March 31, 2016, across 19 secondary and tertiary hospitals throughout Japan. The overall design of the study has been previously described in detail.[11] Briefly, we enrolled consecutive patients with AHF and with congestion, as defined by the modified Framingham criteria, who were admitted to the participating centers and who underwent HF-specific treatment involving intravenous drugs administered within 24 h of hospital presentation.

Among the 4,056 patients who were enrolled in the KCHF registry, we excluded 271 patients who died during the index hospitalization, 11 patients with missing EF data during hospitalization, 1,383 patients with HFrEF (EF <40%), 57 patients who were lost to follow up, and 1,476 patients who were already taking ACE-I/ARBs and/or β-blockers at admission. Therefore, the current study population consisted of 858 patients who were not taking ACE-I/ARBs or β-blockers at admission and who were discharged alive (**Figure 1**). We classified the patients into 4 groups based on the use of the neurohormonal antagonists at discharge: (1) those who started neither ACE-I/ARB nor β-blockers at discharge (the no neurohormonal antagonist group); (2) those who started only ACE-I/ARB (the ACE-I/ARB only group); (3) those who started only β-blockers (the β-blocker only group); and (4) those who started both ACE-I/ARB and β-blockers (the both ACE-I/ARB and β-blocker group). We collected data on patient demographics, medical histories, underlying heart disease, signs, symptoms, medications, laboratory tests, chest radiographs on admission and at discharge, electrocardiography, and echocardiography during the index hospitalization.[11] The timing of echocardiography varied among the patients, but we adopted the data at the earliest echocardiographic examination during the index hospitalization.

Ethics

The investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the institutional review boards of: Kyoto University Graduate School of Medicine (approval number: E2311), Shiga General Hospital (approval number: 20141120-01), Tenri Hospital (approval number: 640), Kobe City Medical Center General Hospital (approval number: 14094), Hyogo Prefectural Amagasaki General Medical Center (approval number: Rinri 26-32), National Hospital Organization Kyoto Medical Center (approval number: 14-080), Mitsubishi Kyoto Hospital (approved 11/12/2014), Okamoto Memorial Hospital (approval number: 201503), Japanese Red Cross Otsu Hospital (approval number: 318), Hikone Municipal Hospital (approval number: 26-17), Japanese Red Cross Osaka Hospital (approval number: 392), Shimabara Hospital (approval number: E2311), Kishiwada City Hospital (approval number: 12), Kansai Electric Power Hospital (approval number: 26-59), Shizuoka General Hospital (approval number: Rin14-11-47), Kurashiki Central Hospital (approval number: 1719), Kokura Memorial Hospital (approval number: 14111202), Kitano Hospital (approval number: P14-11-012), and Japanese Red Cross Wakayama Medical Center (approval number: 328). A waiver of patient written informed consent was granted by the institutional review boards of Kyoto University and each participating center, as the study met the conditions outlined in the Japanese ethical guidelines for medical and health research involving human subjects;[12] there were: (1) we would use clinical information obtained in routine practice on the medical record without any risk to the subjects; (2) the waiver of normal consent procedures would not adversely affect the rights and welfare of the subjects; (3) the research could not be carried out effectively without the waiver; and (4) the subjects were provided with additional pertinent information and had the right to opt out of this study whenever appropriate. We have not got informed consent for inclusion in the prospective study.

Definitions

The detailed definitions of the baseline patient characteristics are as follows. We defined the use of ACE-I/ARB as any prescription of ACE-I and/or ARB. Anemia was defined using the World Health Organization criteria (hemoglobin <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. Renal dysfunction was defined as an eGFR <30 mL/min/1.73 m^2.[11] HF was classified based on EF as HFpEF with EF ≥50%, HFmrEF with EF 40–49%, and HFrEF with EF <40%.[3] B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) was measured in each participating institution using commercially available immunochemical assays. As a conversion formula between

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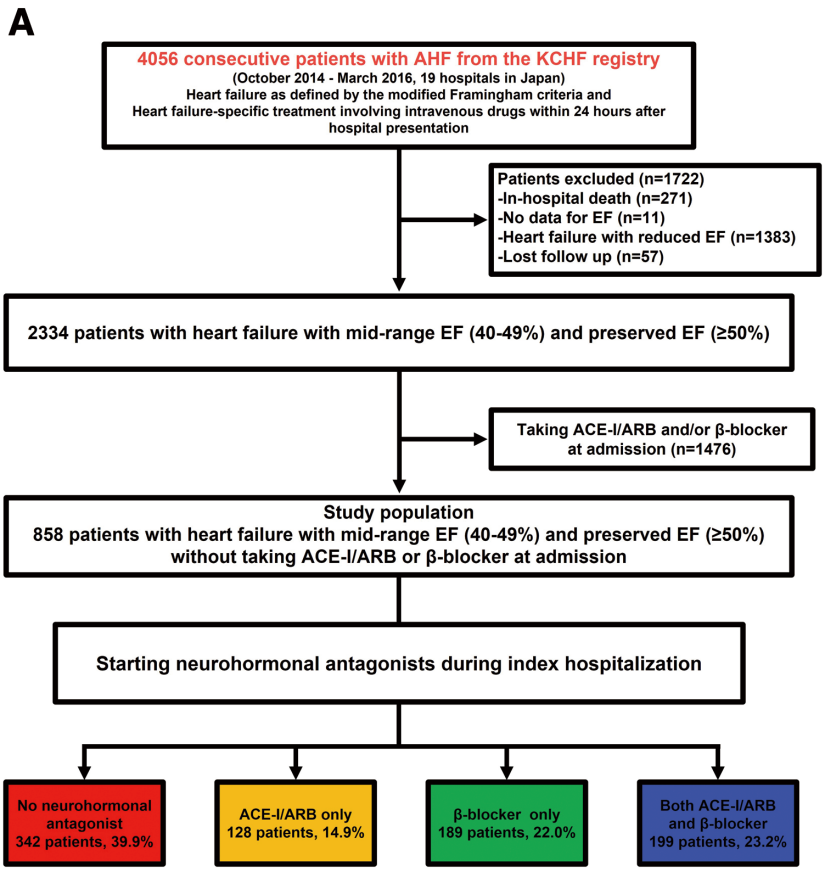


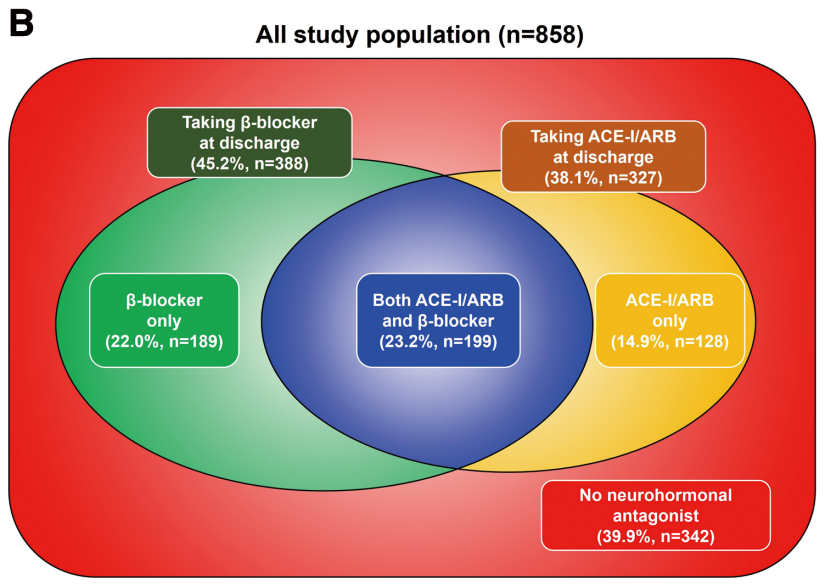


Figure 1. Study flowchart and study population based on the use of ACE-I/ARB and/or β-blocker. (**A**) Study flowchart; and (**B**) breakdown of the study population based on the use of the neurohormonal antagonists at discharge. ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; AHF, acute heart failure; EF, ejection fraction; KCHF, Kyoto Congestive Heart Failure.

BNP and NT-proBNP has not been established in patients with AHF yet, we divided the patients according to the median or quartiles of BNP and NT-proBNP levels, and NT-proBNP values were adopted if no BNP values were measured. High C-reactive protein (CRP) was defined as CRP >10 mg/L according to the previously reported cut-off values.[13] Worsening HF (WHF) during hospitalization was defined as additional i.v. drug treatment (diuretics, vasodilator or inotropic agents) for HF, hemodialysis, or mechanical circulatory or respiratory support, occurring >24 h after therapy initiation.[11,14] Worsening renal function was defined as >0.3 mg/dL increase in serum creatinine during the index hospitalization.[15]

One-year clinical follow-up data with an allowance of 1

Table 1. Baseline Patient Characteristics, Laboratory Findings, and Medications

Variables	Total (n=858)	No neurohormonal antagonist (n=342)	ACE-I/ARB only (n=128)	β-blocker only (n=189)	Both ACE-I/ARB and β-blocker (n=199)	P value	Total number
Clinical characteristic							
Age, years	79.1±11.8	82.2±10.4	79.9±11.8	78.0±11.8	74.4±12.2	<0.001	858
Age ≥80 years*	484 (56.4)	233 (68.1)	76 (59.4)	101 (53.4)	74 (37.2)	<0.001	858
Women*	450 (52.4)	189 (55.3)	71 (55.5)	96 (50.8)	94 (47.2)	0.27	858
BMI, kg/m^2	20.7±4.0	20.0±3.9	20.9±4.2	20.5±3.4	22.0±4.4	<0.001	781
BMI ≤22 kg/m^2*	534 (68.4)	227 (75.4)	77 (64.2)	122 (72.2)	108 (56.5)	<0.001	781
Etiology						<0.001	
Ischemic	173 (20.2)	62 (18.1)	16 (12.5)	41 (21.7)	54 (27.1)		858
Associated with ACS*	53 (6.2)	8 (2.3)	5 (3.9)	12 (6.4)	28 (14.1)		858
Not associated with ACS	120 (14.0)	54 (15.8)	11 (8.6)	29 (15.3)	26 (13.1)		858
Hypertensive heart disease	263 (30.7)	79 (23.1)	50 (39.1)	54 (28.6)	80 (40.2)		858
Valvular heart disease	234 (27.3)	119 (34.8)	36 (28.1)	41 (21.7)	38 (19.1)		858
Cardiomyopathy	59 (6.9)	23 (6.7)	8 (6.3)	14 (7.4)	14 (7.0)		858
Arrhythmia-related	83 (9.7)	29 (8.5)	12 (9.4)	30 (15.9)	12 (6.0)		858
Others	46 (5.4)	30 (8.8)	6 (4.7)	9 (4.8)	1 (0.5)		858
Medical history							
HF hospitalization*	198 (23.5)	122 (36.5)	17 (13.3)	37 (20.0)	22 (11.2)	<0.001	844
Hypertension*	527 (61.4)	180 (52.6)	92 (71.9)	107 (56.6)	148 (74.4)	<0.001	858
Diabetes*	257 (30.0)	104 (30.4)	35 (27.3)	56 (29.6)	62 (31.2)	0.90	858
Dyslipidemia	237 (27.6)	92 (26.9)	35 (27.3)	47 (24.9)	63 (31.7)	0.49	858
AF or flutter*	368 (42.9)	160 (46.8)	49 (38.3)	94 (49.7)	65 (32.7)	0.002	858
VT/VF	6 (0.7)	4 (1.2)	1 (0.8)	1 (0.5)	0 (0)	0.46	858
Previous MI*	87 (10.1)	39 (11.4)	7 (5.5)	18 (9.5)	23 (11.6)	0.24	858
Prior PCI or CABG	105 (12.2)	51 (14.9)	16 (12.5)	23 (12.2)	15 (7.5)	0.09	858
Previous stroke*	113 (13.2)	54 (15.8)	16 (12.5)	30 (15.9)	13 (6.5)	0.01	858
Chronic kidney disease	301 (35.1)	151 (44.2)	39 (30.5)	67 (35.5)	44 (22.1)	<0.001	858
Current smoking*	92 (10.9)	19 (5.6)	6 (4.8)	24 (13.0)	43 (21.7)	<0.001	845
Chronic lung disease*	124 (14.5)	57 (16.7)	23 (18.0)	23 (12.2)	21 (10.6)	0.12	858
Malignancy*	132 (15.4)	55 (16.1)	24 (18.8)	24 (12.7)	29 (14.6)	0.50	858
Cognitive dysfunction*	173 (20.2)	84 (24.6)	30 (23.4)	31 (16.4)	28 (14.1)	0.01	858
Social background							
Poor medical adherence	129 (15.0)	39 (11.4)	24 (18.8)	29 (15.3)	37 (18.6)	0.08	858
Living alone*	166 (19.3)	57 (16.7)	29 (22.7)	39 (20.6)	41 (20.6)	0.41	858
Daily life activities							
Ambulatory*	649 (76.9)	233 (69.4)	102 (81.0)	140 (75.7)	174 (88.3)	<0.001	844
Vital signs at discharge							
Heart rate, beats/min	71.3±13.1	72.9±13.6	70.7±12.7	72.3±13.9	68.1±11.0	<0.001	844
<60*	127 (15.0)	40 (12.1)	23 (18.0)	27 (14.4)	37 (18.7)	0.16	844
Systolic BP, mmHg	118.1±18.0	117.8±18.5	119.0±15.8	115.3±17.9	120.5±18.3	0.04	848
<90*	27 (3.2)	12 (3.6)	2 (1.6)	7 (3.7)	6 (3.0)	0.69	848
Diastolic BP, mmHg	65.0±12.1	64.3±11.8	63.9±13.5	65.1±11.6	66.6±11.9	0.13	848
Rhythms at discharge						<0.001	822
Sinus rhythm	450 (54.7)	161 (49.8)	69 (55.2)	88 (48.6)	132 (68.4)		
AF or flutter	317 (38.6)	135 (41.8)	42 (33.6)	83 (45.9)	57 (29.5)		
Others	55 (6.7)	27 (8.4)	14 (11.2)	10 (5.5)	4 (2.1)		
Echocardiography							
EF, %	56.1±10.2	58.2±10.2	60.1±9.6	54.1±9.5	51.9±9.6	<0.001	834
HFpEF (EF ≥50%)*	590 (68.8)	265 (77.5)	109 (85.2)	119 (63.0)	97 (48.7)	<0.001	858
HFmrEF (EF 40–49%)	268 (31.2)	77 (22.5)	19 (14.8)	70 (37.0)	102 (51.3)		858

(**Table 1** continued the next page.)

Variables	Total (n=858)	No neurohormonal antagonist (n=342)	ACE-I/ARB only (n=128)	β-blocker only (n=189)	Both ACE-I/ARB and β-blocker (n=199)	P value	Total number
Laboratory findings at discharge							
BNP, pg/mL	218.5 (100.9–406.9)	246.0 (124.2–426.9)	89.5 (39.0–209.5)	253.6 (128.0–500.7)	226.8 (110.5–408.6)	<0.001	556
NT-proBNP, pg/mL	1,777 (801–3,637)	1,653 (212–5,938)	1,739 (703–2,302)	1,686 (881–2,988)	1,870 (718–5,150)	0.87	62
BNP or NT-proBNP > median value*	309 (50.0)	129 (54.7)	21 (22.8)	79 (57.7)	80 (52.3)	<0.001	618
Serum creatinine, mg/dL	0.99 (0.76–1.39)	1.05 (0.78–1.63)	0.90 (0.69–1.11)	1.05 (0.81–1.47)	0.96 (0.75–1.27)	<0.001	843
eGFR, mL/min/1.73 m^2	49.7±24.3	46.9±26.3	57.5±25.3	47.0±23.0	52.0±20.0	<0.001	843
<30 mL/min/1.73 m^2*	166 (19.7)	89 (26.6)	10 (7.9)	44 (23.8)	23 (11.7)	<0.001	843
Blood urea nitrogen, mg/dL	23.2 (17.0–33.8)	26.0 (18.0–38.9)	21.0 (16.0–28.9)	24.0 (18.6–34.4)	21.7 (16.0–29.0)	<0.001	839
Albumin, g/dL	3.30±0.50	3.24±0.53	3.37±0.50	3.28±0.50	3.36±0.43	0.02	750
<3.0*	181 (24.1)	85 (28.6)	23 (20.0)	39 (23.6)	34 (19.7)	0.10	750
Sodium, mEq/L	138.6±3.8	138.2±4.0	138.5±3.9	138.3±3.9	139.4±3.1	0.005	838
<135*	107 (12.8)	49 (14.8)	21 (16.7)	26 (14.1)	11 (5.6)	0.006	838
Hemoglobin, g/dL	11.3±2.1	10.8±1.9	11.5±2.1	11.2±2.1	12.1±2.1	<0.001	838
Anemia*	593 (70.8)	266 (80.1)	81 (64.8)	133 (71.5)	113 (57.9)	<0.001	838
CRP, mg/L	4.4 (1.7–12.3)	5.2 (1.8–14.0)	3.7 (1.9–9.8)	4.4 (1.6–13.2)	3.7 (1.3–10.0)	0.21	794
>10*	230 (29.0)	103 (33.3)	29 (23.8)	53 (29.8)	45 (24.3)	0.09	794
Medication at discharge							
ACE-I or ARBs	327 (38.1)	0 (0)	128 (100)	0 (0)	199 (100)	<0.001	858
β-blockers	388 (45.2)	0 (0)	0 (0)	189 (100)	199 (100)	<0.001	858
MRAs*	374 (43.6)	143 (41.8)	57 (44.5)	77 (40.7)	97 (48.7)	0.35	858
Ca blockers	300 (35.0)	115 (33.6)	56 (43.8)	65 (34.4)	64 (32.2)	0.15	858
Loop diuretics	671 (78.2)	272 (79.5)	98 (76.6)	137 (72.5)	164 (82.4)	0.10	858
Tolvaptan*	60 (7.0)	39 (11.4)	3 (2.3)	13 (6.9)	5 (2.5)	<0.001	858
In-hospital events							
Worsening HF	126 (14.7)	55 (16.1)	15 (11.7)	28 (14.8)	28 (14.1)	0.68	858
Worsening renal function	289 (34.2)	125 (37.3)	42 (33.1)	58 (31.2)	64 (32.5)	0.47	845
Length of hospital stay (days)	16 (12–25)	17 (12–27)	16 (12–25)	17 (11–28)	15 (12–21)	0.17	858

*Risk-adjusting variables selected for the Cox proportional hazard models. Data are presented as number (%), mean ± SD, or median (interquartile range). P values were calculated using the chi squared test for categorical variables, and 1-way ANOVA or Kruskal-Wallis test for continuous variables. Chronic kidney disease was defined as eGFR <60 mL/min/1.73 m^2. Renal dysfunction was defined as eGFR <30 mL/min/1.73 m^2. Anemia was defined using the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men). ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft surgery; CRP, C-reactive protein; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; MI, myocardial infarction; NT-pro BNP; N-terminal-pro B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

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 patient consent).

The primary outcome measure was the composite of all-cause death or hospitalization for HF. The secondary outcome measures were all-cause death, cardiovascular death (death related to HF, sudden death, death related to stroke, and other cardiovascular death), and hospitalization for HF. HF hospitalization was defined as hospitalization due to worsening of HF requiring intravenous drug therapy.[11] Outcome events were adjudicated by a clinical event committee.[11]

Statistical Analysis

Categorical variables were presented as numbers and percentages and were compared using the chi-squared test. Continuous variables were expressed as means and standard deviations (SD) or medians with interquartile ranges (IQR) and were compared using a one-way analysis of variance (ANOVA) or Kruskal-Wallis test based on their distributions. We regarded the date of discharge as "time zero" for clinical follow up. We compared the baseline characteristics and clinical outcomes according to the prescription status of ACE-I/ARB and β-blockers at discharge.

The cumulative incidences of clinical events that occurred during a 1-year period after discharge were estimated using the Kaplan-Meier method with intergroup differences assessed by the log-rank test. Multivariable Cox propor-

tional hazard models were developed for the primary and secondary outcome measures to evaluate the risk of the ACE-I/ARB only group, the β-blocker only group, and both ACE-I/ARB and β-blocker group relative to the no neurohormonal antagonist group on the clinical outcome measures by adjusting the potential confounders. The results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We included the following 27 clinically relevant risk-adjusting variables: age ≥80 years, sex, body mass index (BMI) ≤22 kg/m^2, EF ≥50% on echocardiography, etiology of HF hospitalization associated with acute coronary syndrome, previous HF hospitalization, hypertension, diabetes, atrial fibrillation or flutter, previous myocardial infarction, previous stroke, current smoking, chronic lung disease, malignancy, cognitive dysfunction, living alone, ambulatory, systolic blood pressure <90 mmHg, heart rate <60 beats/min, B-type natriuretic polypeptide (BNP) or NT-proBNP if BNP unavailable, >median value, eGFR <30 mL/min/1.73 m^2, albumin <3.0 g/dL, sodium <135 mEq/L, anemia, and CRP >10 mg/L, and use of mineralocorticoid receptor antagonist (MRA) at discharge, and tolvaptan at discharge. We selected these variables according to their clinical relevance to the clinical outcomes and based on previous studies.[3,11] Continuous variables were dichotomized using clinically meaningful reference values or median values. For sensitivity analysis, we changed the variables such as age, BMI, EF, systolic blood pressure, heart rate, BNP, eGFR, albumin, sodium, hemoglobin and CRP as the continuous variable in the multivariable Cox proportional hazard models. For the other sensitivity analysis, we added MRA as a neurohormonal antagonist (**Supplementary Figure 1**). We analyzed the Kaplan-Meier curves and developed multivariable Cox proportional hazard models, as per the main analysis, to evaluate the risk of the ACE-I/ARB/MRA only group, the β-blocker only group, and both ACE-I/ARB/MRA and β-blocker group relative to the no neurohormonal antagonist group on the clinical outcome measures. In the subgroup analyses, we evaluated the interactions between the 7 subgroup factors (EF ≥50%, age ≥80 years, de novo HF hospitalization, atrial fibrillation or flutter, eGFR <30 mL/min/1.73 m^2, calcium blocker prescription at discharge, and MRA prescription at discharge) and the effects of ACE-I/ARB and β-blocker prescription at discharge on the primary outcome measure. All statistical analyses were conducted by 2 physicians (Y. Seko and T. Kato) and a statistician (T. Morimoto) using JMP Pro software (version 15; SAS Corp., Cary, NC, USA). All the reported P values were 2-tailed, and the level of statistical significance was set at P <0.05.

Patient and Public Involvement

This research was conducted without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Baseline Characteristics

We classified the 858 study patients who were not taking ACE-I/ARB or β-blockers at admission and were discharged alive into 4 groups: no neurohormonal antagonist (n=342, 39.9%), ACE-I/ARB only (n=128, 14.9%), β-blocker only (n=189, 22.0%), and both ACE-I/ARB and β-blocker (n=199, 23.2%) groups (**Figure 1A**,**B**). The mean patient age in the study was 79.1±11.8 years and 52.4% of the patients were women. The ischemic etiology of HF was 20.2% of the patients; the mean LVEF was 56.1±10.2% (**Table 1**). Regarding the baseline characteristics (**Table 1**), the patients in the both ACE-I/ARB and β-blocker group were younger, and had a higher BMI, and a higher prevalence of ischemic etiology than those in the no neurohormonal antagonist group. The patients in the ACE-I/ARB only, β-blocker only, and both ACE-I/ARB and β-blocker groups had a lower prevalence of previous HF hospitalization, and CKD. The patients in the ACE-I/ARB only and both ACE-I/ARB and β-blocker groups had a higher prevalence of hypertension and were more often ambulatory than those in the no neurohormonal antagonist group. The patients in the ACE-I/ARB only and both ACE-I/ARB and β-blocker groups exhibited a lower prevalence of atrial fibrillation or flutter than those in the no neurohormonal antagonist group. The patients in the β-blocker only and both ACE-I/ARB and β-blocker groups exhibited a lower prevalence of cognitive dysfunction and were more likely to exhibit a lower EF than those in the no neurohormonal antagonist group. The systolic blood pressure at discharge was higher in the ACE-I/ARB only and both ACE-I/ARB and β-blocker group than in the no neurohormonal antagonist group. The heart rate at discharge was lower in the ACE-I/ARB only and both ACE-I/ARB and β-blocker group than in the no neurohormonal antagonist group.

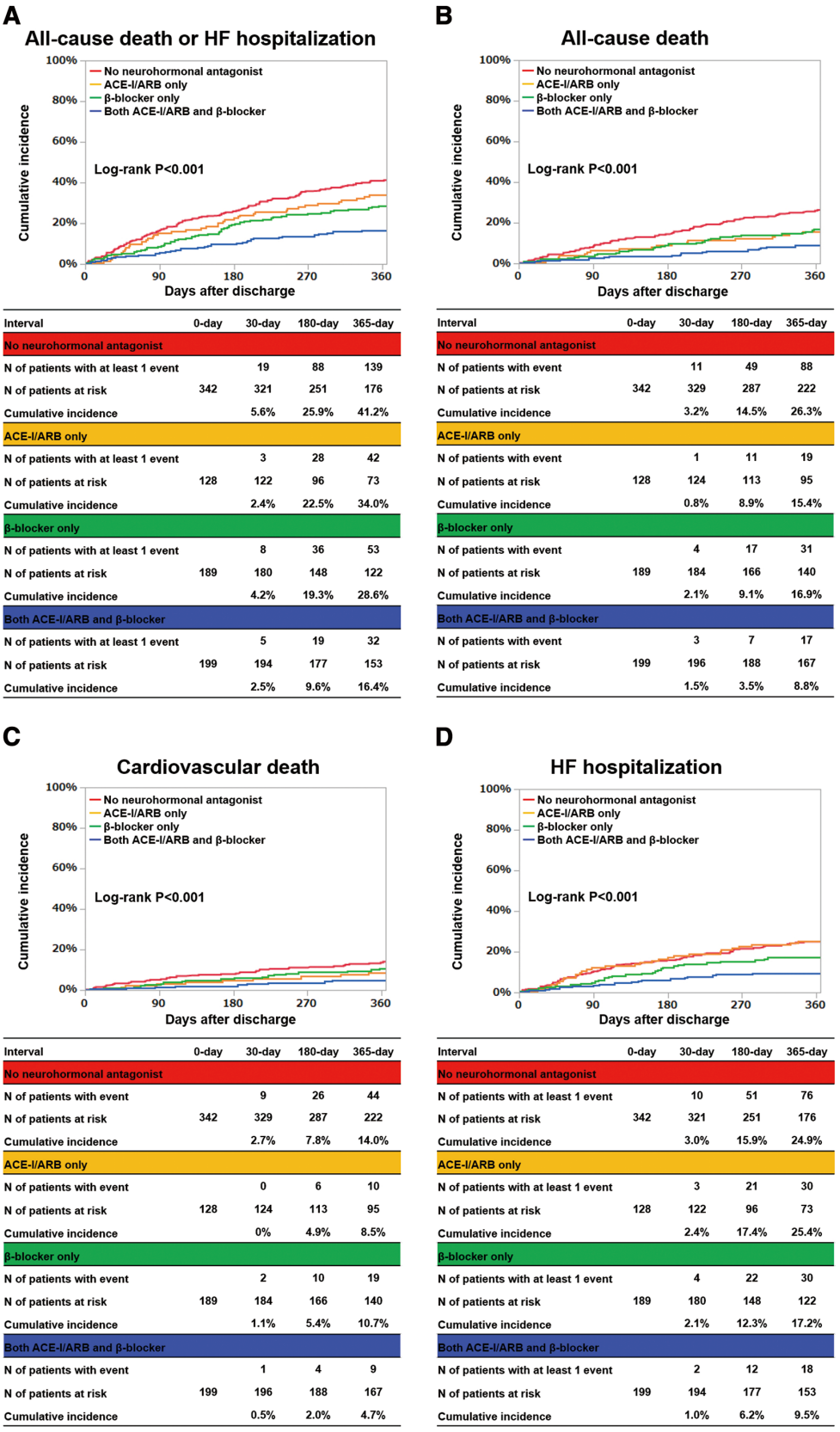
As for the laboratory findings at discharge (**Table 1**), the patients in the ACE-I/ARB only group exhibited a lower BNP level than those in the no neurohormonal antagonist group. The patients in the ACE-I/ARB only and both ACE-I/ARB and β-blocker groups had a higher eGFR than those in the no neurohormonal antagonist group. Patients in the both ACE-I/ARB and β-blocker group exhibited a higher hemoglobin level and sodium level than those in the no neurohormonal antagonist group.

Regarding the medications prescribed at discharge (**Table 1**), there was no significant difference in the prescription rate of MRAs, calcium blockers, and loop diuretics. The prescription rate of tolvaptan was higher in the no neurohormonal antagonist group than in other groups. The types and dose of ACE-I, ARB and β-blocker are summarized in **Supplementary Table 1**. Number of days until the date of starting ACE-I, ARB and β-blocker are presented in **Supplementary Table 2**.

Regarding in-hospital events (**Table 1**), the prevalence of WHF and worsening renal function were similar among groups. There was no significant difference in length of hospital stay.

Clinical Outcomes

The median follow-up duration was 484 (IQR: 357–666) days with 95.7% follow-up rate during a 1-year period. The cumulative 1-year incidence of the primary outcome measure was 41.2% in the no neurohormonal antagonist group, 34.0% in the ACE-I/ARB only group, 28.6% in the β-blocker only group, and 16.4% in the both ACE-I/ARB and β-blocker group (P<0.001) (**Figure 2A**). After adjustment for the confounders, starting either ACE-I/ARB or β-blocker alone was not associated with a lower risk of the primary outcome compared with not starting ACE-I/ARB or a β-blocker (HR: 0.83; 95% CI: 0.52–1.33; P=0.44 and



Interval	0-day	30-day	180-day	365-day
No neurohormonal antagonist				
N of patients with at least 1 event		19	88	139
N of patients at risk	342	321	251	176
Cumulative incidence		5.6%	25.9%	41.2%
ACE-I/ARB only				
N of patients with at least 1 event		3	28	42
N of patients at risk	128	122	96	73
Cumulative incidence		2.4%	22.5%	34.0%
β-blocker only				
N of patients with at least 1 event		8	36	53
N of patients at risk	189	180	148	122
Cumulative incidence		4.2%	19.3%	28.6%
Both ACE-I/ARB and β-blocker				
N of patients with at least 1 event		5	19	32
N of patients at risk	199	194	177	153
Cumulative incidence		2.5%	9.6%	16.4%

Interval	0-day	30-day	180-day	365-day
No neurohormonal antagonist				
N of patients with event		11	49	88
N of patients at risk	342	329	287	222
Cumulative incidence		3.2%	14.5%	26.3%
ACE-I/ARB only				
N of patients with event		1	11	19
N of patients at risk	128	124	113	95
Cumulative incidence		0.8%	8.9%	15.4%
β-blocker only				
N of patients with event		4	17	31
N of patients at risk	189	184	166	140
Cumulative incidence		2.1%	9.1%	16.9%
Both ACE-I/ARB and β-blocker				
N of patients with event		3	7	17
N of patients at risk	199	196	188	167
Cumulative incidence		1.5%	3.5%	8.8%

Interval	0-day	30-day	180-day	365-day
No neurohormonal antagonist				
N of patients with event		9	26	44
N of patients at risk	342	329	287	222
Cumulative incidence		2.7%	7.8%	14.0%
ACE-I/ARB only				
N of patients with event		0	6	10
N of patients at risk	128	124	113	95
Cumulative incidence		0%	4.9%	8.5%
β-blocker only				
N of patients with event		2	10	19
N of patients at risk	189	184	166	140
Cumulative incidence		1.1%	5.4%	10.7%
Both ACE-I/ARB and β-blocker				
N of patients with event		1	4	9
N of patients at risk	199	196	188	167
Cumulative incidence		0.5%	2.0%	4.7%

Interval	0-day	30-day	180-day	365-day
No neurohormonal antagonist				
N of patients with at least 1 event		10	51	76
N of patients at risk	342	321	251	176
Cumulative incidence		3.0%	15.9%	24.9%
ACE-I/ARB only				
N of patients with at least 1 event		3	21	30
N of patients at risk	128	122	96	73
Cumulative incidence		2.4%	17.4%	25.4%
β-blocker only				
N of patients with at least 1 event		4	22	30
N of patients at risk	189	180	148	122
Cumulative incidence		2.1%	12.3%	17.2%
Both ACE-I/ARB and β-blocker				
N of patients with at least 1 event		2	12	18
N of patients at risk	199	194	177	153
Cumulative incidence		1.0%	6.2%	9.5%

Figure 2. Kaplan-Meier curves for the primary and secondary outcome measures. (**A**) Composite of all-cause death or HF hospitalization. (**B**) All-cause death. (**C**) Cardiovascular death. (**D**) HF hospitalization. ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; HF, heart failure; N, number.

Table 2. Crude and Adjusted Clinical Outcomes

	No neurohormonal antagonist	ACE-I/ARB only	β-blocker only	Both ACE-I/ARB and β-blocker
	N of patients with event/N of patients at risk (Cumulative 1-year incidence [%])			
Primary outcome measure				
Composite of all-cause death or HF hospitalization	139/342 (41.2)	42/128 (34.0)	53/189 (28.6)	32/199 (16.4)
Secondary outcome measures				
All-cause death	88/342 (26.3)	19/128 (15.4)	31/189 (16.9)	17/199 (8.8)
Cardiovascular death	44/342 (14.0)	10/128 (8.5)	19/189 (10.7)	9/199 (4.7)
HF hospitalization	76/342 (24.9)	30/128 (25.4)	30/189 (17.2)	18/199 (9.5)

	Variables	Unadjusted		Adjusted	
		HR (95% CI)	P value	HR (95% CI)	P value
Primary outcome measure					
Composite of all-cause death or HF hospitalization	No neurohormonal antagonist	1 (Ref.)		1 (Ref.)	
	ACE-I/ARB only	0.69 (0.50–0.96)	0.03	0.83 (0.52–1.33)	0.44
	β-blocker only	0.63 (0.48–0.84)	0.002	0.82 (0.55–1.21)	0.32
	Both ACE-I/ARB and β-blocker	0.32 (0.22–0.45)	<0.001	0.46 (0.28–0.76)	0.002
Secondary outcome measures					
All-cause death	No neurohormonal antagonist	1 (Ref.)		1 (Ref.)	
	ACE-I/ARB only	0.43 (0.27–0.69)	<0.001	0.75 (0.39–1.46)	0.40
	β-blocker only	0.59 (0.41–0.83)	0.003	0.94 (0.57–1.55)	0.81
	Both ACE-I/ARB and β-blocker	0.27 (0.17–0.42)	<0.001	0.42 (0.20–0.86)	0.02
Cardiovascular death	No neurohormonal antagonist	1 (Ref.)		1 (Ref.)	
	ACE-I/ARB only	0.38 (0.20–0.74)	0.005	0.67 (0.26–1.69)	0.39
	β-blocker only	0.64 (0.41–1.02)	0.06	1.18 (0.63–2.21)	0.61
	Both ACE-I/ARB and β-blocker	0.24 (0.12–0.45)	<0.001	0.41 (0.15–1.11)	0.08
HF hospitalization	No neurohormonal antagonist	1 (Ref.)		1 (Ref.)	
	ACE-I/ARB only	0.91 (0.61–1.36)	0.65	1.03 (0.58–1.81)	0.93
	β-blocker only	0.62 (0.42–0.92)	0.02	0.71 (0.42–1.21)	0.21
	Both ACE-I/ARB and β-blocker	0.32 (0.20–0.52)	<0.001	0.43 (0.22–0.83)	0.01

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CI, confidence interval; HF, heart failure; HR, hazard ratio.

HR: 0.82; 95% CI: 0.55–1.21; P=0.32, respectively), whereas starting both ACE-I/ARB and β-blocker was associated with a significantly lower risk of the primary outcome measure compared with not starting ACE-I/ARB or β-blocker (HR: 0.46; 95% CI: 0.28–0.76; P=0.002) (**Table 2**). For the secondary outcomes, the risk for all-cause death was fully consistent with the trend of the primary outcome measure (**Figure 2B**, **Table 2**). The risk for cardiovascular death was mostly consistent with the trend of the primary outcome measure, but the lower risk of starting both ACE-I/ARB and β-blocker was no longer significant (HR: 0.41; 95% CI: 0.15–1.11; P=0.08) (**Figure 2C**, **Table 2**). The risk for HF hospitalization was fully consistent with the trend of the primary outcome measure (**Figure 2D**, **Table 2**).

Sensitivity Analysis

When we changed the variables such as age, BMI, EF, systolic blood pressure, heart rate, BNP, eGFR, albumin, sodium, hemoglobin and CRP as the continuous variable in the multivariable Cox proportional hazard models, the results were consistent with the main analysis (**Supplementary Table 3**).

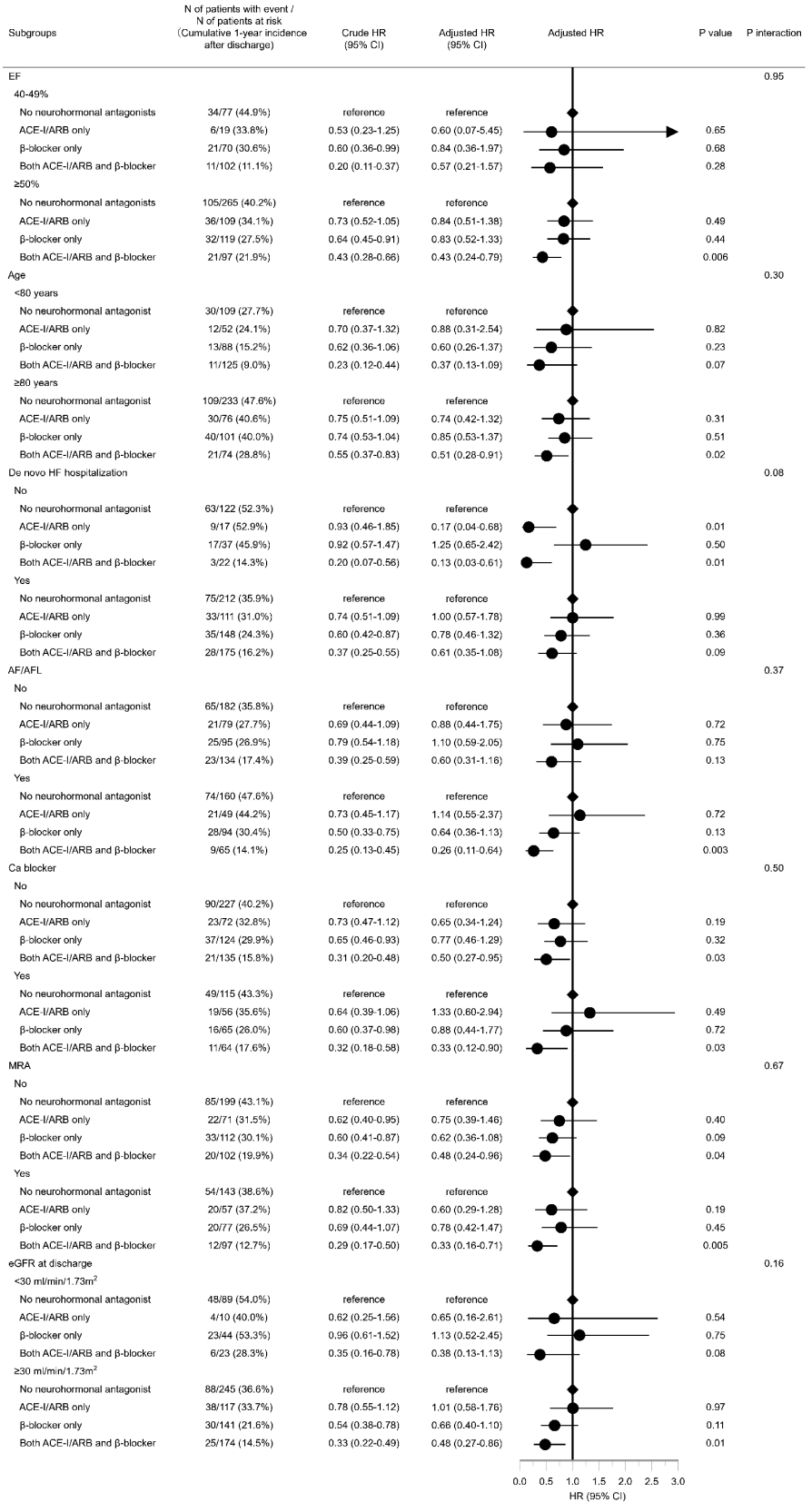


Figure 3. Subgroup analyses for the primary outcome measure. ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AFL, atrial flutter; ARB, angiotensin II receptor blockers; Ca, calcium; CI, confidence interval; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; N, number.

When we included MRA as neurohormonal antagonists and developed multivariable Cox proportional hazard models, which was the same as main analysis, the results were consistent with the main analysis (**Supplementary Table 4**).

Subgroup Analysis

In the post-hoc subgroup analysis stratified by EF ≥50%, age ≥80 years, de novo HF hospitalization, atrial fibrillation or flutter, eGFR <30 mL/min/1.73 m^2, calcium blocker prescription, and MRA prescription, there were no significant interactions between subgroups and the effect of ACE-I/ARB only, β-blocker only, and both ACE-I/ARB and β-blocker groups compared with the no neurohormonal antagonist (**Figure 3**). The cumulative 1-year incidence of the primary outcome measure stratified by EF ≥50% or <50% (40–49%) is presented in **Supplementary Figure 2A,B**.

Discussion

The main findings of the present study are as follows: (1) starting both ACE-I/ARB and β-blocker during HF hospitalization in patients with HFmrEF and HFpEF was associated with a reduced risk of a composite of all-cause death or HF hospitalization along with cardiovascular death, compared with not starting ACE-I/ARB or β-blocker; (2) the effects of starting ACE-I/ARB and β-blocker were consistent regardless of the HFmrEF and HFpEF classifications and other subgroups.

Starting Neurohormonal Antagonist Therapy in Patients With HFmrEF and HFpEF Who Were Hospitalized for AHF

No previous studies have investigated the effect of starting ACE-I/ARB and β-blocker, respectively, or in combination, on post-discharge outcomes in patients with HFmrEF and HFpEF who were hospitalized for AHF. The HF guidelines recommend starting ACE-I/ARB and β-blocker early after stabilization in hospitalized patients with HFrEF.[3,16] The recommendations for hospitalized patients with HFrEF were based on several observational studies that investigated the following factors: (1) safety of β-blockers in patients with chronic severe HF;[17] (2) association of continuation or starting β-blocker therapy with a decrease in mortality;[18] and (3) association of the discontinuation of β-blocker therapy with an increase in mortality.[19] Regardless of EF, a large proportion of patients with AHF develop neurohormonal abnormalities, such as excessive activation of the sympathetic nervous system and renin-angiotensin-aldosterone system,[20] and are at a high risk of rehospitalization and mortality. In addition, neurohormonal abnormalities are observed in patients with stable chronic HFmrEF and HFpEF.[21] Therefore, starting neurohormonal antagonists in patients with HFmrEF and HFpEF who are hospitalized for AHF may be effective in preventing subsequent acute exacerbation of HF. Preventing a decrease in left ventricular contractility and myocardial fibrosis are important strategies in the management of HFmrEF and HFpEF. In this viewpoint, ACE-I and β-blockers might inhibit ventricular remodeling, improve left ventricular contractility,[22,23] and inhibit fibrosis.[24] Early introduction of a neurohormonal antagonist is important regardless of administration during hospitalization or after discharge. However, considering that the median hospital stay is 16 days, the introduction of cardioprotective agents might be completed during hospitalization and it might affect the usage rate of them after discharge. In addition, the titration as well as the timing of the introduction may be very important for the protective role, which needs further investigation.

Effects of the Combination of ACE-I/ARB and β-Blocker

Regarding patients with HFrEF, a previous report revealed that those on both ACE-I/ARB and β-blocker at discharge exhibit more favorable survival outcomes than those on either ACE-I/ARB or β-blocker at discharge.[25] Other reports have indicated that β-blockers have a remarkably favorable effect on mortality and hospitalization rates in patients with HFrEF when added to background ACE-I therapy.[26] ACE-I/ARB and β-blocker combination could further slow down the progression of left ventricular systolic dysfunction resulting from neurohormonal activation in patients with HFrEF.[27] In this study that focused on the patients with HFmrEF and HFpEF, starting either ACE-I/ARB or β-blocker alone was not associated with an improvement in the post-discharge prognosis compared with not starting ACE-I/ARB or β-blocker. These results may be related to the heterogeneous nature of HFmrEF and HFpEF in the AHF setting,[21,28] and unlike in patients with HFrEF, treatment with one drug class alone might not be sufficient for improving the prognosis in patients with HFpEF and HFmrEF. The effects of starting ACE-I/ARB and β-blocker for all-cause death or HF hospitalization was consistent when we stratified by HFpEF or HFmrEF in patients with AHF. In patients with stable HF, a meta-analysis of 11 randomized controlled trials (RCTs) of β-blockers showed that the effectiveness of β-blockers may differ in patients with HFmrEF and HFpEF.[29] In addition, there was an expert opinion that the cut-off of EF appears to be ~55%, where neuroendocrine targets provide risk reduction in patients with stable HF.[30] However, no previous study reported the effects of starting ACE-I/ARB and β-blocker in patients with AHF. Although our study may be underpowered to assess this interaction in the subgroup analyses, our results may be hypothesis-generating and indicate that there is an unmet need to identify and specify the optimal neurohormonal antagonist treatment for patients with HFmrEF and HFpEF who are hospitalized with AHF.

Differences in the Characteristics of Patients Starting Neurohormonal Antagonist

In the present study, the decision to start neurohormonal antagonists was based on the judgment of the treating physician. Patients who did not start ACE-I/ARB or β-blocker therapy were older and had a lower eGFR than those patients in the other groups. The patients who started ACE-I/ARB alone had a higher eGFR than those patients in the other groups. In contrast, the patients who started β-blocker alone and both ACE-I/ARB and β-blocker exhibited a lower EF than those patients in the other groups. The patients who started both ACE-I/ARB and β-blocker were younger than those patients in the other groups. Thus, the decision to start ACE-I/ARB might have been made after considering renal function and other comorbidities, and the decision to start a β-blocker might be related to a lower EF. In this study, starting the 2 neurohormonal antagonists remained to be associated with a reduced risk of all-cause death and HF hospitalization, even after controlling for factors associated with the

decision to start treatment with a neurohormonal antagonist and those associated with post-discharge outcomes. The health status of patients who were discharged on both ACE-I/ARB and β-blocker were better than those who were discharged without a prescribed neurohormonal antagonist. Further research, particularly clinical trials, would be warranted to evaluate the clinical benefit of administering neurohormonal antagonists to patients with HFmrEF and HFpEF who are hospitalized with AHF.

Study Limitations

The present study had several limitations. First, the observational nature of the study design could have introduced confounding factors and selection bias. Most importantly, patients who started both ACE-I/ARB and β-blocker were basically less sick than those who did not start ACE-I/ARB or β-blocker. Thus, the favorable outcomes in patients who started both ACE-I/ARB and β-blocker might simply be explained by the differences in baseline characteristics. To overcome this important limitation, we conducted an extensive multivariable adjustment using a greater number of clinically relevant risk-adjusting variables than that used in previous studies from our registry.[11] Second, the rate of introduction of cardioprotective agents during hospitalization may affect the usage rate of them in the chronic phase. There are no data on the prescription and adherence status as well as the titration of medication after discharge. Third, we did not consider the doses of ACE-I/ARB and β-blockers. Fourth, post-discharge follow-up frequency may affect prognosis, but we do not have data on the frequency of outpatient follow-up visits. Finally, as the current study only included patients who were hospitalized with AHF, we should carefully consider whether the results of our study could be generalized to patients under different settings.

Conclusions

In hospitalized patients with HFmrEF and HFpEF, starting both ACE-I/ARB and β-blocker during hospitalization, was associated with a reduced risk of a composite of all-cause death or HF hospitalization compared with not starting ACE-I/ARB or β-blocker.

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Disclosures

T. Kimura and K. Kuwahara are members of *Circulation Journal*'s Editorial Team.

IRB Information

The study was approved by the institutional review boards of Kyoto University Graduate School of Medicine (approval number: E2311), Shiga General Hospital (approval number: 20141120-01), Tenri Hospital (approval number: 640), Kobe City Medical Center General Hospital (approval number: 14094), Hyogo Prefectural Amagasaki General Medical Center (approval number: Rinri 26-32), National Hospital Organization Kyoto Medical Center (approval number: 14-080), Mitsubishi Kyoto Hospital (approved 11/12/2014), Okamoto Memorial Hospital (approval number: 201503), Japanese Red Cross Otsu Hospital (approval number: 318), Hikone Municipal Hospital (approval number: 26-17), Japanese Red Cross Osaka Hospital (approval number: 392), Shimabara Hospital (approval number: E2311), Kishiwada City Hospital (approval number: 12), Kansai Electric Power Hospital (approval number: 26-59), Shizuoka General Hospital (approval number: Rin14-11-47), Kurashiki Central Hospital (approval number: 1719), Kokura Memorial Hospital (approval number: 14111202), Kitano Hospital (approval number: P14-11-012), and Japanese Red Cross Wakayama Medical Center (approval number: 328).

Data Availability

For a systematic review and comparison study to improve generalizability, the deidentified participant data, including characteristics of patients, outcomes, and additional related documents, will be shared on a request basis to the corresponding author by academics after the ethical approval of the institutional review board and during the periods under the permission of the institutional review board. The data will be shared by file sharing.

References

1. Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992; **327:** 685–691.
2. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; **344:** 1651–1658.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 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* 2016; **37:** 2129–2200.
4. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; **27:** 2338–2345.
5. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359:** 2456–2467.
6. van Veldhuisen DJ, Cohen-Solal A, Böhm M, Anker SD, Babalis D, Roughton M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol* 2009; **53:** 2150–2158.
7. Lund LH, Benson L, Dahlström U, Edner M. Association between use of renin-angiotensin system antagonists and mortality in patients with heart failure and preserved ejection fraction. *JAMA* 2012; **308:** 2108–2117.
8. Lund LH, Benson L, Dahlstrom U, Edner M, Friberg L. Association between use of beta-blockers and outcomes in patients with heart failure and preserved ejection fraction. *JAMA* 2014; **312:** 2008–2018.
9. Choi KH, Choi JO, Jeon ES, Lee GY, Choi DJ, Lee HY, et al. Guideline-directed medical therapy for patients with heart failure with midrange ejection fraction: A patient-pooled analysis from the Kor HF and Kor AHF Registries. *J Am Heart Assoc* 2018; **7:** e009806.
10. Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: Findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol* 2009; **53:** 184–192.
11. Yaku H, Ozasa N, Morimoto T, Inuzuka Y, Tamaki Y, Yamamoto E, et al. Demographics, management, and in-hospital outcome of hospitalized acute heart failure syndrome patients in contemporary real clinical practice in Japan: Observations from the Prospective, Multicenter Kyoto Congestive Heart Failure (KCHF) Registry. *Circ J* 2018; **82:** 2811–2819.
12. Ministry of Health, Labour and Welfare. Ethical guidelines for medical and health research involving human subjects. https://www.lifescience.mext.go.jp/files/pdf/n2181_01.pdf (accessed September 28, 2020).
13. Nishimoto Y, Kato T, Morimoto T, Yaku H, Inuzuka Y, Tamaki Y, et al. C-reactive protein at discharge and 1-year mortality in hospitalised patients with acute decompensated heart failure: An observational study. *BMJ Open* 2020; **10:** e041068.
14. Butler J, Gheorghiade M, Kelkar A, Fonarow GC, Anker S, Greene SJ, et al. In-hospital worsening heart failure. *Eur J Heart*

Fail 2015; **17:** 1104–1113.
15. Filippatos G, Farmakis D, Parissis J. Renal dysfunction and heart failure: Things are seldom what they seem. *Eur Heart J* 2014; **35:** 416–418.
16. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33:** 1787–1847.
17. Krum H, Roecker EB, Mohacsi P, Rouleau JL, Tendera M, Coats AJ, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: Results from the COPERNICUS Study. *JAMA* 2003; **289:** 712–718.
18. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: Findings from the OPTIMIZE-HF program. *J Am Coll Cardiol* 2008; **52:** 190–199.
19. Butler J, Young JB, Abraham WT, Bourge RC, Adams KF Jr, Clare R, et al. Beta-blocker use and outcomes among hospitalized heart failure patients. *J Am Coll Cardiol* 2006; **47:** 2462–2469.
20. Gheorghiade M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol* 2009; **53:** 557–573.
21. Vergaro G, Aimo A, Prontera C, Ghionzoli N, Arzilli C, Zyw L, et al. Sympathetic and renin-angiotensin-aldosterone system activation in heart failure with preserved, mid-range and reduced ejection fraction. *Int J Cardiol* 2019; **296:** 91–97.
22. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. *Circulation* 1992; **86:** 431–438.
23. Gilbert EM, Abraham WT, Olsen S, Hattler B, White M, Mealy P, et al. Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. *Circulation* 1996; **94:** 2817–2825.
24. Pahor M, Bernabei R, Sgadari A, Gambassi G Jr, Lo Giudice P, Pacifici L, et al. Enalapril prevents cardiac fibrosis and arrhythmias in hypertensive rats. *Hypertension* 1991; **18:** 148–157.
25. Seo WW, Park JJ, Park HA, Cho HJ, Lee HY, Kim KH, et al. Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: A cohort study. *BMJ Open* 2020; **10:** e030514.
26. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999; **353:** 9–13.
27. Cohn JN. Interaction of beta-blockers and angiotensin receptor blockers/ACE inhibitors in heart failure. *J Renin Angiotensin Aldosterone Syst* 2003; **4:** 137–139.
28. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction: A report from the CHART-2 Study. *Eur J Heart Fail* 2017; **19:** 1258–1269.
29. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: An individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018; **39:** 26–35.
30. Bohm M, Bewarder Y, Kindermann I. Ejection fraction in heart failure revisited- where does the evidence start? *Eur Heart J* 2020; **41:** 2363–2365.

Supplementary Files

Please find supplementary file(s);
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