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ORIGINAL ARTICLE
Heart Failure

Population Gap for Chronic Heart Failure Patients Between Randomized Controlled Trials and Japan's Super-Aged Society

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Background: Heart failure (HF) management has been improved by guideline-directed medical therapy (GDMT) based on findings of major randomized controlled trials (RCTs). However, the applicability of these findings to real-world HF populations, especially Japan's current super-aged society, remains uncertain.

Methods and Results: We analyzed findings for chronic HF patients from the KUNIUMI registry, a prospective observational study conducted on Awaji Island, Japan, representative of a super-aged society (aging rate ≈37%). We determined what percentage of these patients met the inclusion criteria as well as the exclusion criteria of 6 major representative RCTs (PARADIGM-HF, PARAGON-HF, DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved) and compared the incidence of cardiovascular death and HF hospitalization over 3 years for patients who did and did not meet the exclusion criteria. Of the 1,646 patients from the KUNIUMI registry, 225 were eligible for PARADIGM-HF, DAPA-HF and EMPEROR-Reduced, 554 for PARAGON-HF, and 631 for DELIVER and EMPEROR-Preserved. The exclusion percentages for the overall eligible population were 48.4% (PARADIGM-HF), 36.4% (DAPA-HF), 42.7% (EMPEROR-Reduced), 57.9% (PARAGON-HF), 32.3% (DELIVER), and 31.4% (EMPEROR-Preserved). It should be noted that ineligible patients had a poorer prognosis than eligible patients ($P<0.05$ for each trial).

Conclusions: The population gap between HF patients in major RCTs and the current super-aged society underscores the need for further evidence of GDMT in real-world settings.

Key Words: Guideline-directed medical therapy; Heart failure; Randomized controlled trials; Real-world heart failure populations

Heart failure (HF) is a major cause of morbidity and mortality globally, with its prevalence projected to rise. Recent advances in HF drug therapy, such as angiotensin-receptor-neprilysin inhibitors (ARNI) and sodium–glucose cotransporter 2 (SGLT2) inhibitors, have significantly improved HF management. Major randomized controlled trials (RCTs) using ARNI and SGLT2 inhibitors, comprising PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction), DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), DELIVER (Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction), EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction), and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction), have demonstrated reductions in HF hospitalizations and deaths of HF patients.[1–6] The results

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of these RCTs have precipitated a paradigm shift in HF treatment guidelines, emphasizing the need for integration of these therapies into standard care.[7,8]

However, the generalizability of the application of these findings for the broader HF patient population remains controversial because RCTs often use strict inclusion and exclusion criteria, resulting in a particular cohort that may not fully represent the diverse demographics and clinical characteristics of patients encountered in real-world settings. This selection bias raises concerns about the applicability and effectiveness of these guideline-directed medical therapies (GDMT) in clinical practice. For the elderly HF population in particular, characterized by comorbidities, frailty, and medication intolerance, the gap between RCT outcomes and real-world results can be expected to widen. Therefore, it is crucial to assess the extent to which real-world patients in aging populations meet the inclusion and exclusion criteria of these RCTs and to evaluate the real-world effectiveness of GDMT for HF management in the future.

The KUNIUMI (Kobe UNIversity Heart FailUre Registry in Awaji MedIcal Center) registry chronic cohort is a community-based, prospective, observational study designed to collect and analyze real-world data for chronic HF patients on Awaji Island, Japan. The registry includes a diverse range of HF patients, thus differing from those analyzed in RCTs. Japan is currently the first and only country to become a super-aged society, with >21% of its population aged ≥65 years, and this aging trend is expected to spread to other countries in the coming decades. Awaji Island is one of the most super-aged societies in the world, with a demographic profile similar to that projected for Japan in 20 years.[9] For our study we used the KUNIUMI registry to determine the proportion of patient cohorts meeting the exclusion criteria of the 6 representative RCTs cited by international guidelines as the basis for GDMT and to clarify the applicability of GDMT for HF practice in the future. Furthermore, by studying the patient cohorts satisfying the inclusion criteria of the RCTs, we aim to identify patient groups requiring further evidence supporting the need for GDMT in a real-world context.

Methods

Study Cohort

Patients with chronic HF enrolled in the KUNIUMI registry chronic cohort between March 2019 and March 2021 were analyzed in this study. With an aging rate of approximately 37%, Awaji Island is representative of a super-aged society. Approximately 2,700 patients, or 2% of the total population, are currently enrolled in this comprehensive study.[9] Details of the KUNIUMI registry chronic cohort have been reported elsewhere. Briefly, patients aged ≥20 years with either significant coronary artery disease or Stage B, C, or D HF, as defined by the American College of Cardiology/American Heart Association guidelines, were enrolled.[8] This current study was approved by the Ethics Committee of Hyogo Prefectural Awaji Medical Center in conformity with the Declaration of Helsinki (approval No. 21-20, 5 October 2018).

Selection of RCTs

The RCTs selected for this study were PARADIGM-HF, PARAGON-HF, DAPA-HF, DELIVER, EMPEROR-Reduced, and EMPEROR-Preserved. We examined the proportion of patients from the KUNIUMI Registry who met the inclusion criteria of each RCT and the respective exclusion criteria. The inclusion criteria for PARADIGM-HF, DAPA-HF and EMPEROR-Reduced were symptomatic HF and left ventricular ejection fraction (LVEF) ≤40%; for PARAGON-HF, they were symptomatic HF and LVEF >45%; and for DELIVER and EMPEROR-Preserved they were symptomatic HF and LVEF >40%. The main exclusion criteria derived from each RCT are shown in the **Supplementary Table**.

Outcomes

We compared the incidence of the composite endpoint of cardiovascular death and HF hospitalization as the primary outcome over 3 years for patients who met the exclusion criteria ("ineligible population") and those who did not ("eligible population"). Cardiovascular death was defined as death resulting from HF, myocardial infarction, or stroke, cardiac death, or any documented sudden death without an apparent noncardiovascular cause.

To clarify a comprehensive framework for understanding HF populations in a super-aged society, we analyzed 856 patients with symptomatic HF as part of an overall prognostic comparison. In this analysis, the exclusion criteria of all relevant RCTs were applied based on each patient's LVEF. Patients were classified into the "excluded group" if they met at ≥1 exclusion criterion across these RCTs. Conversely, those who did not meet any exclusion criteria were assigned to the "eligible group".

Furthermore, we analyzed the differences in primary outcomes based on adherence to GDMT in the excluded population. Our survey period was between March 2019 and March 2021, and SGLT2 inhibitors were not approved for HF with preserved EF (HFpEF) patients in Japan at that time. Considering this situation, we analyzed the relationship between the primary outcome and adherence to GDMT at baseline only in the HF with reduced EF (HFrEF) population. We defined the number of GDMT drugs patients described, including angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA), β-blocker, and SGLT2 inhibitor, as the parameter of adherence to GDMT.

Statistical Analysis

Continuous variables are expressed as the mean±standard deviation for normally distributed data and as median with interquartile range for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. Differences between groups were assessed using Student's t-test for continuous variables and χ^2 test for categorical variables. Survival curves excluding composite endpoints were determined using the Kaplan-Meier method, and cumulative event rates were compared using the log-rank test. For all steps, a $P<0.05$ was considered statistically significant. All analyses were performed using commercially available software (MedCalc software version 22.030; MedCalc Software, Mariakerke, Belgium).

Results

Percentages of Patients Meeting the Inclusion Criteria for Each RCT

Between March 2019 and March 2021, 1,646 patients with chronic HF were enrolled in the KUNIUMI registry chronic

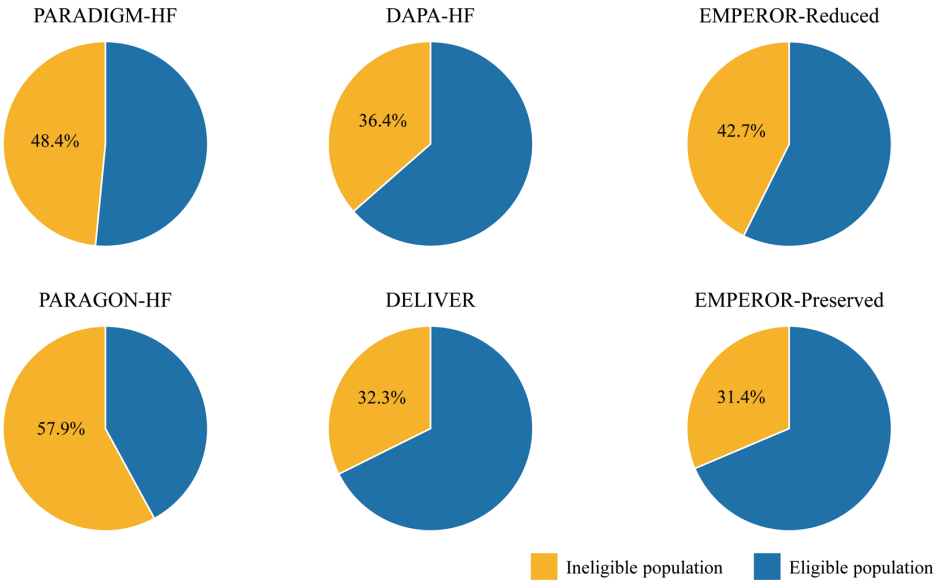

Figure 1. Exclusion rate for each randomized controlled trial.

cohort. Among them, 856 patients were symptomatic HF, defined as Stage C or D. Of these 856 patients analyzed in this study, 225 met the inclusion criteria based on LVEF for each of the trials individually: PARADIGM-HF, DAPA-HF, and EMPEROR-Reduced. Additionally, 554 patients were eligible for PARAGON-HF. For DELIVER and EMPEROR-Preserved, 631 patients met the inclusion criteria for each trial individually. We categorized the patients into 2 groups: the ineligible population, who met the exclusion criteria for each of the RCTs, and the eligible population, who were suitable for randomization in the RCTs. Based on the exclusion criteria for PARADIGM-HF, 109 patients were ineligible, and 116 patients were eligible, resulting in an exclusion rate, defined as the number of ineligible patients divided by the number of patients meeting the inclusion criteria, of 48.4%. For PARAGON-HF, 321 patients were ineligible (57.9% exclusion rate), for DAPA-HF, 82 (36.4%), for DELIVER, 204 (32.3%) for EMPEROR-Reduced, 96 (42.7%), and for EMPEROR-Preserved, 198 (31.4%) (**Figure 1**). Of the 856 patients included in the analysis, 480 (56.1%) were classified as the overall ineligible population.

Patients' Characteristics

The characteristics of the examined population from the KUNIUMI registry based on RCTs inclusion/exclusion criteria, are shown in the **Table**. Baseline data, medical history, and medications for the eligible and ineligible populations of each RCT were compared. The median age for all RCTs was approximately 80 years old for the 2 groups and not statistically different. All 6 RCTs showed that systolic blood pressure (SBP) was lower for the ineligible population than the eligible population, hemoglobin, albumin, and estimated glomerular filtration rate (eGFR) were also lower, but serum creatinine and B-type natriuretic peptide levels were higher for the ineligible group. The prevalence of diabetes mellitus, hypertension and atrial fibrillation was similar for all studies, although diabetes mellitus was higher for the ineligible population of DELIVER and EMPEROR-Preserved, and hypertension was lower for the ineligible population of PARADIGM-HF. The history of hospitalization for HF was statistically higher for the ineligible than for the eligible population. ACE-I or ARB use was detected more frequently in the eligible population of DELIVER, EMPEROR-Reduced, and EMPEROR-Preserved. MRA use was lower for the ineligible population of DELIVER, while diuretic use was higher for PARAGON-HF.

Cause and Incidence of Exclusions

The cause and incidence of exclusions for each RCT are shown in **Figure 2**. The ratio of exclusion factors was calculated based on the number of patients meeting the exclusion criteria in the included population. Low SBP and low eGFR were the most common exclusions for all RCTs of the real-world population. The percentages of low SBP and low eGFR for the population included in each of the RCTs were, respectively: 24.0% and 20.4% for PARADIGM-HF, 23.6% and 26.0% for PARAGON-HF, 13.8% and 20.4% for DAPA-HF, 7.1% and 18.5% for DELIVER, 24.0% and 11.1% for EMPEROR-Reduced, 10.6% and 13.3% for EMPEROR-Preserved.

Age Group Comparison

Because the median age of the population for all RCTs was approximately 80 years, the patients were divided into 3 groups: very elderly (≥85 years), elderly (65–84 years), and non-elderly (<65 years). The exclusion rate was then analyzed in accordance with age (**Figure 3**). There were no significant differences in the exclusion rates between each two of the age groups in any of the RCTs. The overall analysis also revealed no significant associations with exclusion rate and age (**Supplementary Figure 1**, P=0.35, χ^2 test for trend).

Table. Baseline Characteristics of Patients in 6 Selected Randomized Controlled Trials (RCTs)

Characteristic	RCTs								
	PARADIGM-HF			DAPA-HF			EMPEROR-Reduced		
	Eligible	Ineligible	P value	Eligible	Ineligible	P value	Eligible	Ineligible	P value
n (%)	116 (51.6)	109 (48.4)		143 (63.6)	82 (36.4)		129 (57.3)	96 (42.7)	
Age, years	77.5 (70.0–86.0)	79.0 (70.0–87.0)	0.63	77.0 (70.0–85.0)	81.0 (69.0–87.0)	0.39	78.0 (70.0–86.0)	79.0 (70.0–86.0)	0.62
Female sex, n (%)	25 (21.6)	41 (37.6)	<0.05	35 (24.5)	31 (37.8)	<0.05	29 (22.5)	37 (38.5)	<0.05
BMI, kg/m^2	23.0 (20.5–25.0)	20.7 (18.3–23.9)	<0.05	22.5 (19.6–24.8)	21.0 (18.4–24.0)	0.06	23.0 (20.4–25.1)	20.6 (18.2–23.2)	<0.05
SBP, mmHg	119 (109–131)	100 (93.8–121)	<0.05	115 (104–128)	108 (92–124)	<0.05	119 (110–130)	98.0 (92.0–118)	<0.05
Heart rate, beats/min	71.0 (60.5–80.0)	73.0 (65.0–83.3)	0.20	71.0 (61.3–82.0)	73.5 (65.0–83.0)	0.42	71.0 (60.0–80.0)	74.0 (66.0–84.5)	<0.05
Hemoglobin, g/dL	13.3 (11.8–14.8)	12.0 (10.5–13.9)	<0.05	13.1 (11.7–14.6)	12.0 (10.5–14.0)	<0.05	13.3 (11.8–14.7)	11.9 (10.1–13.8)	<0.05
Potassium, mEq/L	4.00 (3.80–4.30)	4.20 (3.80–4.60)	<0.05	4.00 (3.80–4.38)	4.20 (3.80–4.60)	<0.05	4.10 (3.80–4.40)	4.20 (3.70–4.55)	0.48
Albumin, g/dL	3.80 (3.50–4.10)	3.60 (3.20–3.90)	<0.05	3.70 (3.40–4.10)	3.60 (3.20–4.00)	<0.05	3.80 (3.50–4.10)	3.50 (3.20–3.90)	<0.05
Serum creatinine, mg/dL	1.00 (0.85–1.26)	1.36 (0.98–2.24)	<0.05	1.03 (0.85–1.26)	1.65 (1.06–2.56)	<0.05	1.08 (0.85–1.33)	1.27 (0.92–2.21)	<0.05
eGFR, mL/min/1.73 m^2	52.0 (42.0–63.5)	35.0 (20.0–53.0)	<0.05	50.0 (41.3–62.0)	27.5 (17.0–52.0)	<0.05	49.0 (37.0–62.3)	40.0 (19.0–55.0)	<0.05
Clinical features of HF									
Ischemic cause, n (%)	52 (44.8)	42 (38.5)	0.34	62 (43.4)	32 (39.0)	0.53	60 (46.5)	34 (35.4)	0.10
LVEF, %	32.0 (27.0–37.0)	33.0 (28.4–36.0)	0.87	33.0 (29.0–37.0)	31.0 (26.0–36.0)	<0.05	33.0 (28.0–37.2)	31.5 (27.0–35.9)	0.06
BNP, pg/mL	284 (133–630)	466 (246–874)	<0.05	302 (138–577)	524 (216–1,085)	<0.05	275 (129–627)	500 (274–902)	<0.05
Medical history, n (%)									
Diabetes	50 (43.1)	44 (40.4)	0.68	65 (45.5)	29 (35.4)	0.14	54 (41.9)	40 (41.7)	0.98
Hypertension	87 (75.0)	67 (61.5)	<0.05	104 (72.7)	50 (61.0)	0.07	93 (72.1)	61 (63.5)	0.17
Atrial fibrillation	48 (41.4)	59 (54.1)	0.06	65 (45.5)	42 (51.2)	0.41	55 (42.6)	52 (54.2)	0.09
Hospitalization for HF	80 (69.0)	93 (85.3)	<0.05	102 (71.3)	71 (86.6)	<0.05	91 (70.5)	82 (85.4)	<0.05
Treatment, n (%)									
ACE-Is or ARBs	89 (76.7)	74 (67.9)	0.14	106 (74.1)	57 (69.5)	0.46	101 (78.3)	62 (64.6)	<0.05
β-blockers	104 (89.7)	95 (87.2)	0.56	129 (90.2)	70 (85.4)	0.28	116 (89.9)	83 (86.5)	0.42
MRAs	67 (57.8)	61 (56.0)	0.79	84 (58.7)	44 (53.7)	0.46	75 (58.1)	53 (55.2)	0.66
Diuretics	78 (76.7)	88 (80.7)	0.46	114 (79.7)	63 (76.8)	0.61	100 (77.5)	77 (80.2)	0.63

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid antagonist; RCT, randomized controlled trial; SBP, systolic blood pressure.

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

Clinical Outcomes

In the overall population analysis of clinical outcomes, 856 patients with symptomatic HF, irrespective of LVEF, were included. The primary endpoint was recorded for 156 patients (32.5%) in the overall ineligible group and for 90 patients (23.9%) in the overall eligible population. **Figure 4** shows the Kaplan-Meier curves representing the primary endpoint for the ineligible and eligible groups in the overall population, showing that outcomes for the eligible group were better than for the ineligible group (hazard ratio, 0.68; 95% confidence interval [CI], 0.53 to 0.87; P<0.05). In addition, rates of death from cardiovascular causes and hospitalization for HF were higher for the ineligible than for the eligible group in the overall study population (**Figure 5**). Individual analyses of primary outcomes for each RCT demonstrated that the ineligible population showed worse primary outcomes than did the eligible population in RCTs for HFpEF (PARAGON-HF, DELIVER, and EMPEROR-Preserved), though this was not observed in RCTs for HFrEF (PARADIGM-HF, DAPA-HF, and EMPERO-Reduced) (**Figures 6**,**7**).

The results of the subgroup analysis examining the relationship between primary outcomes and adherence to GDMT at baseline in the HFrEF population are presented in **Supplementary Figure 2**. Of the 226 HFrEF patients enrolled in this study, participants were categorized into 3 groups based on the number of GDMT drugs used at baseline: 0, 1–2, and 3–4. The incidence of primary outcome events was 42.9% (3/7) in patients receiving no GDMT drugs, 40.0% (24/60) in those receiving 1–2 drugs, and 23.6% (13/55) in those receiving 3–4 drugs. Although the differences were not statistically significant, a greater number of GDMT drugs at baseline was associated with more favorable outcomes.

Characteristic	RCTs								
	PARAGON-HF			DELIVER			EMPEROR-Preserved		
	Eligible	Ineligible	P value	Eligible	Ineligible	P value	Eligible	Ineligible	P value
n (%)	233 (42.1)	321 (57.9)		427 (67.7)	204 (32.3)		433 (68.6)	198 (31.4)	
Age, years	82.0 (74.0–87.0)	82.0 (74.0–88.0)	0.64	82.0 (74.0–87.0)	82.0 (73.5–87.0)	0.93	82.0 (74.0–88.0)	81.0 (73.0–87.0)	0.48
Female sex, n (%)	119 (51.1)	147 (45.8)	0.22	203 (47.5)	88 (43.1)	0.30	203 (46.9)	88 (44.4)	0.57
BMI, kg/m^2	22.4 (20.2–24.7)	21.4 (18.9–24.0)	<0.05	21.8 (19.2–24.1)	22.0 (19.6–24.5)	0.22	22.0 (19.6–24.3)	21.2 (18.7–24.0)	0.06
SBP, mmHg	131 (120–143)	115 (103–136)	<0.05	123 (112–138)	119 (100–142)	<0.05	124 (113–138)	114 (96.0–141)	<0.05
Heart rate, beats/min	69.0 (61.0–79.0)	71.0 (63.0–79.0)	0.47	70.0 (62.0–79.0)	72.0 (63.0–79.0)	0.54	70.0 (62.0–79.0)	72.0 (64.8–79.0)	0.32
Hemoglobin, g/dL	12.5 (11.5–13.5)	11.3 (9.70–12.6)	<0.05	12.1 (10.9–13.4)	11.4 (9.75–12.6)	<0.05	12.2 (11.0–13.5)	11.1 (9.40–12.5)	<0.05
Potassium, mEq/L	4.10 (3.80–4.40)	4.10 (3.90–4.43)	0.15	4.10 (3.80–4.40)	4.10 (3.80–4.50)	0.43	4.10 (3.80–4.40)	4.10 (3.80–4.50)	0.96
Albumin, g/dL	3.90 (3.50–4.10)	3.50 (3.10–3.90)	<0.05	3.70 (3.30–4.10)	3.50 (3.10–3.80)	<0.05	3.80 (3.40–4.10)	3.40 (3.00–3.73)	<0.05
Serum creatinine, mg/dL	0.92 (0.75–1.12)	1.29 (0.96–2.28)	<0.05	0.98 (0.78–1.21)	1.82 (1.06–4.10)	<0.05	0.99 (0.80–1.32)	1.58 (0.97–4.40)	<0.05
eGFR, mL/min/1.73 m^2	52.0 (42.0–64.0)	33.0 (20.0–54.0)	<0.05	49.0 (39.0–63.0)	22.0 (11.0–47.0)	<0.05	48.0 (36.0–61.0)	29.5 (10.0–55.0)	<0.05
Clinical features of HF									
Ischemic cause, n (%)	62 (26.6)	80 (24.9)	0.65	108 (25.3)	61 (29.9)	0.22	117 (27.0)	52 (26.3)	0.84
LVEF, %	60.0 (54.0–66.0)	58.0 (52.0–63.0)	<0.05	57.6 (51.0–64.0)	57.0 (49.6–63)	0.55	57.3 (50.2–64.0)	57.0 (50.0–63.0)	0.86
BNP, pg/mL	173 (82.3–307)	223 (94.7–433)	<0.05	179 (82.4–335)	263 (141–555)	<0.05	187 (85.1–348)	241 (124–528)	<0.05
Medical history, n (%)									
Diabetes	72 (30.9)	104 (32.4)	0.71	118 (27.6)	80 (39.2)	<0.05	122 (28.2)	76 (38.4)	<0.05
Hypertension	184 (79.0)	234 (72.9)	0.10	315 (73.8)	157 (77.0)	0.39	327 (75.5)	145 (73.2)	0.54
Atrial fibrillation	94 (40.3)	154 (48.0)	0.07	198 (46.4)	90 (44.1)	0.60	205 (47.3)	83 (41.9)	0.20
Hospitalization for HF	112 (48.1)	227 (70.7)	<0.05	244 (57.1)	147 (72.1)	<0.05	246 (56.8)	145 (73.2)	<0.05
Treatment, n (%)									
ACE-Is or ARBs	155 (66.5)	195 (60.7)	0.16	288 (67.4)	113 (55.4)	<0.05	292 (67.4)	109 (55.1)	<0.05
β-blockers	156 (67.0)	209 (65.1)	0.65	287 (67.2)	135 (66.2)	0.80	296 (68.4)	126 (63.6)	0.24
MRAs	82 (35.2)	116 (36.1)	0.82	175 (41.0)	67 (32.8)	<0.05	169 (39.0)	73 (36.9)	0.60
Diuretics	135 (57.9)	227 (70.7)	<0.05	279 (65.3)	142 (69.6)	0.29	289 (66.7)	132 (66.7)	0.98

Discussion

Summary of Results

We investigated the percentages of real-world patients meeting the exclusion criteria of representative RCTs and found that 30–60% of patients fulfilled them, indicating that the findings obtained from these RCTs did not entirely apply to a significant number of patients. The primary reasons for exclusion were hypotension and renal impairment. The exclusion rate increased with age for patients in HFrEF RCTs, but not in HFpEF RCTs. Finally, clinical outcome analyses revealed that prognoses were poorer for ineligible patients. This difference was statistically significant for HFpEF RCTs but not for HFrEF RCTs.

Global Increase in Elderly Population and Associated Comorbidities

As the global population ages, the prevalence of HF among elderly patients is expected to rise significantly, and Japan, with its high proportion of elderly citizens, serves as a precursor of global demographic trends. Such a change will result in more patients with multiple comorbid conditions, thus complicating HF management, and these elderly HF patients will often also have functional and cognitive impairments. Comorbidities such as diabetes mellitus, chronic kidney disease (CKD), and cerebrovascular disease increase mortality risk, while an increase in comorbidity leads to higher all-cause mortality and HF rehospitalization rates. It should further be noted that the comorbidity burden lowers GDMT prescription rates and undermines the benefits of GDMT. For example, some comorbidities, such as diabetes mellitus and CKD, delay the initiation of novel GDMT (i.e., SGLT2 inhibitors and ARNI) in clinical practice. Moreover, selection bias in RCTs can be significant, often resulting in the omission of patients with comorbid conditions that do not agree with the criteria. Elderly patients with multiple comorbidities are therefore commonly excluded from RCT populations, so, when evaluating the applicability of RCT-derived insights to real-world practice, it is imperative to take into consideration the entire spectrum of comorbid conditions characterizing the patient population. Although our findings showed the age-

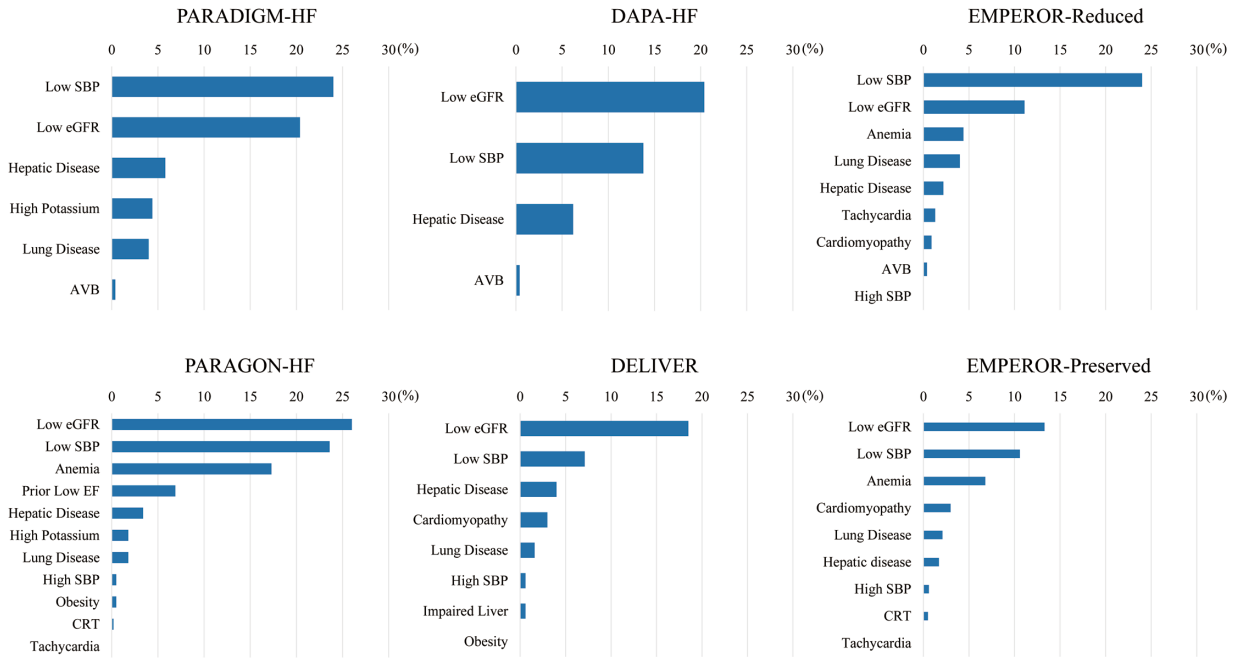

Figure 2. Cause and frequency for exclusion of each randomized controlled trial. AVB, atrioventricular block; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

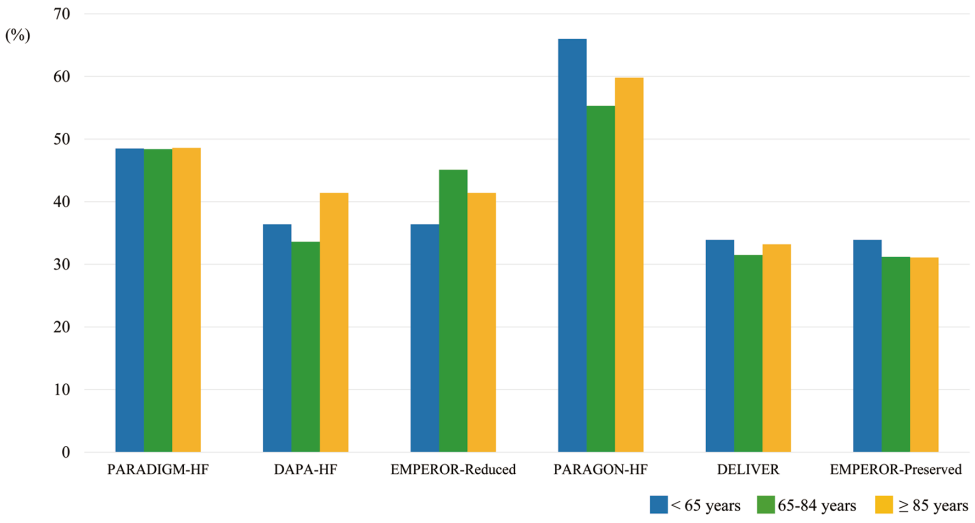

Figure 3. Age group comparison of exclusion rates for each randomized controlled trial.

based exclusion rate did not vary significantly, RCTs may also exclude patients for reasons such as frailty and dementia. Therefore, exclusion rate by age requires caution when interpretating our results.

Evidence Gaps for Super-Aged HF Populations

The efficacy of GDMT for the super-aged population remains unclear. The target of our study was a super-aged society with an average age (78.7 years) considerably higher than that of the selected 6 RCTs (av. 63–73 years), especially as 35.6% of the patients in our study were aged ≥85 years. The determination of medication efficacy for such an elderly population was based on subgroup analysis in the representative 6 RCTs, although evaluation for a super-aged population (≥85 years) is inadequate. PARADIGM-HF and PARAGON-HF did not demonstrate efficacy of

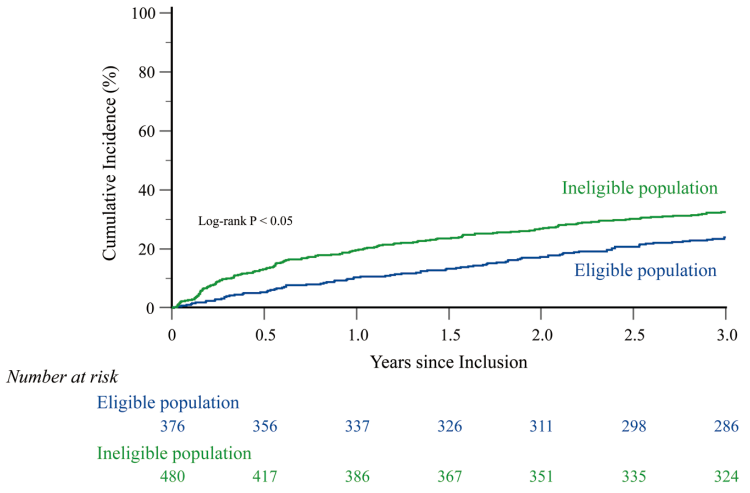

Figure 4. Kaplan-Meier curves representing the primary endpoint for the ineligible group and the eligible group in the overall population, showing that outcomes for the eligible group were better than for the ineligible group.

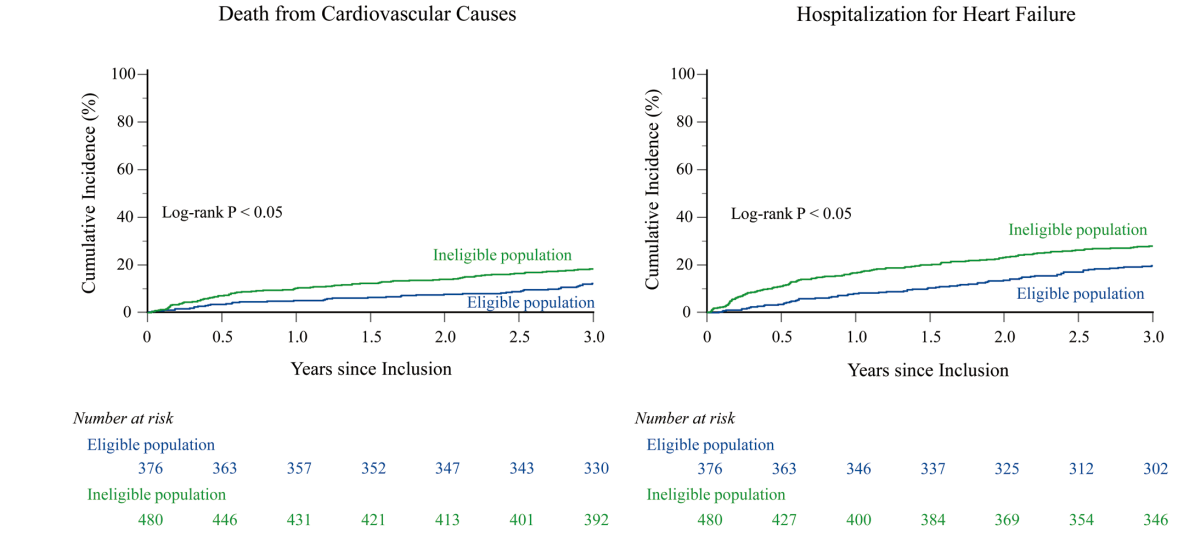

Figure 5. Kaplan-Meier curves representing the secondary endpoints including deaths from cardiovascular causes and hospitalizations for heart failure, showing that these outcomes for the eligible group were also better than for the ineligible group.

ARNI for patients aged >75 years.[1,2] However, secondary analysis of PARADIGM-HF reported that ARNI was beneficial across the age spectrum, although cardiovascular death and HF hospitalization occurred more frequently in the oldest patients.[10] Although ARNI tolerance was observed in a real-world cohort of HFrEF patients aged ≥80 years, symptomatic hypotension increased with age.[11] Dapagliflozin proved to be more efficacious than a placebo for elderly groups with age cutoffs of 65 years for DAPA-HF and 73 years for DELIVER.[3,4] The EMPEROR-Reduced and EMPEROR-Preserved trials, with age cutoffs of 65 and 70 years, respectively, reported empagliflozin was beneficial for HF of elderly groups.[5,6] Those RCTs did not include subgroup analyses for individuals aged ≥85 years, however, nor did they provide detailed age distributions. Additional analysis of the RCTs, analyzing 4 studies of the effect of dapagliflozin or empagliflozin on HFrEF and HFpEF, focused on the association of age with the effect of SGLT2 inhibitors on HF hospitalization and cardiovascular death.[12–14] The age cutoffs for the 4 studies varied from 75 to 80 years, while the secondary analysis of the DAPA-HF trial specifically analyzed a subgroup of patients aged ≥85 years. The results indicated that, although dapagliflozin did not reduce cardiovascular deaths and HF hospitalizations in this super-aged group, symptoms significantly improved.[12] In contrast, in the SOLD (SGLT2i in Older Diabetic patients) study conducted in a real-world setting, diabetes patients aged ≥80 years discontinued SGLT2 inhibitor therapy due to adverse events almost twice as often as younger patients.[15] The benefit-risk profile of ARNI and SGLT2 inhibitors for super-elderly patients in clinical practice therefore needs further exploration.

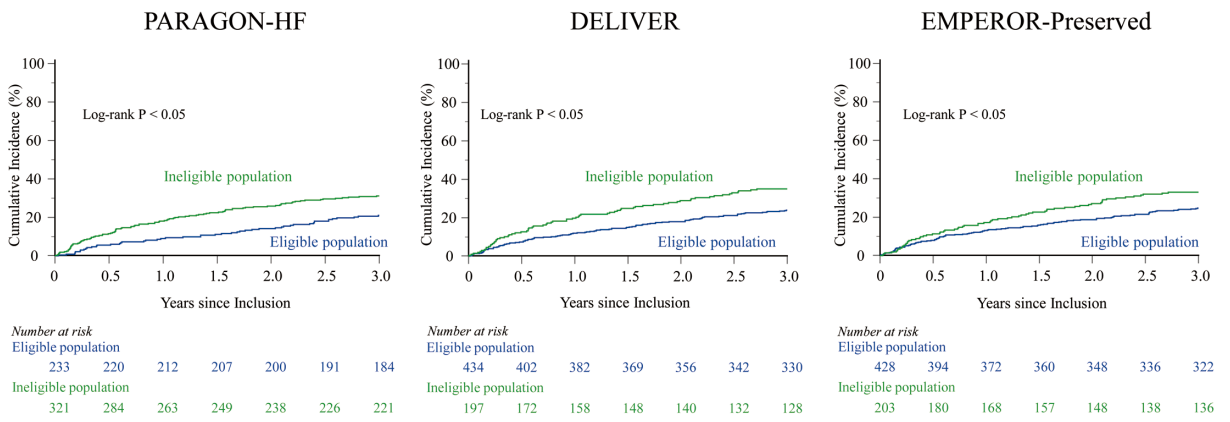

Figure 6. Kaplan-Meier curves representing the primary endpoint for the randomized controlled trials for heart failure patients with preserved ejection fraction comprising PARAGON-HF, DELIVER, and EMPEROR-Preserved, showing that outcomes for the eligible group were better than for the ineligible group.

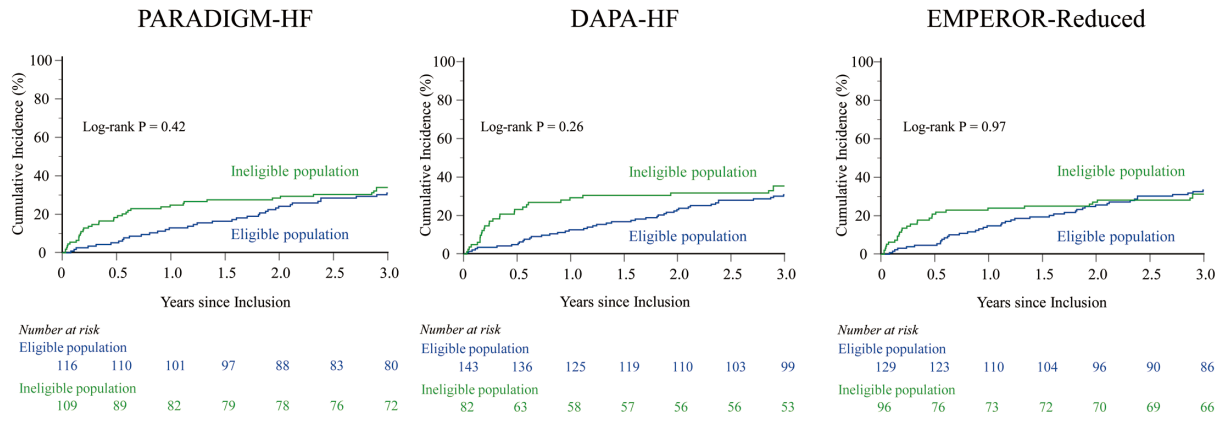

Figure 7. Kaplan-Meier curves representing the primary endpoint for randomized controlled trials for heart failure patients with reduced ejection fraction comprising PARADIGM-HF, DAPA-HF, and EMPEROR-Reduced, showing that outcomes for the eligible group and the ineligible group were similar.

It has been reported that conventional GDMT (β-blockers and MRAs) is efficacious for super-aged patients, although there are limits to their use in real-world settings. For HFrEF patients aged ≥80 years, β-blocker use has been associated with improvements in all-cause and cardiovascular mortality rates, even though reaching target doses in practice is challenging. Real-world data revealed that 86% of patients aged ≥80 years received β-blockers, but only 19% received the target doses, while 47.6% received <50% of the target dose.[16] Reasons for underuse in the aged population include safety concerns, hypotension, comorbidities, frailty, polypharmacy, and age itself.[16] Although guidelines have recommended MRAs for all patients with HFrEF to reduce mortality and HF hospitalization risks, worsening renal function and hyperkalemia related to MRAs have frequently been identified in older patients.[17] Consequently, there is a lack of robust evidence for the efficacy and safety of GDMT for the very elderly, especially those aged >85 years, underscoring the need for more inclusive research that reflects real-world practice.

Problems Implementing GDMT for Hypotensive and Renally Impaired Populations Excluded in RCTs

The exclusion criterion for hypotension in the 6 representative RCTs was SBP <95–110 mmHg. A retrospective study indicated that 25% of hospitalized HF patients had SBP <105 mmHg, which correlated with an increase in deaths.[18] Hypotension often limits the use and uptitration of GDMT drugs. Global registry data consistently show less use of GDMT than do RCTs,[19] despite strong recommendations in practice guidelines.[7,8] These recommendations are based on some secondary analyses of RCTs indicating ARNI and SGLT2 inhibitors benefit hypotensive patients as much as they do non-hypotensive populations.[20,21] It should be noted, however, that because these findings have been obtained from RCT-selected patients, they may not be

applicable for real-world patients. Available evidence related to hypotension of patients on GDMT indicates MRAs are the only drugs proven effective for hypotensive patients.[22] Beta-blockers are essential for HFrEF treatment, but are rarely discontinued despite possible hypotension risks. ARNI usage was found to be more strongly associated with symptomatic hypotension than was enalapril in the PARADIGM-HF trial,[1] but not in the PIONEER-HF trial.[23] It should be noted, however, that those trials only included patients with SBP ≥100 mmHg and there are no data for ARNI usage for hypotensive patients, so current evidence does not support the initiation of ARNI for patients with SBP <100 mmHg. A previous study of ours showed ARNI improve left ventricular reverse remodeling in patients with SBP <100 mmHg, suggesting it may be beneficial even for hypotensive patients.[24] Data are limited on managing hypotension in patients treated concomitantly with SGLT2 inhibitors and other GDMT drugs. The DAPA-HF trial showed only a slight drop in SBP resulting from the use of dapagliflozin, indicating its potential safety for hypotensive populations,[3] while the SHIFT study reported no hypotensive effect of ivabradine.[25] Finally, vericiguat proved to be safe and tolerable for hypotensive patients in a post hoc analysis of the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial.[26]

The key RCTs excluded patients with eGFR <20–30 mL/min/1.73 m^2. Worsening renal function indicated by biomarkers often precludes GDMT initiation in clinical practice, so evidence of the need for GDMT for patients with Stage 4 and 5 CKD (eGFR <30 mL/min/1.73 m^2) is required. Evidence of the efficacy of β-blockers and ACE-I/ARB has been modest for these patients.[27] Several cohort studies have shown β-blockers' efficacy for Stage 4 and 5 CKD patients, while that of ACE-I/ARBs is varied,[27] and data for MRAs do not show that they are safe or efficacious for eGFR <30 mL/min/1.73 m^2. However, MRAs have been found to reduce HF hospitalization for Stage 4 CKD patients, although hyperkalemia should be a matter of concern in clinical practice.[28] The DAPA-CKD trial and the EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) trial report a reduction in kidney disease progression or death for patients with eGFR ≥25 and ≥20 mL/min/1.73 m^2, respectively.[29] Thus, SGLT2 inhibitors, if administered with appropriate monitoring, can be safe for Class 4 CKD patients.[27] Although current guidelines do not recommend ARNI for HF patients with eGFR <30 mL/min/1.73 m^2, more recent evidence suggests ARNI are beneficial and safe for these patients. The latest post hoc analysis of PARADIGM-HF and PARAGON-HF found that continuation of ARNI was associated with lasting clinical benefits and no additional safety risks for patients with kidney function deterioration to eGFR <30 mL/min/1.73 m^2.[30] Vericiguat has also been shown to be efficacious for Stage 4 CKD patients.[26]

There is no strong consensus regarding HF management of patients with severe hypotension and renal impairment,[27] although guidelines emphasize the need for evidence of the efficacy of therapies targeting HF patients with profiles excluded from clinical trials, such as those with advanced kidney failure or hypotension.[8] Part of our results suggested that adherence to GDMT may provide benefits even in ineligible populations. However, efficacy likely varies depending on the severity and type of comorbidities and underlying clinical conditions. Hypotension and impaired renal function, the most common reasons for RCT exclusion, are highly heterogeneous in both cause and severity across patients. Personalized treatment strategies are essential to optimize outcomes in this population, including careful adjustment of GDMT dosages, close monitoring of adverse events, and consideration of alternative therapies. For instance, SGLT2 inhibitors and vericiguat may offer benefits for patients with hypotension with a lower risk of adverse effects. Similarly, for patients with advanced CKD, emerging evidence supports the use of SGLT2 inhibitors and ARNI under appropriate monitoring. However, these strategies require further validation in aged patients. The super-aged population presents additional challenges, as advanced age is often associated with frailty, polypharmacy, and limited physiological reserves, complicating GDMT implementation. Our study highlights the need for tailored therapeutic approaches to address these complexities and improve patient outcomes. Real-world evidence and observational studies are critical tools to bridge the evidence gap. Registry data and advanced statistical approaches, such as target trial emulation, can provide valuable insights into the effectiveness of GDMT and its adherence in these populations. Additionally, future research should prioritize the inclusion of ineligible aged populations, such as those with hypotension or impaired renal function, in specifically designed clinical trials to improve the applicability of evidence.

Study Limitations

First, we did not analyze all the exclusion criteria of each RCT. The representative RCTs had approximately 20–30 exclusion criteria, but the data available to us made it difficult to investigate all of them. For example, criteria such as "SBP <95 mmHg at the second outpatient visit" or "life expectancy of <1 year in the opinion of investigators" could not be included in our data, so we may have underestimated the exclusion rates. However, in the reference RCTs, the number of cases meeting such exclusion criteria was very small, so the effect of their inclusion would have been minimal. Second, all participants in this study were inhabitants of Awaji Island, which is unlikely to be representative of the typical Japanese patient population or that of any developed country. Although Awaji Island is located near large cities and therefore not isolated, its unique demographic and environmental characteristics may have caused selection bias and influenced the findings. Therefore, further studies covering a variety of regions and ethnic groups are needed to validate our findings.

Conclusions

Our findings revealed a significant disparity between the characteristics of HF patient populations enrolled in RCTs and those residing in a super-aged society. This emphasizes the critical need for further research to verify the effectiveness of GDMT in real-world clinical settings.

Disclosures

H.T. received remuneration from AstraZeneca plc, Ono Pharmaceutical Company, Limited, Pfizer Inc., Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Eli Lilly and Company, Boehringer Ingelheim GmbH, Abbott Japan LLC, and Novartis International AG. The remaining authors have no conflicts of interest to declare.

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IRB Information

The Ethical Committee of Hyogo Prefectural Awaji Medical Center approved this study (No. 20-11)

References

1. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371:** 993–1004.
2. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; **381:** 1609–1620.
3. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381:** 1995–2008.
4. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022; **387:** 1089–1098.
5. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383:** 1413–1424.
6. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385:** 1451–1461.
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023; **44:** 3627–3639.
8. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of heart failure: Executive Summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022; **79:** 1757–1780.
9. Fujimoto W, Toh R, Takegami M, Imanishi J, Hamana T, Odajima S, et al. Aetiology of chronic heart failure in patients from a super-aged society: The KUNIUMI registry chronic cohort. *ESC Heart Fail* 2023; **10:** 100–110.
10. Jhund PS, Fu M, Bayram E, Chen CH, Negrusz-Kawecka M, Rosenthal A, et al. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: Insights from PARADIGM-HF. *Eur Heart J* 2015; **36:** 2576–2584.
11. Esteban-Fernández A, Díez-Villanueva P, Vicent L, Bover R, Gómez-Bueno M, De Juan J, et al. Sacubitril/valsartan is useful and safe in elderly people with heart failure and reduced ejection fraction: Data from a real-word cohort. *Rev Esp Geriatr Gerontol* 2020; **55:** 65–69.
12. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: Insights from DAPA-HF. *Circulation* 2020; **141:** 100–111.
13. Peikert A, Martinez FA, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, et al. Efficacy and safety of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to age: The DELIVER trial. *Circ Heart Fail* 2022; **15:** e010080.
14. Böhm M, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Abdin A, et al. Empagliflozin improves outcomes in patients with heart failure and preserved ejection fraction irrespective of age. *J Am Coll Cardiol* 2022; **80:** 1–18.
15. Lunati ME, Cimino V, Gandolfi A, Trevisan M, Montefusco L, Pastore I, et al. SGLT2-inhibitors are effective and safe in the elderly: The SOLD study. *Pharmacol Res* 2022; **183:** 106396.
16. Stolfo D, Uijl A, Benson L, Schrage B, Fudim M, Asselbergs FW, et al. Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction: A propensity score-matched analysis from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2020; **22:** 103–112.
17. Ferreira JP, Rossello X, Eschalier R, McMurray JJV, Pocock S, Girerd N, et al. MRAs in elderly HF patients: Individual patient-data meta-analysis of RALES, EMPHASIS-HF, and TOPCAT. *JACC Heart Fail* 2019; **7:** 1012–1021.
18. Ambrosy AP, Vaduganathan M, Mentz RJ, Greene SJ, Subačius H, Konstam MA, et al. Clinical profile and prognostic value of low systolic blood pressure in patients hospitalized for heart failure with reduced ejection fraction: Insights from the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial. *Am Heart J* 2013; **165:** 216–225.
19. Seferović PM, Polovina M, Adlbrecht C, Bělohlávek J, Chioncel O, Goncalvesová E, et al. Navigating between Scylla and Charybdis: Challenges and strategies for implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. *Eur J Heart Fail* 2021; **23:** 1999–2007.
20. Böhm M, Young R, Jhund PS, Solomon SD, Gong J, Lefkowitz MP, et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: Results from PARADIGM-HF. *Eur Heart J* 2017; **38:** 1132–1143.
21. Bhm M, Anker S, Mahfoud F, Lauder L, Filippatos G, Ferreira JP, et al. Empagliflozin, irrespective of blood pressure, improves outcomes in heart failure with preserved ejection fraction: The EMPEROR-Preserved trial. *Eur Heart J* 2023; **44:** 396–407.
22. Serenelli M, Jackson A, Dewan P, Jhund PS, Petrie MC, Rossignol P, et al. Mineralocorticoid receptor antagonists, blood pressure, and outcomes in heart failure with reduced ejection fraction. *JACC Heart Fail* 2020; **8:** 188–198.
23. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019; **380:** 539–548.
24. Nishihara Y, Nishimori M, Sawa T, Uemura K, Nagai S, Todo S, et al. Left ventricular reverse remodeling following initiation of sacubitril/valsartan for heart failure with reduced ejection fraction and low blood pressure. *Heart Vessels* 2024; **39:** 95–104.
25. Komajda M, Böhm M, Borer JS, Ford I, Robertson M, Manolis AJ, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. *Eur J Heart Fail* 2014; **16:** 810–816.
26. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020; **382:** 1883–1893.
27. Mullens W, Martens P, Testani JM, Tang WHW, Skouri H, Verbrugge FH, et al. Renal effects of guideline-directed medical therapies in heart failure: A consensus document from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2022; **24:** 603–619.
28. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: The FIDELITY pooled analysis. *Eur Heart J* 2022; **43:** 474–484.
29. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023; **388:** 117–127.
30. Chatur S, Beldhuis IE, Claggett BL, McCausland FR, Neuen BL, Desai AS, et al. Sacubitril/valsartan in patients with heart failure and deterioration in eGFR to <30 mL/min/1.73 m(2). *JACC Heart Fail* 2024; **12:** 1692–1703.

Supplementary Files

Please find supplementary file(s);
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