Association Between Physical Status and the Effects of Combination Therapy With Renin-Angiotensin System Inhibitors and *β*-Blockers in Patients With Acute Heart Failure

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Background: This study investigated whether combination therapy (CT) with renin-angiotensin system inhibitors and *β*-blockers improved endpoints in acute heart failure (AHF).

Methods and Results: AHF patients were recruited to this prospective multicenter cohort study between April 2015 and August 2017. Patients were divided into 3 categories based on ejection fraction (EF), namely heart failure (HF) with reduced EF (HFrEF), HF with midrange EF (HFmrEF), and HF with preserved EF (HFpEF), and a further into 2 groups according to physical status (those who could walk independently outdoors and those who could not). The composite endpoint included all-cause mortality and hospitalization for HF. Data at the 1-year follow-up were available for 1,018 patients. The incidence of the composite endpoint was significantly lower in the CT than non-CT group for HFrEF patients, but not among HFmrEF and HFpEF patients. For patients who could walk independently outdoors, a significantly lower rate of the composite endpoint was recorded only in the HFrEF group. The differences were maintained even after adjustment for comorbidities and prescriptions, with hazard ratios (95% confidence intervals) of 0.39 (0.20–0.76) and 0.48 (0.22–0.99), respectively.

Conclusions: In this study, CT was associated with the prevention of adverse outcomes in patients with HFrEF. Moreover, CT prevented adverse events only among patients without a physical disorder, not among those with a physical disorder.

Key Words: HFmrEF; HFpEF; HFrEF; Physical disorder; Prognosis

C ombination treatment (CT) with an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) and *β*-blocker improves outcomes in patients with heart failure (HF) with reduced ejection fraction (HFrEF), and these drugs are strongly recommended in current guidelines.[1–3] These guidelines suggest that patients with HF should be divided into following 3 groups based on ejection fraction (EF): HFrEF (EF ≤40%), HF with mid-range EF (HFmrEF; EF 40–49%), and HF with preserved EF (HFpEF ≥50%).[1,2] Many studies have reported the effectiveness of using ARB, ACEI, and *β*-blockers for patients with HFrEF, but not for those with HFpEF and HFmrEF.[4–8] Thus, there are limited clinical data regarding specific medications in patients with HFpEF and HFmrEF.

Major clinical trials revealed that CT with renin-angiotensin system (RAS) inhibitors and *β*-blockers improved outcomes in HFrEF patients.[5,6] However, these randomized clinical trials excluded elderly patients or frail patients.[9] A previous study showed that CT was effective in reducing mortality in both elderly and non-elderly HFrEF patients.[10] In contrast, another study in Japan reported that CT was not associated with better clinical outcomes among elderly HFrEF patients.[11] In real-world clinical situations, some elderly patients with HF maintain good physical activity levels, whereas some non-elderly patients with HF already exhibit decreased physical activity levels. Although reduced activities of daily living (ADL) are

Figure 1. Flow chart showing patient disposition in the present study. In all, 1,253 patients with acute heart failure (AHF) were identified from the Kitakawachi Clinical Background and Outcome of Heart Failure (KICKOFF) Registry. Of these patients, 135 were excluded because they died in hospital. Another, 100 patients were excluded because of end-stage chronic kidney disease (CKD; estimated glomerular filtration rate <15 mL/min/1.73 m²) or dialysis therapy (n=84), a lack of detailed data regarding ejection fraction (n=15), and no follow-up data (n=1). This left 1,018 patients with complete data who were included in the study.

strongly associated with worse outcomes in patients with acute HF (AHF),[12] it is unknown whether the effects of CT will be the same across different physical activity levels in HF patients.

The Kitakawachi Clinical Background and Outcome of Heart Failure (KICKOFF) Registry was designed as a prospective multicenter community-based cohort of Japanese patients with acute HF.[13] The aim of the present study was to compare the efficacy of CT with non-CT on the incidence of a composite endpoint of all-cause mortality and hospitalization for HF, with a focus on EF and ADL, in patients with AHF. First, differences in outcomes over a 1-year follow-up period were assessed between patients prescribed CT at discharge and those who were not according to EF (i.e., HFrEF, HFmrEF, and HFpEF). Second, differences in outcomes according to physical activity levels were assessed in the different EF groups.

Methods

Data for AHF patients were obtained from the KICKOFF Registry, which registered patients hospitalized between April 2015 and August 2017. Thirteen hospitals, 1 cardiovascular center, and 12 small- and medium-sized hospitals serving as primary and secondary referral medical centers participated in the registry.[13] The diagnosis of HF was established according to the Framingham criteria based on the presence of at least 2 major criteria or 1 major criterion

in conjunction with 2 minor criteria.[2,14] There were no exclusion criteria.

The KICKOFF Registry is registered with the UMIN Clinical Trials Registry (UMIN000016850), from which a detailed study design, patient enrollment, and the definition of measurements are available (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000019092&language=J, accessed March 4, 2021).

The clinical data of all patients were collected by an Internet database system and automatically checked for missing or contradictory entries, as well as values that were not in the normal range by physicians in charge at each institution. The general office of the Registry checked all data collected after registration. Data were collected from a review of medical records and from interviews with patients or other family members. This registry protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Hirakata Kohsai Hospital (Osaka, Japan). Informed consent was obtained from all study participants. Direct patient identifiers were not registered to preserve patient confidentiality. The study did not alter any treatment specified in the protocol or any other method of outpatient care.

In all, 1,253 patients with AHF were identified in the KICKOFF Registry. Of these patients, 135 were excluded because they died while in hospital. Another 100 patients

Table 1. Baseline Clinical Characteristics of Patients Receiving CT or Non-CT According to EF Category

	HFrEF			HFmrEF			HFpEF		
	All	**CT**	**Non-CT**	**All**	**CT**	**Non-CT**	**All**	**CT**	**Non-CT**
No. patients	308	181	127	125	62	63	585	216	369
Age (years)	74.2±12.6	71.1±12.8*	78.6±10.9	76.2±10.7	74.9±11.3	77.4±9.9	79.7±10.5	77.9±10.4*	80.8±10.5
Male sex (%)	61.7	64.6	57.5	52.0	51.6	52.4	43.7	44.9	43.1
Comorbidities (%)									
History of HF	67.9	63.0*	74.8	55.2	58.1	52.4	51.1	50.0	51.8
Coronary artery disease	38.0	34.8	42.5	36.0	33.9	38.1	20.2	26.9*	16.3
Cardiomyopathy	25.0	26.0	23.6	12.8	11.3	14.3	10.1	11.1	9.5
Hypertension	59.7	70.7*	44.1	72.8	82.3*	63.5	67.2	80.1*	59.6
Diabetes	37.7	37.6	37.8	41.6	46.8	36.5	29.4	35.7*	25.8
Atrial fibrillation	39.3	34.8	45.7	46.4	38.7	54.0	45.6	50.0	43.1
CKD	52.9	50.8	55.9	49.6	46.8	52.4	48.2	47.2	48.8
History of stroke	11.7	7.7*	17.3	17.6	16.1	19.1	9.4	7.4	10.6
LVEF (%)	30.4±7.0	30.0±6.9	31.0±7.0	45.2±2.3	45.1±2.4	45.4±2.3	65.2±8.7	65.3±8.9	65.2±8.6
eGFR (mL/min/1.73 m²)	47.6 [35.9–61.9]	48.9 [37.8–62.4]	43.2 [33.1–61.3]	48.9 [35.0–62.6]	49.8 [36.0–59.0]	46.1 [34.4–67.4]	48.5 [35.3–64.5]	48.0 [35.8–63.3]	49.6 [34.1–66.3]
BNP (pg/mL)	299 [128–559]	249 [112–490]*	365 [151–639]	270 [96–503]	243 [102–491]	291 [94–560]	166 [78–348]	171 [68–352]	163 [79–342]
Medication (%)									
RAS inhibitors (ARB/ACEI)	71.1	100*	29.9	62.4	100*	25.4	60.0	100*	36.6
β-blocker	81.2	100*	54.3	74.4	100*	49.2	55.2	100*	29.0
Diuretic	93.5	92.8	94.5	84.0	85.5	82.5	72.8	79.2*	69.1
MRA	19.8	18.8	21.3	22.4	22.6	22.2	14.2	12.5	14.9
Calcium channel blocker	11.4	13.3	8.7	16.8	17.4	15.9	23.1	21.8	23.9
Oral inotropic agent	12.3	7.7*	18.9	4.8	1.6	7.9	3.8	3.2	4.1
Digitalis	5.5	3.3*	8.7	7.2	4.8	9.5	3.9	6.5*	2.4
ADL at discharge									
Independent outdoor walking	64.9	75.7*	49.6	62.4	62.9	61.9	54.4	63.9*	48.8
Non-independent outdoor walking	35.1	24.3*	50.4	37.6	37.1	38.1	45.6	36.1*	51.2
Independent indoor walking	18.5	16.0	22.0	16.8	24.2	9.5	24.4	23.1	25.2
Indoor walking with assistance	9.1	5.5	14.2	10.4	9.7	11.1	11.8	8.8	13.6
Abasia	7.5	2.8	14.2	10.4	3.2	17.5	9.4	4.2	12.5

Unless indicated otherwise, data are presented as the mean±SD or as the median [interquartile range]. *P<0.05 compared with the non-CT group. ACEI, angiotensin-converting enzyme inhibitor; ADL, activities of daily living; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CT, combination therapy; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure (HF) with mid-range ejection fraction (EF); HFpEF, HF with preserved EF; HFrEF, HF with reduced EF; LVEF, left ventricle EF; MRA, mineralocorticoid receptor antagonist; Non-CT, not CT; RAS, renin-angiotensin system.

were excluded because they had end-stage chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m²) or were undergoing dialysis therapy (n=84), data regarding EF was lacking (n=15), or no follow-up data were available (n=1). This left 1,018 patients for whom complete data were available (**Figure 1**).

In this study we defined HFrEF as a left ventricular (LV) EF of ≤40%, HFmrEF as an LVEF of 40–50%, and HFpEF as an LVEF ≥50% at discharge.[1,2] Echocardiography data were registered only before discharge. Of the 1,018 patients included in the study, follow-up data were available for 308 who had HFrEF, 125 who had HFmrEF, and 585 who had HFpEF. Patients were categorized into the following ADL 4 groups: Group 1, independent outdoor walking; Group 2, independent indoor walking; Group 3,

indoor walking with assistance; or Group 4, abasia before admission and at discharge.[13] In this study, patients in each EF group were divided into a further 2 groups: patients who could walk independently outdoors at discharge (ADL Group 1) and all other patients (ADL Groups 2–4).

To analyze differences in outcomes, patients were classified into 2 groups according to the medication prescribed at discharge: (1) CT, patients prescribed both RAS inhibitors and β-blockers; and (2) non-CT, patients who prescribed RAS inhibitors only or β-blockers only. RAS inhibitors included ARBs and ACEI. The definitions of other comorbidities have been described elsewhere.[13]

The primary endpoint was a composite endpoint of all-cause death and an incidence of hospitalization for HF during the follow-up period.[15] Additional clinical end-
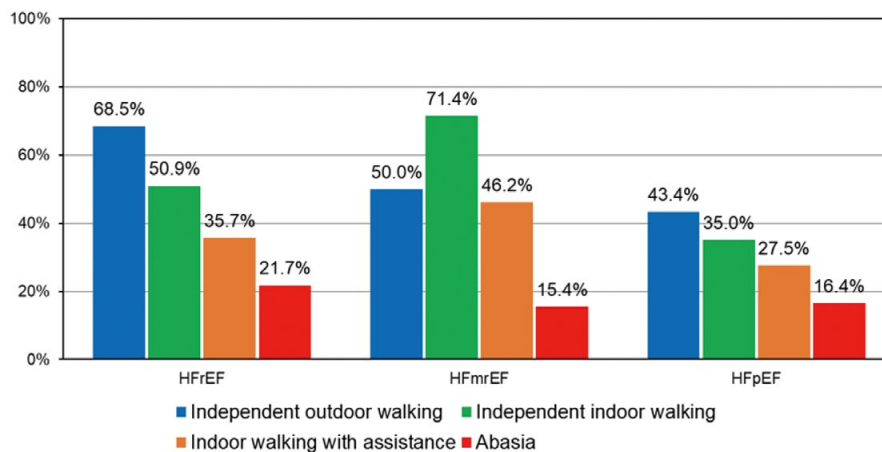
Figure 2. Distribution of combination therapy (CT) according to activities of daily living (ADL) in each ejection fraction (EF) category. Among patients with HF with reduced or persevered EF (HFrEF and HFpEF, respectively), the highest proportion of CT prescriptions was found for the independent outdoor walking group, and the rate of CT prescription decreased with declining ADL. In patients with HF and mid-range EF (HFmrEF), the highest proportion of CT prescriptions was for the independent indoor walking group.

points were the incidence of all-cause death and the incidence of hospitalization for HF during the follow-up period. Follow-up data were collected at 6 months and 1 year after hospital discharge. Follow-up data were obtained primarily from a review of hospital records, and additional follow-up data were obtained via telephone or mail contact with the patients or their relatives.

In this study population, baseline clinical characteristics were first compared between the CT and non-CT groups within each EF group (i.e., HFrEF, HFmrEF, and HFpEF). In addition, baseline clinical characteristics were compared between the CT and non-CT groups within the independent and non-independent outdoor walking groups for patients in each EF category (i.e., HFrEF, HFmrEF, and HFpEF). For subgroup analysis, the study population was divided into elderly and non-elderly subgroups (age ≥80 and <80 years, respectively) as per previous studies.[10,11]

Statistical Analysis
Continuous variables are expressed as the mean±SD or as the median with interquartile range, and categorical variables are expressed as percentages. Chi-squared tests were used to compare categorical variables, whereas Student's t-test was used to compare continuous variables. The Kaplan-Meier method was used to evaluate the cumulative incidence of the composite endpoint in each EF group and in both physical activity groups (i.e., independent and non-independent outdoor walking) within each EF group. The significance of differences was assessed using log-rank tests.

Multivariate analysis with a Cox proportional hazard model was used to evaluate the association between CT and the incidence of the composite endpoint. The timing of each event from discharge was determined. Data were censored if there were no events by the 1-year follow-up. Furthermore, hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

To investigate the effects of CT in preventing the composite endpoint, 2 multivariable models were used: Model 1 was adjusted for sex, age (10-year intervals), eGFR (<30,

30–45, 45–60, and ≥60 mL/min/1.73 m²),[16] and comorbidities (yes/no; e.g., history of HF, coronary artery disease, cardiomyopathy, atrial fibrillation, and stroke); Model 2 was adjusted for sex, age, eGFR, other prescriptions at discharge (yes/no; e.g., mineralocorticoid receptor antagonists [MRA], calcium channel blockers, oral inotropic agents, and digitalis), and the number of prescriptions at discharge. These variables were used based on clinical relevance and previous studies.[10–12]

Statistical analyses were performed using JMP version 14 (SAS Institute, Cary, NC, USA). Two-tailed P<0.05 was considered significant.

Results
One-year follow-up data were available for 1,018 AHF patients. The baseline clinical characteristics of all eligible patients with AHF in the CT and non-CT groups for each of the EF categories are presented in **Table 1**. Of the patients included in this study, there were 308 (30.3%), 125 (12.3%), and 585 (57.4%) with HFrEF, HFmrEF, and HFpEF, respectively.

HFrEF patients receiving CT were younger, more likely to have a history of HF, more likely to have hypertension, and less likely to have a history of stroke than those in the non-CT group. HFpEF patients receiving CT were more likely to have coronary artery disease, hypertension, and diabetes than those in the non-CT group. Among HFrEF patients, prescriptions of oral inotropic agents and digitalis were lower for those in the CT than non-CT group. Among HFpEF patients, prescriptions of diuretics and digitalis were higher for those in the CT than non-CT group. Among HFrEF and HFpEF patients, a higher proportion of patients were able to walk independently outdoors in the CT than in the non-CT group. The distribution of CT according to ADL levels in the HFrEF, HFmrEF, and HFpEF categories is shown in **Figure 2**. Among HFrEF and HFpEF patients, the highest proportion of CT prescriptions was for those in the independent outdoor walking

Table 2. Baseline Clinical Characteristics of Patients Receiving CT or Non-CT in the Different EF Categories Stratified According to Activity Levels

	HFrEF				HFmrEF				HFpEF			
	Independent outdoor walking		Not independent outdoor walking		Independent outdoor walking		Not independent outdoor walking		Independent outdoor walking		Not independent outdoor walking	
	CT	Non-CT	CT	Non-CT	CT	Non-CT	CT	Non-CT	CT	Non-CT	CT	Non-CT
No. subjects	137	63	44	64	39	39	23	24	138	180	78	189
Age (years)	67.7± 12.0*	73.1± 11.3	81.7± 8.7	83.9± 7.2	70.8± 10.9	73.7± 8.8	81.9± 8.3	83.4± 8.7	74.2± 10.1	75.2± 9.9	84.4± 7.2	86.0± 8.1
Male sex (%)	70.8	63.5	45.5	51.6	69.2	59.0	21.7	41.7	55.1	53.3	26.9	33.3
Comorbidities (%)												
History of HF	60.6*	76.2	70.5	73.4	56.4	48.7	60.9	58.3	47.1	44.4	55.1	58.7
Coronary artery disease	32.9	42.9	40.9	42.2	35.9	41.0	30.4	33.3	29.0*	17.8	23.1	14.8
Cardiomyopathy	27.0	27.0	22.7	20.3	12.8	18.0	8.7	8.3	10.1	11.1	12.8	7.9
Hypertension	70.1*	41.3	72.7*	46.8	84.6	69.2	78.3	54.2	79.7*	60.6	80.8*	58.7
Diabetes	37.2	38.1	38.6	37.5	46.2	41.0	47.8	29.2	37.7*	26.1	32.1	25.4
Atrial fibrillation	30.7	39.7	47.7	51.6	28.2	46.2	56.5	66.7	54.4	45.0	42.3	41.3
CKD	44.5	52.4	70.5	59.4	38.5	51.3	60.9	54.2	44.2	46.7	52.6	50.8
History of stroke	2.2*	12.7	25.0	21.9	15.4	7.7	17.4	37.5	3.6	7.8	14.1	13.2
LVEF (%)	29.2± 6.7	31.1± 7.4	32.4± 7.1	30.9± 6.6	45.1± 2.3	45.3± 2.4	45.1± 2.6	45.5± 2.2	64.4± 8.2	64.9± 8.3	65.5± 9.8	65.5± 8.8
eGFR (mL/min/1.73 m²)	53.6 [41.4– 64.5]	46.6 [34.5– 64.9]	41.1 [31.8– 51.2]	41.4 [31.1– 59.0]	53.9 [42.2– 63.2]	47.1 [35.7– 70.7]	42.0 [29.7– 57.3]	44.3 [29.6– 63.0]	49.7 [37.2– 64.6]	50.7 [36.7– 65.1]	46.3 [31.8– 66.9]	45.0 [32.8– 56.2]
BNP (pg/dL)	202 [90– 428]	342 [129– 558]	392 [261– 693]	443 [183– 679]	206 [75– 491]	282 [93– 560]	347 [135– 516]	312 [109– 688]	156 [60– 298]	152 [61– 292]	222 [108– 458]	173 [93– 403]
Medications (%)												
Diuretic	91.2	95.2	97.7	93.8	84.6	82.1	87.0	83.3	78.3*	65.5	80.8	72.5
MRA	19.7	20.6	15.9	21.9	20.5	25.6	26.1	16.7	13.8	12.8	10.3	16.9
Calcium channel blocker	13.9*	4.8	11.4	12.5	15.4	20.5	21.7	8.3	20.3	23.9	24.4	23.8
Oral inotropic agent	9.5	15.9	2.3*	21.9	2.6	7.7	0.0	8.3	2.9	1.7	3.9	6.4
Digitalis	2.9	7.9	4.6	9.4	5.1	7.7	4.4	12.5	8.7*	2.2	2.6	2.7

Unless indicated otherwise, data are presented as the mean±SD or as the median [interquartile range]. *P<0.05 compared with the non-CT group. Abbreviations as in Table 1.

group, with the rate of CT prescriptions decreasing with declining ADL. Among HFmrEF patients, the highest proportion of CT prescriptions is in the independent indoor walking group.

Clinical characteristics of patients in the CT and non-CT groups according to activity levels within each EF category are presented in **Table 2**. Among HFrEF patients, those in the independent outdoor walking group receiving CT were younger, with a lower proportion of a history of HF or stroke, lower prescriptions of calcium channel blockers, and a higher proportion of hypertension than those on non-CT. Among HFrEF patients that were not able to walk independently outdoors, the proportion of patients with hypertension was higher and the prescription of oral inotropic agents was lower for those on CT than non-CT.

At the 1-year follow-up, cumulative event rates were comparable between the CT and non-CT groups. The composite endpoint occurred in 354 patients (34.8%), and there were no significant differences in the number of patients with the composite endpoint among the EF groups: 104 (33.8%), 47 (37.6%), and 203 (34.7%) in the HFrEF, HFmrEF, and HFpEF groups, respectively. Kaplan-Meier analysis indicated that there was no signifi-

cant difference in the rate of the composite endpoint between CT and non-CT groups in the HFmrEF and HFpEF categories, but there rate of the composite endpoint was significantly lower in the CT than non-CT group for the HFrEF category (**Figure 3**).

Figure 4 shows the rate of the composite endpoint according to activity levels. Among patients with HFrEF, significantly lower rates of the composite endpoint were recorded in the CT than non-CT group only for those in the independent outdoor walking group (P<0.001), and not for those in the non-independent outdoor walking group (P=0.847). There were no significant differences in the rate of the composite endpoint between these 2 activity levels in the HFmrEF and HFpEF categories. Similar results were seen for the composite endpoint with regard to age (<80 and ≥80 years; **Supplementary Figure**): significantly lower rates of the composite endpoint in non-elderly HFrEF patients on CT (P<0.001) and no significant differences in the composite endpoint between the CT and non-CT groups of elderly HFrEF patients (P=0.165).

Results of the Cox proportional hazard model (**Table 3**) revealed that, in the HFrEF group, CT was associated with a significantly lower risk of the composite endpoint in each
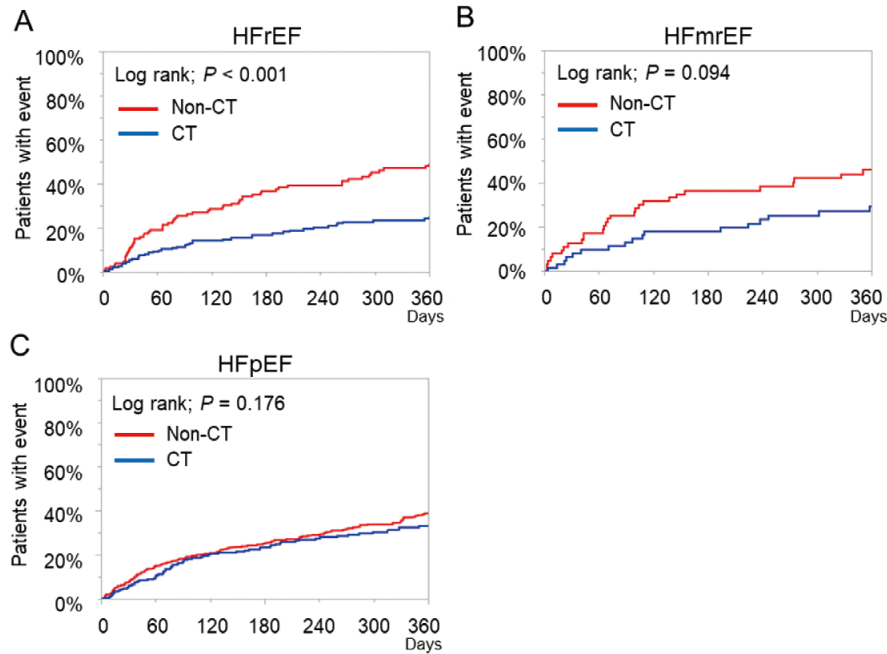
Figure 3. Kaplan-Meier curves for the composite endpoint (all-cause mortality and hospitalization for heart failure [HF]) over the 1-year follow-up period according to combination therapy (CT) in each ejection fraction (EF) category: (**A**) HF with reduced EF (HFrEF), (**B**) HF with mid-range EF (HFmrEF), and (**C**) HR with preserved EF (HFpEF). Kaplan-Meier analysis revealed that there was no significant difference in the rate of the composite endpoint between the CT and non-CT groups for patients with HFmrEF (**B**) and HFpEF (**C**), but there was a significantly lower rate of the composite endpoint in the CT than non-CT group among patients with HFrEF (**A**).

model in all patients, as well as among those in the independent outdoor walking group (Model 1, adjusted [a] HR 0.39, 95% CI 0.20–0.76; Model 2, aHR 0.48, 95% CI 0.22–0.99). However, among patients in the non-independent outdoor walking group, CT had no significant effect on the risk of the composite endpoint in each model (Model 1, aHR 0.87, 95% CI 0.49–1.48; Model 2, aHR 0.79, 95% CI 0.39–1.56). In the HFmrEF and HFpEF groups, the crude and adjusted HRs of the composite endpoint were not significant in each model. Furthermore, similar results were obtained in subgroup analyses based on endpoints of all-cause death or hospitalization for HF in both adjusted models for all subgroups (**Supplementary Table**).

Discussion

This prospective registry study of patients with AHF in Japan revealed that the use of CT (the prescription of both RAS inhibitors and β-blockers) was associated with the prevention of the composite endpoint only in patients with HFrEF, and not in patients with HFmrEF or HFpEF. Among patients with AHF, those with a physical disorder, defined as non-independent outdoor walking, were prescribed CT less often than those without a physical disorder. Furthermore, among patients with HFrEF, there was no significant difference in the endpoint between the CT and non-CT groups for those with physical disorder. However, among patients with good physical activity, the use of CT was associated with a significantly lower risk of the composite endpoint than the use of non-CT. Importantly, these

differences were maintained even after adjustment for differences in age, sex, renal function, comorbidities, or other prescriptions for HF management. To the best of our knowledge, this is the first study to reveal the association between the effect of CT and physical status on the endpoint in patients with AHF.

Association Between CT and Outcomes in HFrEF Patients
The main finding of this study is that CT had an effect on outcome in HFrEF patients without a physical disorder, but not in HFrEF patients with a physical disorder. There are several possible explanations for this observation. First, the characteristics of patients without a physical disorder were similar to those of patients who participated in previous randomized clinical trials. In general, the results of previous large randomized clinical trials were valuable for clinical decisions, but had limited direct adoption to all patients in real-world settings because of the exclusion criteria used by those trials (e.g., age, severe comorbidities, prescriptions, cognitive impairment, and physical disabilities).[9] However, many patients with AHF in real-world settings are older and have many comorbidities, many prescriptions, and are frail.[12,17] Second, physical activity severely affects drug pharmacokinetics in individual patients. Lower physical activity primarily depresses the metabolism and changes drug pharmacodynamics, drug absorption, distribution, and elimination.[18] Moreover, patients with physical disorders had muscle and adipose mass loss.[19,20] Patients with AHF had many comorbidities and were likely prescribed many drugs for the management
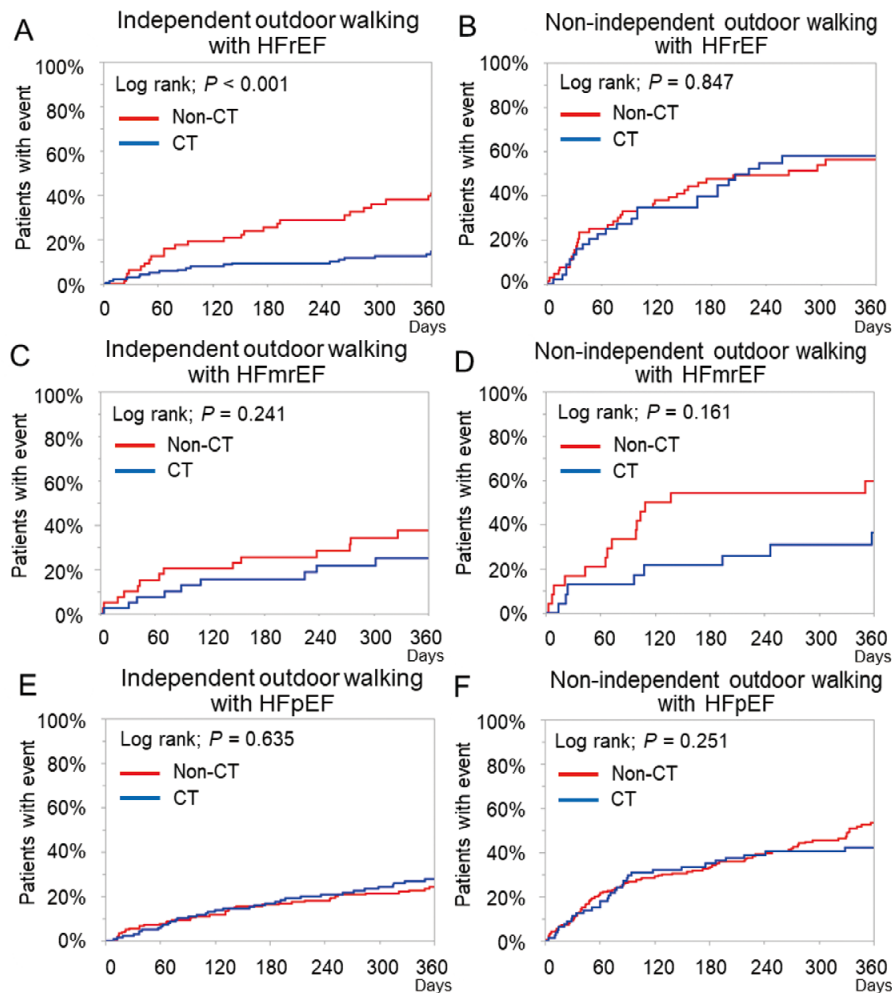
Figure 4. Kaplan-Meier curves for the composite endpoint (all-cause mortality and hospitalization for heart failure [HF]) over the 1-year follow-up period according to combination therapy (CT) in patients with (**A**,**B**) HF with reduced EF (HFrEF), (**C**,**D**) HF with mid-range EF (HFmrEF), and (**E**,**F**) HR with preserved EF (HFpEF) stratified according to physical activity. The rate of the composite endpoint was significantly lower in the CT than non-CT group only for HFrEF patients who could walk independently outdoors (**A**), and not for those who could not walk independently outdoors (**B**). There were no significant differences in the composite endpoint between the CT and non-CT groups of patients with HFmrEF (**C**,**D**) and HFpEF (**E**,**F**), regardless of physical activity status.

of these comorbidities; there may be strong drug interactions between these medications resulting in occasional or weak adverse events. In addition, the drug dosage used in CT may not have been sufficient to prevent adverse events.[21,22]

Some previous studies analyzed the association between the outcomes and use of CT in patients with AHF according to age (older and younger than 80 years). A study in a Korean registry revealed that the use of CT was associated with a reduced risk of all-cause mortality not only in elderly patients, aged ≥80 years, but also in non-elderly patients with HFrEF.[10] In contrast, another registry in Japan revealed that the use of CT was not associated with improvements in the rate of cardiac death and HF readmission risk in elderly patients with HFrEF.[11] In the present study, CT had no significant effect on the composite endpoint in elderly patients. Although it is difficult to reach a strong conclusion regarding the efficacy of CT for elderly

patients because of differences in the criteria and endpoints used in the different studies, we can discuss medication therapy for elderly patients. On the basis of the findings of the present study, we should focus not only on age, but also on physical activity.

The physical status of AHF patients is significantly associated with outcomes,[12,23,24] and is one of the most important factors in clinical decision making.[25] A previous study reported that HF patients with impaired ADL took as many medications as those without impaired ADL.[26] However, in the present study, the prescription rate of CT decreased with decreases in ADL for patients with HFrEF and HFpEF. The patients in the present study were older and had a greater reduction in physical status than patients in previous studies. Other studies reported that the proportion of CT prescriptions decreased with increasing age.[10,11] In the present study, we found that most physicians con-

Table 3. Hazard Ratios of Combination Therapy for the Composite Endpoint During the 1-Year Follow-up

	Crude model		Adjusted Model 1		Adjusted Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
HFrEF						
All	0.42 (0.28–0.63)	<0.001	0.61 (0.40–0.92)	0.019	0.58 (0.38–0.88)	0.010
Independent outdoor walking	0.32 (0.17–0.58)	<0.001	0.39 (0.20–0.76)	0.005	0.48 (0.22–0.99)	0.049
Non-independent outdoor walking	0.95 (0.56–1.58)	0.847	0.87 (0.49–1.48)	0.601	0.79 (0.39–1.56)	0.497
HFmrEF						
All	0.61 (0.34–1.09)	0.094	0.77 (0.39–1.46)	0.426	0.54 (0.26–1.09)	0.088
Independent outdoor walking	0.61 (0.25–1.39)	0.241	0.63 (0.21–1.85)	0.393	0.40 (0.10–1.33)	0.137
Non-independent outdoor walking	0.56 (0.24–1.26)	0.163	0.61 (0.19–1.92)	0.400	0.63 (0.11–4.21)	0.611
HFpEF						
All	0.82 (0.61–1.09)	0.173	0.89 (0.66–1.20)	0.444	0.87 (0.63–1.18)	0.375
Independent outdoor walking	1.11 (0.71–1.74)	0.636	1.10 (0.69–1.76)	0.674	1.07 (0.65–1.75)	0.787
Non-independent outdoor walking	0.79 (0.52–1.17)	0.244	0.78 (0.51–1.16)	0.225	0.77 (0.48–1.22)	0.274

The composite endpoint was all-cause mortality and hospitalization for HF. Model 1 was adjusted for age (10-year intervals), sex, eGFR (<30, 30–45, 45–60 and ≥60 mL/min/1.73 m²) and comorbidities (yes/no; history of HF, coronary artery disease, cardiomyopathy, atrial fibrillation and stroke). Model 2 was adjusted for age, sex, eGFR, medication at discharge (yes/no; mineralocorticoid receptor antagonist, calcium channel blocker, oral inotropic agent and digitalis), and the number of prescriptions at discharge. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

sider patient factors such as age, comorbidities, socioeconomic status, and ADL in an aging clinical situation.

Association Between CT and EF Categories
For patients with HFrEF, several treatments are known to be effective in prolonging patient survival and preventing hospitalization. However, for patients with HFmrEF and HFpEF, it is not clear whether the same medical treatments are effective in improving outcomes.[27] We found that CT was associated with the prevention of adverse events only in patients with HFrEF, and not in patients with HFmrEF or HFpEF. Patients with HFpEF had different clinical characteristics and benefits of CT than patients with HFrEF.[28] Some studies reported that the prognosis of HFmrEF was similar to that of HFrEF.[29,30] In contrast, others reported that the prognosis of HFmrEF was similar to that of HFpEF.[31,32] In a previous study, the clinical characteristics and outcomes of patients with HFmrEF were reported to be between those of patients with HFrEF and HFpEF.[33] In the present study, on the basis of Kaplan-Meier analysis, the use of CT tended to prevent adverse outcomes among patients with HFmrEF compared with HFpEF. The results of the outcomes analysis support the findings of other previous studies. However, unfortunately, we had no EF data during the follow-up period and could not determine the proportion of patients with HF in whom EF recovered. RAS inhibitors and β-blockers have the potential to prevent decreases in EF and sudden cardiac death.[34,35] In our study population, there were 3 sudden cardiac deaths in HFrEF group, none in the HFmrEF group, and 7 in the HFpEF group. We expect that further studies will reveal more detailed associations between outcomes and each EF category.

In the guidelines, MRA are recommended for patients with HFrEF, especially those with EF <35% and who remain symptomatic despite CT treatment.[1,2] MRA are associated with a reduction in adverse outcomes in addition to CT for patients with HFrEF.[36,37] A previous trial could not reveal the benefit of spironolactone therapy in patients with HFpEF,[38] and there has been no trial investigating the benefit of MRA in patients with HFmrEF. In

the present study, we did not focus on MRA, but found a benefit of the use of MRA in patients with HFrEF after adjusting for MRA. We conclude that one of the most fundamental therapies for patients with AHF without physical disorders is the use of RAS inhibitors and β-blockers.

Study Limitations
This registry study has several limitations. First, the diagnosis of AHF was made only by physicians using the Framingham criteria. There is a possibility of selection or referral bias. However, previous major cohort studies of HF in Japan also used the Framingham criteria to diagnose HF.[39] Second, we did not have data to evaluate patients' ADL using a more quantitative index or score, and so categorized ADL into 4 levels only; however, this categorization is quite simple and crucial for daily living. Therefore, clinical physicians could easily use it for patients with HF in their respective clinical situations. Third, we did not have data regarding changes in ADL and prescriptions after discharge. Fourth, we did not have data regarding patient adherence to the medications and the dose of medications. Patient adherence and the dose of medications are important in evaluating the effectiveness of medications. Previous studies had similar limitations regarding the adherence to or dose of medications.[10,11] Fifth, we defined all-cause mortality and hospitalization for HF as the composite endpoint. However, when we used cardiovascular death and hospitalization for HF as the composite endpoint, similar results were obtained compared with the original composite endpoints. Sixth, in this study, we did not have data on the implementation of comprehensive cardiac rehabilitation during the hospital stay and after discharge. It is obvious that a comprehensive cardiac rehabilitation program for patients with AHF is valuable in avoiding adverse events.[40] Finally, this study had small sample sizes, especially in the HFmrEF category. Therefore, we anticipate that future large studies will reveal the association between CT and outcomes in HFmrEF. Although this registry had some limitations, it revealed that CT is correlated with preventing adverse outcomes in patients

with HFrEF, particularly in HFrEF patients without a physical disorder.

Conclusions

In this study, the use of CT was associated with the prevention of adverse outcomes in patients with HFrEF, but not patients with HFmrEF or HFpEF. Moreover, adverse events after discharge in AHF patients prescribed CT were prevented only among those patients without a physical disorder, and not among those with a physical disorder.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-20-0123