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ORIGINAL ARTICLE
Heart Failure

Relationship Between Left Ventricular Ejection Fraction and Treatment Characteristics in Hospitalized Patients With Heart Failure

— A Japanese Database Analysis —

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Background: Triple combination therapy with a renin–angiotensin system modulator, a β-blocker, and a mineralocorticoid receptor antagonist is currently recommended for patients with heart failure (HF) with reduced ejection fraction. However, there is limited evidence on the extent to which triple combination therapy is currently prescribed to patients at the time of discharge from hospital in Japan.

Methods and Results: Japanese patients hospitalized for HF (n=3,582) were evaluated in subgroups defined by left ventricular ejection fraction (LVEF) using anonymized claims and electronic health record data. At discharge, triple combination therapy prescription rates were low (40.4%, 30.0%, 20.8%, 14.0%, and 12.5% for patients with LVEF <30%, 30–<40%, 40–<50%, 50–<60%, and ≥60%, respectively). Advanced age, lower levels of B-type natriuretic peptide, and renal impairment were all significantly associated with lower rates of triple combination therapy use in the overall population. There were no significant differences in rehospitalization rates between LVEF subgroups; however, triple combination therapy use was associated with a significantly reduced risk of rehospitalization for HF in patients with LVEF <30%, 30–<40%, and 40–<50%.

Conclusions: The use of triple combination therapy was significantly associated with a lower risk of rehospitalization for HF within 1 year of discharge in patients with LVEF <30%, 30–<40%, and 40–<50%. However, patients were undertreated with triple combination therapy.

Key Words: Guideline-directed medical therapy; Heart failure; Hospitalization; Left ventricular ejection fraction

The prevalence of heart failure (HF) increases with age and is associated with a poor prognosis.[1] Patients with HF can be divided into 3 subgroups based on left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF; LVEF <40%), HF with mildly reduced ejection fraction (HFmrEF; LVEF 40–<50%), and HF with preserved ejection fraction (HFpEF; LVEF ≥50%).[1,2] There is robust evidence demonstrating that angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), β-blockers, mineralocorticoid receptor antagonists (MRA), and sodium–glucose cotransporter 2 inhibitors (SGLT2i) can significantly improve the prognosis for patients with HFrEF.[3–16] Per the latest update of the European Society of Cardiology (ESC) guidelines at the time this study was conducted, triple therapy with an ACEi/ARB, a β-blocker, and an MRA was recommended as the gold standard treatment for HFrEF patients.[1] However, few data are available on the extent to which triple combination therapy is prescribed to patients at the time of discharge from hospital.

For patients with HFmrEF or HFpEF, evidence supporting the value of HFrEF therapies is limited, although data on the benefits of SGLT2i in patients with HFmrEF or HFpEF have recently been reported[17,18] and there are some data on the effectiveness of β-blockers, MRA, and ARNI in patients with LVEF <50%, <60%, and ≤57%, respectively.[16,19,20] Furthermore, patients with LVEF <58% have been shown to have systolic dysfunction, and it may therefore be reasonable to use HFrEF treatments for

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patients with HFmrEF or HFpEF with a lower LVEF.[21] The ESC guidelines currently recommend diuretics for patients with HFmrEF and, based on data from subgroup analyses, state that an ACEi, ARB, β-blocker, MRA, or ARNI may be considered.[1] For HFpEF, the ESC guidelines recommend the use of diuretics, but state that there is a lack of evidence for specific disease-modifying therapies in these patients.[1]

In Japan, physicians can use HFrEF treatments for patients with HFmrEF or HFpEF based on their clinical judgment, with real-world studies demonstrating that HFrEF treatments are used more frequently for HFmrEF patients than for HFpEF patients.[22,23] However, there are no data on patients' treatment and clinical characteristics across LVEF categories. Therefore, the objective of this study was to evaluate the treatment and clinical characteristics of patients hospitalized for HF in subgroups defined by LVEF. The data generated during this study will contribute to a greater understanding of how these therapeutic agents are used in clinical practice. This will further improve our understanding of the optimal management of HF and enable physicians to generate and examine hypotheses related to clinical decision making.

Methods

Study Design

This was a non-interventional retrospective study that used anonymized health claims and electronic health record data obtained from the Voluntary Hospital of Japan database purchased from AsMediX Co. (Tokyo, Japan). Data were provided from 17 large hospitals (300–1,100 beds) located nationwide and were extracted for all adult patients who were hospitalized due to HF between April 2017 and September 2019 (the identification period). All patients were followed for 1 year after discharge or until the date of death. For patients with more than 1 hospitalization, the first hospitalization record was used. In this study, the index date was defined as the date of first hospital admission for HF during the identification period; the hospitalization period was defined as the time from the index date to discharge; and the observation period was defined as the day after discharge to the end of the study period.

The database used in this study was based on the Japanese Registry Of All cardiac and vascular Disease-Diagnostic Procedure Combination (JROAD-DPC) database. Heart failure diagnoses were validated in this database in 2021 and were found to show acceptable concordance with clinical datasets.[24]

This study was approved by the Research Institute of Healthcare Data Science Ethics Review Board on March 25, 2020 (Protocol no. RI2020031).

Patients

Eligible patients were those aged ≥18 years with an HF-related hospitalization (defined as a primary inpatient claim with an International Classification of Diseases [ICD]-10 code I50x in the primary position on an inpatient claim) and an LVEF record during the hospitalization period. Patients were excluded if they were receiving dialysis, died during the hospitalization period, or had a planned hospitalization (coded 100 or 101). For all analyses, patients were included in subgroups defined by the first measurement of LVEF after admission of the index hospitalization: <30%, 30–<40%, 40–<50%, 50–<60%, and ≥60%. Patient comorbidities were defined by the ICD-10 code using data for 'comorbidities at hospitalization' for index hospitalization. The ICD-10 code definitions for each disease are provided in **Supplementary Table 1**. The Barthel Index was used to calculate the activities of daily living (ADL) score.

Efficacy Outcomes

The primary endpoint was the prescription rate for ACEi, ARB, β-blockers, and MRA including prescriptions for double or triple combination therapy. Prescription rates were calculated as the number of patients taking ≥1 of these medications at discharge divided by the number of patients in the study. In addition, rates are presented for the overall population and for each LVEF subgroup. Secondary endpoints included patient demographics, characteristics, comorbidities, factors associated with prescription rates, and the incidence of rehospitalization for HF (identified by the disease name listed in the summary information for the hospitalization).

Statistical Analysis

All analyses were performed by the Data Analysis Group of JMDC, Inc. (Tokyo, Japan) using SAS version 9.4 TS1M6 (SAS Institute, Cary, NC, USA). A sample size of 5,000 was considered to be sufficient for the study based on the following: the estimated proportions of patients within each LVEF category based on previous studies,[22,23,25] reported prescription rates for ACEi or ARB and a linear regression analysis that estimated the relationship between LVEF and ACEi/ARB prescription rates,[25] and 95% confidence intervals (CIs) from 50% to 70% for the prescription rates. A descriptive analysis was performed for patient demographics, characteristics, and comorbidities. Categorical variables are summarized as frequencies (n) and proportions (%) with 95% CIs. Continuous variables are summarized as the mean±SD, 95% CIs, median, minimum, and maximum. The relationship between LVEF range and patient characteristics was evaluated using the Cochran–Armitage test for categorical variables and the Jonckheere–Terpstra test for continuous variables.

Primary endpoint data were summarized using descriptive statistics, including n (%), with 95% CIs constructed using the Clopper–Pearson method. Logistic regression models were used to estimate the adjusted odds ratio (OR) for the prescription of HF medications at discharge for the following explanatory variables: systolic blood pressure (SBP) at discharge and B-type natriuretic peptide (BNP) at admission. Covariates included in the model were estimated glomerular filtration rate (eGFR) at admission, age, sex, ADL score at discharge, and the presence of ischemic heart disease (IHD), atrial fibrillation (AF), valvular disease, or neoplasm. Two-sided 95% CIs were calculated based on the Wald statistic.

The cumulative incidence of rehospitalization for HF was estimated by the Kaplan–Meier method, with patients without an event censored at the date of death or the end of the study period. To account for differences in baseline characteristics, rehospitalization rates were adjusted for age, and analyses were performed separately for male and female patients. The significance of differences between LVEF categories was analyzed using the log-rank test. Hazard ratios (HRs) for the association between HF treatments and rehospitalization for HF were calculated based on a Cox proportional hazards model adjusted for SBP at

discharge, BNP at admission and discharge, eGFR at admission and discharge, age at admission, sex, ADL score at discharge, and the presence of IHD, AF, valvular disease, or neoplasm. Two-sided 95% CIs and P values based on the Wald statistic were also calculated.

Missing Data

Endpoints were evaluated for the OR and HR with multiple imputations for missing values as sensitivity analyses. We assumed missing data in this study were missing at random. The multiple imputation method (the fully conditional specification method) was used to impute both continuous and categorical covariates of the analysis model with arbitrary missing data patterns.

When imputing missing values for analysis model covariates, the analysis model outcome was included in the imputation model. Moreover, if the imputed data were to be used to fit several different analysis models, then the imputation model contained every variable included in any of the analysis models.[26] LVEF was added as an auxiliary variable to the imputation model because we considered it could improve the imputation and may support the missing-at-random assumption. For example, the imputation model for SBP at discharge included BNP at admission,

Table 1. Patient Demographics, Characteristics, and Comorbidities in the Overall Population and by LVEF Subgroup

	Overall (n=3,582)	LVEF <30% (n=783)	LVEF 30–<40% (n=691)	LVEF 40–<50% (n=626)	LVEF 50–<60% (n=593)	LVEF ≥60% (n=889)	P value*
LVEF at admission (%)	45.1±17.0	22.4±5.2	34.7±2.9	44.3±2.8	54.7±2.9	67.3±5.4	<0.0001
Age (years)	81.0 [71.0–87.0]	74.0 [63.0–82.0]	78.0 [69.0–85.0]	82.0 [74.0–88.0]	83.0 [76.0–88.0]	84.0 [77.0–89.0]	<0.0001
BMI (kg/m²)							
At admission	n=1,378 23.7±4.5	n=332 23.9±4.8	n=267 23.7±4.6	n=248 23.3±3.8	n=233 23.7±4.9	n=298 23.8±4.3	0.5161
At discharge	n=224 22.7±4.9	n=57 23.2±5.2	n=33 23.2±5.1	n=36 22.4±6.0	n=32 22.3±3.9	n=66 22.4±4.5	0.3729
No. (%) women [95% CI]	1,583 (44.2) [42.6–45.8]	242 (30.9) [27.7–34.3]	261 (37.8) [34.1–41.5]	272 (43.5) [39.5–47.4]	266 (44.9) [40.8–49.0]	542 (61.0) [57.7–64.2]	<0.0001
SBP (mmHg)							
At admission	n=2,663 128.9±21.0	n=606 122.9±19.4	n=516 127.6±20.0	n=462 132.6±22.0	n=440 132.6±21.9	n=639 130.3±20.5	<0.0001
At discharge	n=3,011 116.4±17.4	n=682 110.6±16.0	n=588 115.7±16.3	n=535 117.4±17.6	n=504 119.9±17.4	n=702 119.3±17.9	<0.0001
DBP (mmHg)							
At admission	n=2,663 74.3±14.7	n=606 76.8±15.8	n=516 75.7±15.3	n=462 75.5±14.7	n=440 73.5±13.1	n=639 70.3±13.4	<0.0001
At discharge	n=3,011 65.2±11.9	n=682 66.4±12.1	n=588 66.0±12.3	n=535 64.8±12.0	n=504 64.8±12.0	n=702 64.1±10.8	0.0002
BNP (pg/mL)							
At admission	n=2,516 700.3 [390.0–1,189.9]	n=550 1,006.0 [612.3–1,690.7]	n=512 839.8 [490.4–1,348.4]	n=464 746.4 [468.1–1,199.7]	n=438 551.8 [318.0–988.4]	n=552 404.3 [242.3–716.4]	<0.0001
At discharge	n=885 250.2 [129.8–468.2]	n=197 332.3 [186.2–568.7]	n=194 275.5 [138.2–500.9]	n=183 268.9 [129.3–454.4]	n=144 216.1 [116.0–428.5]	n=167 173.5 [81.5–345.6]	<0.0001
NT-proBNP at admission (pg/mL)	n=513 4,624.0 [2,182.6–9,647.2]	n=142 6,403.7 [3,132.3–15,096.0]	n=88 5,968.5 [2,905.5–14,037.0]	n=62 5,506.0 [3,069.0–9,632.5]	n=77 3,569.2 [1,677.3–7,728.0]	n=144 2,745.4 [1,166.2–5,753.0]	<0.0001
eGFR (mL/min/1.73 m²)							
At admission	n=3,537 47.2 [31.7–62.1]	n=773 48.8 [34.4–62.0]	n=686 49.6 [33.1–65.4]	n=612 45.8 [30.8–61.7]	n=587 46.3 [29.9–62.3]	n=879 45.9 [30.8–61.0]	0.0086
At discharge	n=2,363 44.0 [30.7–58.3]	n=517 49.7 [35.8–60.1]	n=462 47.3 [33.5–62.9]	n=415 39.5 [27.1–56.5]	n=405 41.5 [27.8–54.7]	n=564 42.3 [30.3–57.1]	<0.0001
Sodium at admission (mEq/L)	n=3,455 139.5±4.3	n=758 139.4±4.0	n=669 139.7±4.0	n=599 139.8±4.3	n=568 139.5±4.4	n=861 139.3±4.8	0.6794
Hb at admission (g/dL)	n=3,278 12.0±2.4	n=680 13.2±2.2	n=644 12.5±2.4	n=579 11.7±2.3	n=568 11.4±2.2	n=807 11.1±2.2	<0.0001
Potassium at admission (mEq/L)	n=3,425 4.2±0.6	n=761 4.3±0.6	n=662 4.2±0.6	n=592 4.2±0.7	n=564 4.2±0.7	n=846 4.2±0.6	0.0072
ADL score at discharge (all items)	n=3,203 86.4±24.3	n=723 90.2±22.0	n=623 88.2±22.5	n=554 86.1±24.1	n=508 85.3±25.0	n=795 82.5±26.5	<0.0001
Duration of index hospitalization (days)	n=3,582 19.2±15.0	n=783 20.2±15.4	n=691 19.2±13.8	n=626 18.2±11.6	n=593 19.8±20.2	n=889 18.8±13.5	0.0018

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

	Overall (n=3,582)	LVEF <30% (n=783)	LVEF 30–<40% (n=691)	LVEF 40–<50% (n=626)	LVEF 50–<60% (n=593)	LVEF ≥60% (n=889)	P value*
No. (%) comorbidities [95% CI]							
IHD	969 (27.1) [25.6–28.5]	246 (31.4) [28.2–34.8]	229 (33.1) [29.6–36.8]	199 (31.8) [28.2–35.6]	141 (23.8) [20.4–27.4]	154 (17.3) [14.9–20.0]	<0.0001
Arrhythmia	1,500 (41.9) [40.3–43.5]	285 (36.4) [33.0–39.9]	283 (41.0) [37.3–44.7]	258 (41.2) [37.3–45.2]	262 (44.2) [40.1–48.3]	412 (46.3) [43.0–49.7]	<0.0001
AF	1,356 (37.9) [36.3–39.5]	244 (31.2) [27.9–34.5]	247 (35.7) [32.2–39.4]	239 (38.2) [34.4–42.1]	244 (41.1) [37.2–45.2]	382 (43.0) [39.7–46.3]	<0.0001
VF/VT	91 (2.5) [2.1–3.1]	41 (5.2) [3.8–7.0]	26 (3.8) [2.5–5.5]	12 (1.9) [1.0–3.3]	5 (0.8) [0.3–2.0]	7 (0.8) [0.3–1.6]	<0.0001
Bradyarrhythmia	166 (4.6) [4.0–5.4]	20 (2.6) [1.6–3.9]	24 (3.5) [2.2–5.1]	24 (3.8) [2.5–5.7]	34 (5.7) [4.0–7.9]	64 (7.2) [5.6–9.1]	<0.0001
Cardiomyopathy	230 (6.4) [5.6–7.3]	106 (13.5) [11.2–16.1]	53 (7.7) [5.8–9.9]	25 (4.0) [2.6–5.8]	19 (3.2) [1.9–5.0]	27 (3.0) [2.0–4.4]	<0.0001
Valvular heart disease	695 (19.4) [18.1–20.7]	110 (14.0) [11.7–16.7]	125 (18.1) [15.3–21.2]	114 (18.2) [15.3–21.5]	128 (21.6) [18.3–25.1]	218 (24.5) [21.7–27.5]	<0.0001
Hypertension	2,346 (65.5) [63.9–67.1]	484 (61.8) [58.3–65.2]	437 (63.2) [59.5–66.8]	412 (65.8) [62.0–69.5]	421 (71.0) [67.2–74.6]	592 (66.6) [63.4–69.7]	0.0031
Diabetes mellitus	1,035 (28.9) [27.4–30.4]	238 (30.4) [27.2–33.8]	190 (27.5) [24.2–31.0]	205 (32.7) [29.1–36.6]	160 (27.0) [23.4–30.7]	242 (27.2) [24.3–30.3]	0.1745
CKD	718 (20.0) [18.7–21.4]	122 (15.6) [13.1–18.3]	130 (18.8) [16.0–21.9]	142 (22.7) [19.5–26.2]	146 (24.6) [21.2–28.3]	178 (20.0) [17.4–22.8]	0.0033
Hyperuricemia/ gout	597 (16.7) [15.5–17.9]	157 (20.1) [17.3–23.0]	110 (15.9) [13.3–18.9]	97 (15.5) [12.7–18.6]	107 (18.0) [15.0–21.4]	126 (14.2) [11.9–16.6]	0.0116
COPD	184 (5.1) [4.4–5.9]	38 (4.9) [3.5–6.6]	38 (5.5) [3.9–7.5]	37 (5.9) [4.2–8.1]	36 (6.1) [4.3–8.3]	35 (3.9) [2.8–5.4]	0.4820
Anemia	514 (14.3) [13.2–15.5]	68 (8.7) [6.8–10.9]	73 (10.6) [8.4–13.1]	92 (14.7) [12.0–17.7]	122 (20.6) [17.4–24.1]	159 (17.9) [15.4–20.6]	<0.0001
Sleep apnea	57 (1.6) [1.2–2.1]	18 (2.3) [1.4–3.6]	14 (2.0) [1.1–3.4]	7 (1.1) [0.5–2.3]	9 (1.5) [0.7–2.9]	9 (1.0) [0.5–1.9]	0.0263
Neoplasm	196 (5.5) [4.7–6.3]	29 (3.7) [2.5–5.3]	41 (5.9) [4.3–8.0]	38 (6.1) [4.3–8.2]	30 (5.1) [3.4–7.1]	58 (6.5) [5.0–8.4]	0.0447
Dyslipidemia	999 (27.9) [26.4–29.4]	243 (31.0) [27.8–34.4]	187 (27.1) [23.8–30.5]	185 (29.6) [26.0–33.3]	161 (27.2) [23.6–30.9]	223 (25.1) [22.3–28.1]	0.0146

Values are calculated from data for all patients in each subgroup unless stated otherwise (n). Unless indicated otherwise, data are given as the mean ± SD or median [interquartile range]. *P value for trend over LVEF ranges from the Cochran–Armitage test for categorical variables or the Jonckheere–Terpstra test for continuous variables. ADL, activities of daily living; AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; SBP, systolic blood pressure; VF/VT, ventricular fibrillation/ventricular tachycardia.

eGFR at admission, age, sex, all ADL items, IHD, AF, valvular disease, neoplasm, all HF prescription patterns, all event-free survival times, all censoring indicators, and LVEF as predictors. Other variables were imputed in the same manner as SBP. However, predictive mean matching was used for continuous variables, and logistic regression was used for categorical variables.

Results

Patients

Patient disposition is shown in the **Supplementary Figure**. Overall, 8,349 patients were identified in the database as having had a hospitalization event for HF during the identification period. Of these, 3,582 patients were eligible for inclusion in this analysis. Reasons for exclusion included transfer to another hospital or long-term care facility (n=2,222), age <18 years (n=6), no LVEF record at admission (n=1,957), patient on dialysis (n=180), and planned hospitalization (n=286).

Of the patients included in the analysis, 783 (21.9%) had LVEF <30%, 691 (19.3%) had LVEF 30–<40%, 626 (17.5%) had LVEF 40–<50%, 593 (16.6%) had LVEF 50–<60%, and 889 (24.8%) had LVEF ≥60%. Patient characteristics are shown for the overall population and by LVEF category in **Table 1**. Significant differences between LVEF subgroups were observed for several parameters. For example, median age, the proportion of women, mean SBP, and incidence of AF, anemia, and valvular heart disease were positively correlated with LVEF. In contrast, a negative correlation was observed for median BNP/N-terminal pro-BNP (NT-proBNP) concentrations, the incidence of IHD and cardiomyopathy, and mean ADL scores at discharge.

Prescription Rates

At discharge, approximately 85% of the overall population was prescribed at least one of an ACEi/ARB, β-blocker, or MRA. The prescription rate increased with decreasing LVEF category (**Table 2**; P<0.0001); rates were 90.4% for patients with an LVEF <30%, 88.4% for an LVEF of 30–<40%, 85.0% for an LVEF of 40–<50%, 81.3% for an LVEF of 50–<60%, and 77.5% for an LVEF ≥60%. In the overall population, prescription rates for triple combination therapy with an ACEi/ARB, β-blocker, and MRA at discharge were 23.6% and negatively correlated with

Table 2. Medication Prescription Rates at Hospital Discharge in the Overall Population and by LVEF Subgroup

Medication	Overall (n=3,582)	LVEF <30% (n=783)	LVEF 30–<40% (n=691)	LVEF 40–<50% (n=626)	LVEF 50–<60% (n=593)	LVEF ≥60% (n=889)	P value*
ACEi/ARB, β-blocker, and MRA	847 (23.6) [22.3–25.1]	316 (40.4) [36.9–43.9]	207 (30.0) [26.6–33.5]	130 (20.8) [17.7–24.2]	83 (14.0) [11.3–17.1]	111 (12.5) [10.4–14.8]	<0.0001
ACEi/ARB and β-blocker	1,446 (40.4) [38.8–42.0]	442 (56.4) [52.9–60.0]	340 (49.2) [45.4–53.0]	252 (40.3) [36.4–44.4]	170 (28.7) [25.1–32.5]	242 (27.2) [24.3–30.3]	<0.0001
ACEi/ARB and MRA	1,072 (29.9) [28.4–31.5]	345 (44.1) [40.5–47.6]	247 (35.7) [32.2–39.4]	174 (27.8) [24.3–31.5]	125 (21.1) [17.9–24.6]	181 (20.4) [17.8–23.3]	<0.0001
β-blocker and MRA	1,206 (33.7) [32.1–35.2]	410 (52.4) [48.8–55.9]	285 (41.2) [37.5–45.0]	179 (28.6) [25.1–32.3]	149 (25.1) [21.7–28.8]	183 (20.6) [18.0–23.4]	<0.0001
ACEi/ARB	1,904 (53.2) [51.5–54.8]	487 (62.2) [58.7–65.6]	407 (58.9) [55.1–62.6]	334 (53.4) [49.4–57.3]	264 (44.5) [40.5–48.6]	412 (46.3) [43.0–49.7]	<0.0001
ACEi	1,009 (28.2) [26.7–29.7]	329 (42.0) [38.5–45.6]	259 (37.5) [33.9–41.2]	165 (26.4) [22.9–30.0]	98 (16.5) [13.6–19.8]	158 (17.8) [15.3–20.4]	<0.0001
ARB	904 (25.2) [23.8–26.7]	159 (20.3) [17.5–23.3]	148 (21.4) [18.4–24.7]	170 (27.2) [23.7–30.8]	166 (28.0) [24.4–31.8]	261 (29.4) [26.4–32.5]	<0.0001
β-blocker	2,255 (63.0) [61.3–64.5]	615 (78.5) [75.5–81.4]	498 (72.1) [68.6–75.4]	386 (61.7) [57.7–65.5]	324 (54.6) [50.5–58.7]	432 (48.6) [45.3–51.9]	<0.0001
MRA	1,740 (48.6) [46.9–50.2]	487 (62.2) [58.7–65.6]	371 (53.7) [49.9–57.5]	287 (45.8) [41.9–49.8]	255 (43.0) [39.0–47.1]	340 (38.2) [35.0–41.5]	<0.0001
Any prescription of an ACEi/ARB, β-blocker, or MRA	3,022 (84.4) [83.1–85.5]	708 (90.4) [88.1–92.4]	611 (88.4) [85.8–90.7]	532 (85.0) [81.9–87.7]	482 (81.3) [77.9–84.3]	689 (77.5) [74.6–80.2]	<0.0001
Calcium channel blocker	0 (0) [0–0.1]	0 (0) [0–0.5]	0 (0) [0–0.5]	0 (0) [0–0.6]	0 (0) [0–0.6]	0 (0) [0–0.4]	–
Loop diuretic	2,999 (83.7) [82.5–84.9]	682 (87.1) [84.5–89.4]	588 (85.1) [82.2–87.7]	529 (84.5) [81.4–87.3]	494 (83.3) [80.1–86.2]	706 (79.4) [76.6–82.0]	<0.0001
Thiazide diuretic	188 (5.2) [4.5–6.0]	31 (4.0) [2.7–5.6]	24 (3.5) [2.2–5.1]	40 (6.4) [4.6–8.6]	36 (6.1) [4.3–8.3]	57 (6.4) [4.9–8.2]	0.0036
Vasopressin V_2 receptor antagonist	870 (24.3) [22.9–25.7]	247 (31.5) [28.3–34.9]	144 (20.8) [17.9–24.1]	144 (23.0) [19.8–26.5]	136 (22.9) [19.6–26.5]	199 (22.4) [19.7–25.3]	0.0006
SGLT2i	205 (5.7) [5.0–6.5]	60 (7.7) [5.9–9.8]	53 (7.7) [5.8–9.9]	35 (5.6) [3.9–7.7]	26 (4.4) [2.9–6.4]	31 (3.5) [2.4–4.9]	<0.0001

Unless indicated otherwise, data are presented as n (%) [95% confidence interval]. *P value for trend over LVEF ranges from the Cochran–Armitage test. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor. Other abbreviations as in Table 1.

LVEF level (P<0.0001; **Figure 1**; **Table 2**). Only 40.4% of patients with LVEF <30% were prescribed triple combination therapy, and this decreased to 12.5% of patients with LVEF ≥60%. Most patients were prescribed a diuretic on discharge, predominantly a loop diuretic (83.7%; **Table 2**). Prescription rates for loop diuretics ranged from 79.4% in patients with LVEF ≥60% to 87.1% in patients with LVEF <30%. SGLT2i were used infrequently in all LVEF subgroups, with rates of 7.7% (LVEF <30%), 7.7% (LVEF 30–<40%), 5.6% (LVEF 40–<50%), 4.4% (50–<60%), and 3.5% (LVEF ≥60%) reported (**Table 2**; P<0.0001).

Factors Affecting Prescription Rates

Several factors were identified that were associated with prescription rates in the overall population (**Table 3**) and in subgroups defined by LVEF (**Supplementary Table 2**). In the overall population, younger age (<75 years) and higher BNP (≥700.3 pg/mL) were associated with higher prescribing rates for triple combination therapy or any of the drugs individually. Renal impairment (eGFR <30 mL/min/1.73 m^2) was associated with lower prescribing rates for ACEi/ARB, MRA, and triple combination therapy, but not for β-blockers. Higher SBP (≥140 mmHg) was associated with higher prescribing rates for ACEi/ARB, but lower prescribing rates for MRA. The presence of AF was associated with lower prescribing rates for ACEi/ARB, but higher prescribing rates for β-blockers or MRA. The presence of a neoplasm was associated with lower prescribing rates for β-blockers, but not any of the other drugs. Female sex was associated with higher prescribing rates for MRA, but sex did not affect prescribing rates for any other drugs. Factors associated with prescription rates were broadly similar across the overall population and LVEF subgroups.

HF Rehospitalization

There were no significant differences in rehospitalization rates between LVEF subgroups after adjustment for age and sex (**Figure 2A**). In addition, there was no correlation between increasing LVEF and the incidence of rehospitalization (**Figure 2B**). The prescription of triple combination therapy was associated with a significantly reduced risk of rehospitalization for HF in the overall population (adjusted [a] HR 0.63; 95% CI 0.51–0.70; P<0.0001) and in patients with LVEF <30% (aHR 0.44; 95% CI 0.28–0.70; P=0.0004), 30–<40% (aHR 0.52; 95% CI 0.32–0.85; P=0.0092), or 40–<50% (aHR 0.57; 95% CI 0.34–0.97; P=0.0379), but not in patients with a higher LVEF (**Figure 3**). The prescription of an MRA was associated with a reduced risk of rehospitalization for HF in the overall population (aHR 0.75; 95% CI 0.65–0.85; P<0.0001) and in patients with LVEF 30–<40% (aHR

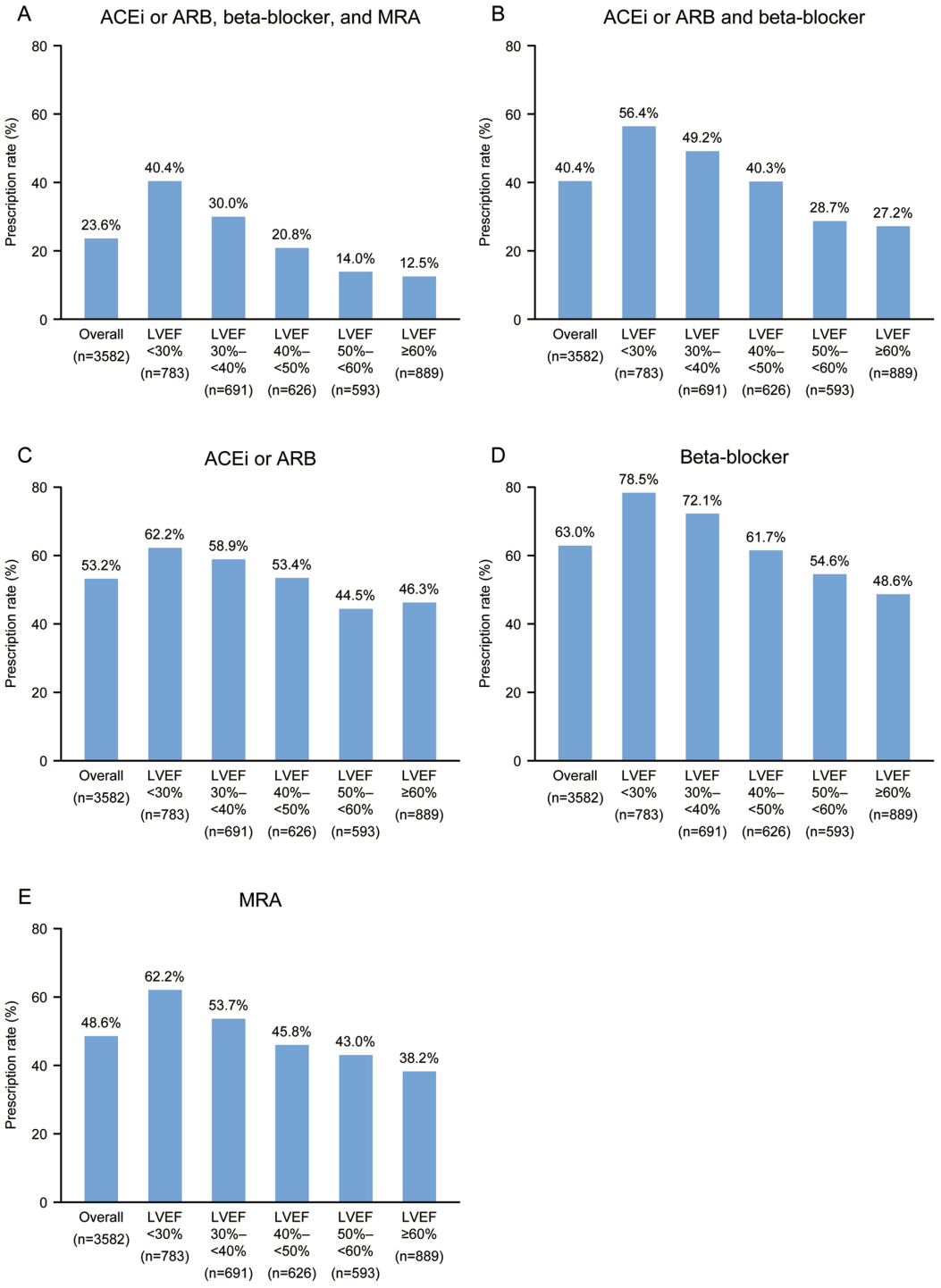

Figure 1. Prescription rates in the overall population and by left ventricular ejection fraction (LVEF) subgroup for (**A**) angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), β-blockers, and mineralocorticoid receptor antagonists (MRA); (**B**) ACEi or ARB and β-blockers; (**C**) ACEi or ARB; (**D**) β-blockers; and (**E**) MRA.

0.67; 95% CI 0.50–0.90; P=0.0083) or 40–<50% (aHR 0.70; 95% CI 0.52–0.96; P=0.0272), but not in the other subgroups (**Figure 3**). Prescription of an ACEi/ARB or β-blocker was not associated with rehospitalization rates in the overall population or any LVEF subgroup.

Discussion

In this study, prescription rates for triple combination therapy for patients discharged following hospitalization for HF were low and decreased significantly with increas-

ing LVEF category. Triple combination therapy significantly decreased the rate of rehospitalization for HF in patients with LVEF <30%, 30–<40%, and 40–<50%. Conversely, triple combination therapy did not affect rates of rehospitalization for HF in patients with LVEF 50–<60% or ≥60%. In addition, rehospitalization rates did not differ between LVEF categories.

In the present study, patients in a lower LVEF category were more likely to be prescribed an ACEi/ARB, a β-blocker, or an MRA than patients in a higher LVEF category. By dividing the LVEF into 10% categories, the differences in prescription patterns were clearly shown, especially for LVEF 30–<40% in the HFrEF population and LVEF 50–<60% or ≥60% in the HFpEF population, which is a novel finding of the present study. A similar prescription pattern was observed in Japanese patients enrolled in the Kyoto Congestive Heart Failure Registry and in the Chronic Heart Failure Analysis and Registry in the Tohoku

Table 3. Factors Affecting Prescription Rates for HF Medications at Hospital Discharge in the Overall Population

HF medications Explanatory variables/covariates	Reference	Categories	OR (95% CI)
ACEi or ARB, β-blocker, and MRA (n=847)			
SBP (mmHg)	<100	100–<140	0.83 (0.66–1.04)
		≥140	0.69 (0.47–1.00)
BNP (pg/mL)	<700.3	≥700.3	1.56 (1.29–1.88)*
eGFR (mL/min/1.73 m²)	<30	30–<45	2.86 (2.08–3.94)*
		≥45	4.70 (3.52–6.28)*
Age (years)	<75	75–84	0.56 (0.46–0.68)†
		≥85	0.31 (0.25–0.39)†
Sex	Male	Female	1.10 (0.92–1.30)
ADL score at discharge	Per 1-unit increase in score		1.01 (1.01–1.01)
IHD	No	Yes	1.03 (0.86–1.24)
AF	No	Yes	1.02 (0.86–1.22)
Valvular disease	No	Yes	0.39 (0.09–1.79)
Neoplasm	No	Yes	0.70 (0.47–1.03)
ACEi or ARB (n=1,904)			
SBP (mmHg)	<100	100–<140	1.18 (0.96–1.45)
		≥140	1.55 (1.15–2.10)*
BNP (pg/mL)	<700.3	≥700.3	1.25 (1.06–1.48)*
eGFR (mL/min/1.73 m²)	<30	30–<45	2.06 (1.67–2.54)*
		≥45	2.85 (2.36–3.43)*
Age (years)	<75	75–84	0.79 (0.66–0.94)†
		≥85	0.54 (0.45–0.65)†
Sex	Male	Female	1.05 (0.91–1.21)
ADL score at discharge	Per 1-unit increase in score		1.01 (1.00–1.01)
IHD	No	Yes	0.95 (0.81–1.11)
AF	No	Yes	0.81 (0.70–0.93)†
Valvular disease	No	Yes	0.43 (0.16–1.17)
Neoplasm	No	Yes	0.85 (0.63–1.14)
β-blocker (n=2,255)			
SBP (mmHg)	<100	100–<140	0.85 (0.68–1.05)
		≥140	0.73 (0.54–1.01)
BNP (pg/mL)	<700.3	≥700.3	1.75 (1.48–2.07)
eGFR (mL/min/1.73 m²)	<30	30–<45	0.97 (0.79–1.20)
		≥45	1.09 (0.90–1.31)
Age (years)	<75	75–84	0.53 (0.44–0.64)†
		≥85	0.33 (0.27–0.40)†
Sex	Male	Female	1.03 (0.88–1.19)
ADL score at discharge	Per 1-unit increase in score		1.01 (1.00–1.01)
IHD	No	Yes	1.17 (0.99–1.38)
AF	No	Yes	1.44 (1.23–1.68)*
Valvular disease	No	Yes	1.21 (0.46–3.15)
Neoplasm	No	Yes	0.63 (0.47–0.86)†

(**Table 3** continued the next page.)

HF medications Explanatory variables/covariates	Reference	Categories	OR (95% CI)
MRA (n=1,740)			
SBP (mmHg)	<100	100–<140	0.71 (0.58–0.88)†
		≥140	0.43 (0.31–0.59)†
BNP (pg/mL)	<700.3	≥700.3	1.37 (1.16–1.61)*
eGFR (mL/min/1.73 m^2)	<30	30–<45	2.42 (1.95–3.00)*
		≥45	3.56 (2.94–4.31)*
Age (years)	<75	75–84	0.75 (0.63–0.89)†
		≥85	0.54 (0.45–0.65)†
Sex	Male	Female	1.16 (1.01–1.35)*
ADL score at discharge	Per 1-unit increase in score		1.00 (1.00–1.00)
IHD	No	Yes	1.05 (0.89–1.22)
AF	No	Yes	1.21 (1.04–1.40)*
Valvular disease	No	Yes	1.07 (0.42–2.69)
Neoplasm	No	Yes	0.84 (0.62–1.14)

*Significant positive associations. †Significant negative associations. HF, heart failure; OR, odds ratio. Other abbreviations as in Tables 1 and 2.

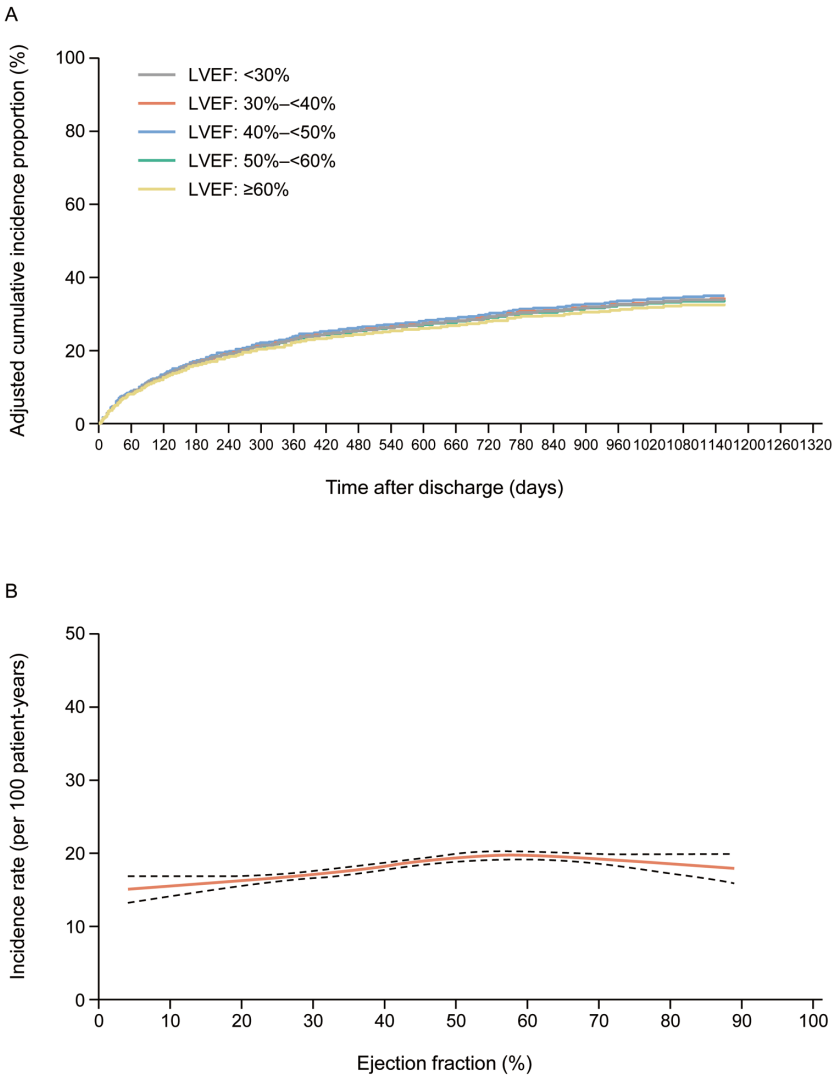

Figure 2. (**A**) Adjusted cumulative incidence of rehospitalization for heart failure (HF) by left ventricular ejection fraction (LVEF) subgroup and (**B**) the incidence of rehospitalization for HF as a function of ejection fraction. Dashed lines indicate 95% confidence intervals.

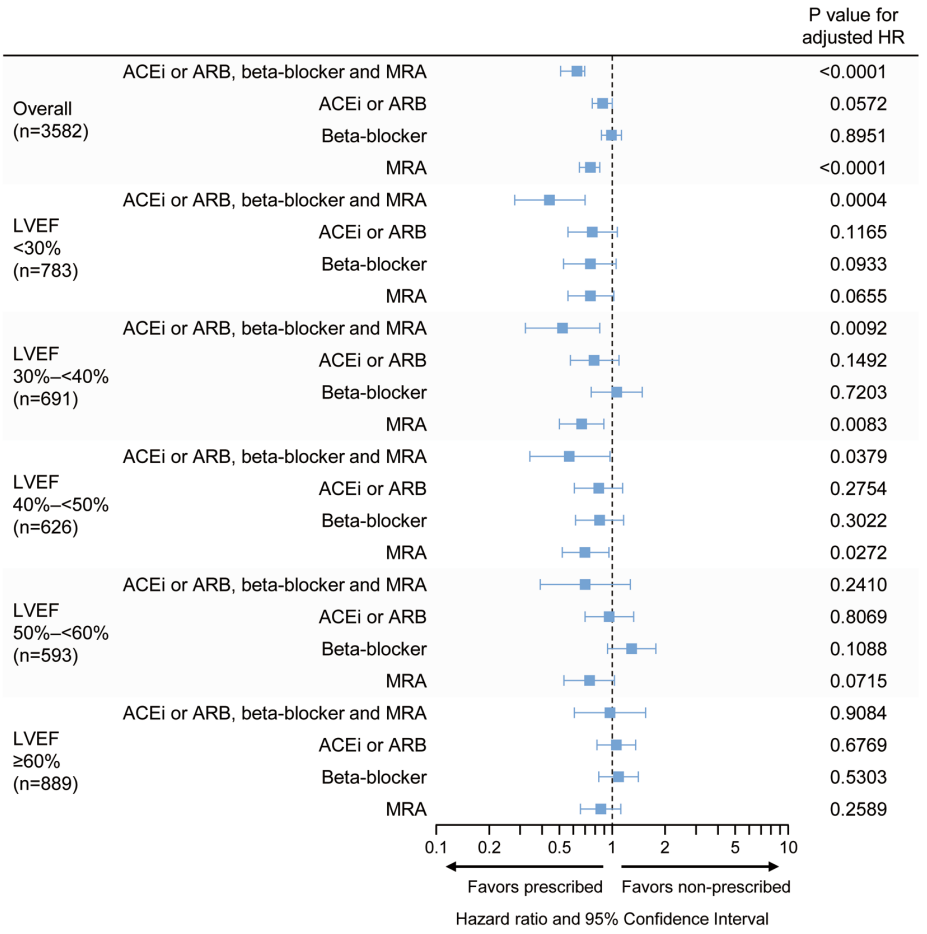

Figure 3. Impact of heart failure (HF) treatments at discharge on rates of rehospitalization for HF. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists.

District-2 Study (CHART-2) who were categorized as having HFpEF, HFmrEF, or HFrEF.[22,23] In the patients evaluated in the present study, a prescription of an ACEi/ARB and a β-blocker was reported for 56.4% and 49.2% of patients with an LVEF of <30% and 30–<40%, respectively, showing that there were differences in prescription rates among patients with HFrEF. When we analyzed the prescription rate for each drug, the rates for β-blocker and MRA prescriptions differed by approximately 5% each between patients with LVEF 50–<60% and those with LVEF ≥60%.

In the present study, we also explored patient characteristics associated with prescription rates in detail. Although factors that were significantly associated with prescription rates differed slightly for different combinations of treatments, a general pattern was identified, with younger patients with more severe ventricular dysfunction and better renal function being more likely to receive more intensive treatment. In the WET-HF study, a potential impact of age on prescribing rates was also observed, with patients aged ≥80 years being less likely to be prescribed a renin–angiotensin system (RAS) inhibitor combined with a β-blocker than patients aged <80 years (46.8% vs. 66.9%).[27] Triple combination therapy includes inhibitors of the RAS, and prescription rates of triple combination therapy, but not β-blockers, were heavily influenced by impaired renal function in the present study. Therefore, patients receiving β-blockers in the present study may reflect a subset of patients with reduced renal function. It has been reported that renal function and eGFR variability affect outcomes in HF patients;[28,29] as such, in the present study, worse renal function may have had a greater influence on outcomes than the benefits that could be achieved with the use of a β-blocker. Gaining a greater understanding of which patients are likely to be undertreated may enable the identification of strategies to improve prescribing rates in the future.

In the present study, the prescription of triple combination therapy was associated with a significantly reduced risk of rehospitalization for HF in patients with LVEF <30%, 30–<40%, or 40–<50%, but not in patients with LVEF 50–<60% or ≥60%, which is a second novel finding of this study in Japan. In the TOPCAT study, treatment with the MRA spironolactone reduced the risk of the composite primary endpoint (cardiovascular death, aborted cardiac arrest, or hospitalization for HF) or hospitaliza-

tion for HF in patients with an LVEF of 45–50%.[16] This is consistent with results of the present study, in which treatment with an MRA reduced the risk of rehospitalization in patients with an LVEF of 40–<50%. Similarly, the PARAGON-HF study indicated that treatment with an ARNI could reduce the risk of a composite endpoint of hospitalization for HF and death from cardiovascular causes in patients with an LVEF of 45–57%.[20] The importance of treating patients with mildly reduced LVEF was illustrated in a study by Goto et al, who showed that patients with an LVEF of <58% had an increased risk of future acute decompensated HF admissions and all-cause mortality than patients with an LVEF above this cut-off.[21] The benefits of medication for patients with an LVEF of 50–<60% and those with an LVEF ≥60% remain to be fully elucidated, and further study will be necessary to optimize treatment, including the use of SGLT2i for those patients. In addition, a treatment regimen comprising an ARNI, an MRA, a β-blocker, and an SGLT2i (together termed 'the fantastic 4') has recently shown efficacy in the treatment of HFrEF.[30] The benefits of this combination across other LVEF categories remain to be established and will require further study.

Study Limitations

This study has several limitations. First, it had a relatively short follow-up duration and a lack of accurate follow-up, which may have led to an underestimation of the impact on prognosis. Second, ARNI and SGLT2i were not approved for HF in Japan at the time the study was conducted, and data on these drug classes were not collected. Third, data on implantable cardioverter or cardiac resynchronization therapy defibrillator use were not available. The use of these devices may have had an impact on prognosis, but this was not taken into account in the present study. Finally, we cannot exclude the possibility of adjustments to patients' treatment regimens (e.g., dose titrations) in the outpatient setting, which may have affected clinical outcomes for these patients.

Conclusions

In this real-world study in Japan, the use of triple combination therapy was significantly associated with a low risk of rehospitalization for HF within 1 year of discharge in patients with LVEF <30%, 30–<40%, or 40–<50%. However, patients were undertreated, with triple combination therapy only prescribed for approximately 40% of patients with an LVEF of <30% and 30% of patients with an LVEF of 30–<40%.

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Disclosures

I.U., S.E., Y.M., H.M., K.I. are employees of, and received consultancy fees from, Novartis Pharma K.K. T.K. received remuneration from Novartis Pharma K.K. for attending meetings.

Author Contributions

I.U., Y.M., T.K. contributed to the conception and design of the study; acquisition, analysis, and interpretation of the data; and drafting and critical revision of the manuscript. S.E., K.I. contributed to the interpretation of the data; and drafting and critical revision of the manuscript. All authors are accountable for the accuracy and integrity of the manuscript contents and approved the final version.

IRB Information

This study was approved by the Research Institute of Healthcare Data Science Ethics Review Board (Protocol no. RI2020031).

Data Availability

For any kind of analyses, the deidentified participant data, study protocol, and statistical analysis plan will be shared with anyone, upon reasonable request made directly to the corresponding author. All analyzable data sets related to the study will be shared. The requested data will be available immediately and up to 1 year following the publication of this article.

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Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circrep.CR-23-0066