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Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study

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ABSTRACT

Objectives and design

Guideline-directed medical therapy (GDMT) with renin-angiotensin system (RAS) inhibitors and beta-blockers has improved survival in patients with heart failure with reduced ejection fraction (HFrEF). Because clinical trials usually do not include very old patients, it is unknown whether the results from clinical trials are applicable to elderly patients with HF. This study was performed to investigate the clinical characteristics of and treatment strategies for elderly patients with HFrEF in a large-prospective cohort.

Setting

The KorAHF registry consecutively enrolled 5,625 patients hospitalized for acute HF from 10 tertiary university hospitals in Korea.

Participants

In this study, 2,045 patients with HFrEF who were aged 65 years or older were included from the KorAHF registry.

Primary outcome measurement

Patient's all-cause mortality data were obtained from the medical record, national insurance data or national death records.

Results

Both beta-blockers and RAS inhibitors were used in 892 (43.8%) patients (GDMT group), beta-blockers only in 228 (11.1%) patients, RAS inhibitors only in 642 (31.5%) patients, and neither beta-blockers nor RAS inhibitors in 283 (13.6%) patients (no GDMT group). With increasing age, the GDMT rate decreased, which was mainly attributed to the decreased

prescription of beta-blockers. In multivariate analysis, GDMT was associated with a 53% reduced risk of all-cause mortality (HR 0.47, 95% CI 0.39-0.57) compared with no GDMT. Use of beta-blockers only (HR, 0.57, 95% CI 0.45-0.73) and RAS inhibitors only (HR 0.58, 95% CI 0.48-0.71) was also associated with reduced risk. In a subgroup of very elderly patients (aged ≥80 years), the GDMT group had the lowest mortality.

Conclusions

GDMT was associated with reduced 3-year all-cause mortality in elderly and very elderly HFrEF patients.

Trial registration

ClinicalTrial.gov NCT01389843

Keywords: heart failure with reduced ejection fraction

Strengths and limitations of this study

- This was a large prospective cohort study that included patients with heart failure with reduced ejection fraction who were aged 65 years or older.
- We could obtain all participants' mortality data from medical record or national death records.
- The registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.

INTRODUCTION

Heart failure (HF) is associated with significant morbidity, mortality, and healthcare burdens.[1] Since the prevalence of HF increases with age, the incidence of elderly patients with HF has been continuously increasing as the aging population increases.[2-4] Elderly patients with HF have worse outcomes: they have more comorbidities, functional and cognitive impairments, and polypharmacy.[5-7] In addition, they are at high risk of re-hospitalization for HF after hospital discharge.[8]

Large clinical trials have shown that guideline-directed medical therapy (GDMT) with renin-angiotensin system (RAS) inhibitors and beta-blockers improved survival in patients with heart failure reduced ejection fraction (HFrEF).[9-11] However, many elderly patients with HF have been excluded from randomized clinical studies because of age, comorbidities, and functional or cognitive impairment, among others.[12] Accordingly, it is unknown whether the results from the clinical trials can be directly applied to elderly patients with HF.

Korea is one of the most rapidly aging societies; and it has become an "aged society" in 2018 and will be a "super-aged society" by year 2026.[13] In 2017, Korea's proportion of individuals aged ≥65 years was 13.8%. Considering that 70% of hospitalizations for HF occurred in patients aged ≥65 years, a better understating of these high-risk patients is critical for proper management.[14] In this study, we investigated the clinical characteristics of and treatment strategies for elderly patients with HFrEF in a large-prospective cohort.

METHODS

Participants and cohort recruitment

The Korean Acute Heart Failure (KorAHF) registry is a prospective multicenter registry designed to reflect the real-world clinical data of Korean patients admitted for acute HF. The study design and primary results of the registry have been published elsewhere [ClinicalTrial.gov NCT01389843].[15, 16] Patients hospitalized for acute HF from 10 tertiary university hospitals in Korea were consecutively enrolled from March 2011 to February 2014. Briefly, patients with signs or symptoms of HF and either lung congestion or objective findings of left ventricle systolic dysfunction or structural heart disease were eligible for enrollment in this registry. To minimize selection bias, we tried to enroll all of the hospitalized patients with acute HF at each hospital. Patients' baseline characteristics, clinical presentation, underlying diseases, vital signs, laboratory tests, treatments, and outcomes were recorded at admission, at discharge, and during the follow-up (30-day, 90-day, 180-day, and 1- to 3-year annually). The mortality data for patients who were lost to follow-up were obtained from the national insurance data or national death records.

In this study, we included patients with HFrEF who were aged 65 years or older. The study protocol was approved by the ethics committee at each hospital. Written informed consent was waived by the institutional review board. The study complied with the Declaration of Helsinki.

Patients and public involvement

Patients were not involved in the conception, design or interpretation of this study. The results of this study will be disseminated to patient and healthcare provider through oral presentations and social media.

Study variables and definition

HFrEF was defined as left ventricular ejection fraction (LVEF) ≤40%. The patients were classified into groups according to the medication prescribed at discharge: the GDMT group (patients who received both beta-blockers and RAS inhibitors), beta-blockers only group, RAS inhibitors only group, and no GDMT group (no beta-blockers or RAS inhibitors). Chronic kidney disease (CKD) was defined as a glomerular filtration rate <60 mL/min/1.72 m^2, and chronic obstructive pulmonary disease (COPD) was defined as a self-reported or physician-confirmed diagnosis of chronic bronchitis, emphysema, or both. The primary outcome was 3-year post-discharge all-cause mortality from index admission.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, whereas categorical variables were presented as numbers and their percentages. Differences among continuous variables were analyzed using the one-way ANOVA and those among categorical variables using the χ^2 test. Logistic regression analysis was used to determine the predictors of GDMT prescription. The cumulative event rate was assessed using the Kaplan-Meier method with post-hoc log-rank analysis. Multivariable Cox regression analysis was used to evaluate the adjusted relative risk of the variables. Multivariable models including age, sex, hypertension, diabetes, previous heart failure history, atrial fibrillation, CKD, cause of heart failure, COPD, and prescription of RAS inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRA), digitalis, and diuretics were chosen according to their clinical relevance and based on the results of previous trials.[3, 11] For the subgroup analyses, P for interaction was calculated using the interaction term for GDMT and each subgroup based on Cox regression. All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA), and a P value of <0.05 was considered statistically significant.

RESULTS

The KorAHF registry includes 5,625 acute HF patients. Of these, we excluded patients with missing LVEF (n=253), those with LVEF >40% (n=1900), age <65 years (n=1268), in-hospital death (n=126), heart transplantation (n=8), and those who were hopelessly discharged (n=25), leaving a total of 2,045 patients available for the final analysis (**figure 1**).

The mean age was 75.9 years and 54.2% were male, 66.7% had hypertension, and 42.0% had diabetes mellitus. The mean LVEF was 28.7 ± 7.4%, and most common cause of HFrEF was ischemic cardiomyopathy (50.5%).

Medication prescription pattern according to patients' characteristics

The beta-blocker prescription rate at discharge was 54.8% in all patients and that of RAS inhibitor was 75.0%. With increasing age, the beta-blocker prescription rate decreased (P for trend <0.001), while that of RAS inhibitor remained unchanged (**figure 2A**).

The baseline characteristics of the study population are summarized in **table 1**. Overall, both beta-blockers and RAS inhibitors were used in 892 (43.8%) patients (GDMT group), beta-blockers only in 228 (11.1%) patients, RAS inhibitors only in 642 (31.5%) patients, and neither beta-blockers nor RAS inhibitors in 283 (13.6%) patients (no GDMT group). The beta-blocker prescription rate was lower in patients with COPD (COPD: 45.5%, vs. no COPD: 56.2%, P = 0.01), whereas the prescription of RAS inhibitors was lower in patients with CKD (CKD: 68.7%, vs. no CKD: 82.2%, P <0.001).

Table 1. Baseline characteristics of patients according to treatment strategy

	GDMT (n=892)	Beta blocker only (n=228)	RAS inhibitor only (n=642)	No GDMT (n=283)	P value
Age, years	75.0 ± 6.5	76.2 ± 7.2	76.7 ± 7.1	76.7 ± 6.7	<0.001
Men, n (%)	472 (52.9)	115 (50.7)	369 (57.5)	149 (54.0)	0.211
BMI, kg/m^2	23.0 ± 3.5	22.6 ± 3.5	22.4 ± 3.4	21.9 ± 3.0	<0.001
Medical history					
Previous heart failure, n (%)	414 (46.4)	136 (59.6)	361 (56.2)	167 (59.0)	<0.001
Hypertension, n (%)	609 (68.3)	162 (71.4)	417 (65.0)	174 (63.0)	0.124
Diabetes, n (%)	399 (44.7)	97 (42.7)	242 (37.7)	119 (43.1)	0.050
Chronic kidney disease, n (%)	430 (48.2)	150 (66.1)	320 (49.8)	186 (67.4)	<0.001
Atrial fibrillation, n (%)	281 (31.5)	89 (39.2)	193 (30.1)	81 (29.3)	0.059
COPD, n (%)	92 (10.3)	30 (13.2)	110 (17.1)	36 (13.0)	0.002
Myocardial infarction, n (%)	194 (21.8)	61 (26.9)	146 (22.7)	65 (23.6)	0.433
Cause of heart failure					
Ischemic, n (%)	443 (49.7)	129 (56.8)	311 (48.4)	146 (52.9)	0.132
Dilated, n (%)	222 (24.9)	36 (15.9)	147 (22.9)	50 (18.1)	0.008
Medication on admission					
Beta-blocker, n (%)	316 (35.4)	117 (51.5)	107 (16.7)	53 (19.2)	<0.001
RAS inhibitor, n (%)	380 (42.6)	58 (25.6)	335 (52.2)	72 (26.1)	<0.001
MRA, n (%)	143 (16.0)	47 (20.7)	122 (19.0)	60 (21.7)	0.096
Medication on discharge					
MRA, n (%)	487 (54.6)	95 (41.9)	316 (49.2)	120 (43.5)	<0.001

Loop diuretics, n (%)	714 (80.0)	174 (76.7)	493 (76.8)	189 (68.5)	0.001
Digoxin, n (%)	269 (30.2)	63 (27.8)	193 (30.1)	86 (31.2)	0.865
Systolic BP on discharge, mm Hg	115.0 ± 17.0	115.7 ± 16.4	114.2 ± 16.5	113.0 ± 16.6	0.067
Diastolic BP on discharge, mm Hg	66.1 ± 10.7	67.5 ± 10.7	65.6 ± 11.2	65.2 ± 10.0	0.026
Heart rate on discharge, beats/min	74.6 ± 12.9	78.1 ± 14.4	77.8 ± 14.3	80.6 ± 13.7	<0.001
NYHA functional class on discharge					0.154
I or II, n (%)	792 (88.8)	205 (90.3)	566 (88.2)	250 (90.6)	
III or IV, n (%)	100 (11.2)	22 (9.7)	76 (11.8)	45 (9.4)	
Echocardiographic parameters					
LVEDD, mm	60.3 ± 8.7	57.6 ± 9.6	61.2 ± 8.9	58.8 ± 9.0	<0.001
LVESD, mm	50.3 ± 9.3	47.6 ± 10.0	51.1 ± 9.6	49.1 ± 9.8	<0.001
LVEF, %	28.8 ± 7.3	28.8 ± 7.5	28.5 ± 7.4	28.6 ± 7.7	0.864
Laboratory data on admission					
Hemoglobin, g/dL	12.4 ± 2.0	11.9 ± 2.2	12.2 ± 2.1	11.7 ± 2.2	<0.001
eGFR, ml/min/1.73m^2	63.8 ± 33.8	52.6 ± 32.3	63.2 ± 30.4	53.2 ± 30.1	<0.001
Sodium, mEq/L	138.0 ± 4.4	137.6 ± 4.4	137.3 ± 5.1	137.0 ± 4.6	0.006
Potassium, mEq/L	4.3 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.8	0.001
BNP, pg/mL	1592.9 ± 1489.8	1849.7 ± 1492.0	1724.8 ± 1381.7	1937.1 ± 1920.8	0.223
NT-pro-BNP, pg/mL	10941.1 ± 11006.9	11535.8 ± 10587.7	9978.0 ± 9484.0	14728.7 ± 12514.7	<0.001

GDMT, guideline-directed medical therapy; RAS, renin angiotensin system; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; BNP, brain natriuretic peptide

With increasing age, the proportion of GDMT prescriptions decreased, while that of RAS inhibitors only increased (**figure 2B**). The predictors of GDMT prescription included age 65-79 years, hypertension, diabetes, de-novo onset of heart failure, and concomitant MRA prescription (**table 2**). Underlying COPD, CKD and concomitant use of loop diuretics were inversely associated with the prescription of GDMT.

Table 2. Predictor of prescription of guideline-directed medical therapy

Variable	Odds ratio	95% CI	P value
Age 65-79 (vs. age ≥80 years)	1.52	1.24 – 1.87	<0.001
Male	0.90	0.75 – 1.08	0.240
Hypertension	1.24	1.01 – 1.51	0.036
Diabetes	1.27	1.05 – 1.54	0.014
De novo heart failure (vs. previous heart failure)	1.55	1.29 – 1.86	<0.001
Atrial fibrillation	1.01	0.82 – 1.25	0.911
Chronic kidney disease	0.76	0.63 – 0.92	0.004
Ischemic CMP (vs. non-ischemic)	0.94	0.78 – 1.14	0.546
COPD	0.67	0.50 – 0.88	0.004
Discharge MRA	1.30	1.08 – 1.56	0.007
Discharge digoxin	0.95	0.77 – 1.18	0.634
Discharge loop diuretics	0.76	0.61 – 0.96	0.018

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist

Clinical outcomes

The median follow-up duration was 833 days (interquartile range 240.5 to 1095 days), and 866 (42.3%) patients had died at 3 years. In the Kaplan-Meier survival analysis, patients in the GDMT group had the lowest mortality, whereas those in the no GDMT group had the worst outcomes. Interestingly, there seemed to be no difference in mortality between the beta-blockers only and RAS inhibitors only groups (**figure 3**). Upon further stratification of the patients according to age above or below 80 years, the GDMT group had the lowest mortality in patients aged above and below 80 years, consistently. In the Cox model after adjustment for significant covariates, GDMT was associated with a 53% reduced risk of all-cause mortality [hazard ratio (HR): 0.47, 95% confidence interval (CI): 0.39-0.57, P <0.001] compared to no GDMT. The beta-blockers only (HR, 0.57, 95% CI 0.45-0.73, P <0.001) and RAS inhibitors only (HR 0.58, 95% CI 0.48-0.71, P<0.001) groups were also associated with reduced risk (**table 3**).

Table 3. Multivariable Cox regression analysis for all-cause mortality

Variable	Hazard ratio	95% CI	P value
Age ≥80 years (vs. age 65-79)	1.60	1.39 – 1.84	<0.001
Male	1.16	1.01 – 1.33	0.039
Hypertension	1.07	0.92 – 1.24	0.392
Diabetes	1.13	0.99 – 1.31	0.080
Previous heart failure (vs. de novo heart failure)	1.39	1.20 – 1.60	<0.001
Atrial fibrillation	0.90	0.77 – 1.07	0.226
Chronic kidney disease	1.50	1.30 – 1.74	<0.001
Ischemic CMP (vs. non-ischemic)	1.29	1.11 – 1.49	<0.001
COPD	1.27	1.04 – 1.53	0.016
Discharge MRA	1.05	0.91 – 1.21	0.499
Discharge digoxin	0.99	0.84 – 1.16	0.885
Discharge loop diuretics	0.90	0.76 – 1.06	0.219
Treatment strategy (vs. no GDMT)			
Beta-blocker only	0.57	0.45 – 0.73	<0.001
RAS inhibitor only	0.58	0.48 – 0.71	<0.001
GDMT	0.47	0.39 – 0.57	<0.001

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; RAS, renin angiotensin system; GDMT, guideline-directed medical therapy

Subgroup analysis

We performed a pre-specified subgroup analysis according to age (65-79 years vs. ≥80 years), CKD, COPD, etiology (ischemic vs. non-ischemic), and HF onset (de-novo HF vs. acute decompensation of chronic HF). There was no significant interaction between medical therapy and any of the subgroups (**figure 4**).

DISCUSSION

The present nationwide multi-center prospective cohort study showed that 1) GDMT was associated with reduced all-cause mortality in elderly patients with HFrEF; 2) prescription of beta-blockers only or RAS inhibitors only was also associated with reduced all-cause mortality compared with no GDMT; and 3) the effect of GDMT also appeared to be effective for reducing all-cause mortality in very elderly patients (age ≥80 years).

GDMT and outcomes in elderly HF patients

Large clinical trials have shown the efficacy of GDMT in patients with HFrEF.[11] However, the patients enrolled in such clinical trials were younger and had fewer comorbidities than real-world elderly patients.[17] Moreover, data from clinical trials supporting the use of GDMT in elderly patients are scarce. The SENIORS study, which included 2,128 patients aged ≥70 years with a history of HF, is considered the representative study conducted in elderly HF patients. It showed that nebivolol reduced the composite of all-cause mortality and rehospitalization for HF, but did not reduce all-cause mortality.[18]

Although observational studies do not provide as high a level of evidence as randomized clinical trials, observational studies may yield real-world evidence.[19, 20] In

previous observational studies, the efficacy of beta-blockers in elderly patients has been controversial. In the OPTIMIZE-HF registry, a beta-blocker was not associated with improved survival in patients aged ≥75 years.[19] Dobre et al. reported that the effect of beta-blockers decreased with increasing age, and was not associated with a reduced risk of cardiac death and readmission heart failure in patients aged ≥80 years.[21] Recently, in a subgroup of 237 elderly patients aged ≥80 years in the WET-HF registry, GDMT with beta-blockers and RAS inhibitors did not reduce rates of cardiac death or HF readmission. By contrast, the present study showed that GDMT was associated with all-cause mortality in elderly HFrEF patients, defined by age ≥65 years. In addition, GDMT was effective in very elderly patients aged ≥80 years. Although the KorAHF and WET-HF studies have included East Asian patients with HF, there are several differences between the 2 studies: KorAHF was larger, especially in terms of the number of patients aged ≥80 years (601 patients in KorAHF vs. 237 patients in WET-HF). As a result, our study was less prone to type II errors, i.e., false negative findings. While WET-HF defined HFrEF as LVEF <45%, the present study enrolled only patients with LVEF ≤40%, which corresponds to the contemporary definition of HFrEF.[11] To our knowledge, this is the first report to show the efficacy of GDMT in very elderly patients with HFrEF.

Prescription of GDMT in elderly patients

The prescription rate of GDMT was 50% in patients aged 65-69 years and 30% in those aged ≥85 years. The decline can be mainly attributed to a decreasing beta-blocker prescription rate. Hamaguchi et al. reported that the prescription rate of beta-blockers was 48% in HFrEF patients aged ≥80 years and that GDMT was applied only in 38% of the patients.[22] In this study, the beta-blocker prescription rate was 55% in all patients and 46% in patients aged ≥80 years. Beta-blockers in very elderly patients may be withheld due to the potential side effects

and uncertainty with regard to the benefit for this high-risk group. In addition, 13% of patients had COPD which was associated with a 30% reduced prescription of beta-blockers (beta-blockers in COPD 46% vs. no COPD 56%, P <0.001) but not of RAS inhibitors. Accordingly, COPD was associated with a 33% reduced prescription of GDMT. This finding reflects the possible side effect of beta-blockers, as non-selective beta-blockers may cause bronchoconstriction in patients with COPD. However, given that multiple studies have shown that beta-1 selective beta-blockers can be used safely in patients with asthma and COPD, beta-1 selective drugs should be considered for patients with COPD.[23, 24]

CKD is very common in patients with HF and is a well-known risk factor in HF patients.[22, 25] In this study, 53% of patients had CKD, and its prevalence increased with age. Since RAS inhibitors can initially aggravate renal function, many physicians withhold RAS inhibitors in patients with CKD. Accordingly, CKD was associated with a 54% reduced prescription of RAS inhibitors (RAS inhibitors in CKD 68% vs. no CKD 83%, P <0.001), resulting in a 24% reduced prescription of GDMT. By contrast, beta-blocker use was not influenced by the presence of CKD. Current guidelines recommend the cautious use of RAS inhibitors in patients with HF and advanced CKD.[11] Our study supports this recommendation, since RAS inhibitor use was associated with a 34% reduced risk of all-cause mortality in patients with CKD.

Limitations

The present study has several limitations. First, owing to the observational nature of the study design, confounding factors may have influenced the study results, despite adjustment for significant covariates. Furthermore, there exists a possibility that unmeasured variables may have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.[26]

Third, we do not know whether the patients actually took the prescribed drugs, because many patients had multiple comorbidities and polypharmacy is associated with poor drug compliance.

CONCLUSIONS

Heart failure is common among the elderly, but elderly patients with HF receive less GDMT. Since elderly and very elderly patients with HFrEF appear to benefit from GDMT, physicians should make an effort to prescribe GDMT to these high-risk patients.

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Conflict of Interest Disclosures: The authors declare no conflict of interest

A data sharing statement: Data are housed at the Research of Korea Centers for Disease Control and Prevention and are not available at this time.

Ethics approval: The study protocol was approved by the ethics committee at each 10 tertiary university hospital in Korea.

Patient consent: Written informed consent was waived by the institutional review board at each 10 tertiary hospital in Korea.

REFERENCES

1 Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;6:606-19.

2 Cowie M, Wood D, Coats A, et al. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;20:421-8.

3 Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.

4 Youn J-C, Han S, Ryu K-H. Temporal trends of hospitalized patients with heart failure in Korea. *Korean Circ J* 2017;47:16-24.

5 Murad K, Goff Jr DC, Morgan TM, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. *JACC: Heart Failure* 2015;3:542-50.

6 Shah RU, Tsai V, Klein L, et al. Characteristics and Outcomes of Very Elderly Patients After First Hospitalization for Heart FailureClinical Perspective. *Circ Heart Fail* 2011;4:301-7.

7 Vidán MT, Blaya-Novakova V, Sánchez E, et al. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail* 2016;18:869-75.

8 Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997;157:99-104.

9 The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.

10 Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.

11 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200.

12 Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011;171:550-6.

13 Statistics Korea 2017. Available at: http://kostat.go.kr/portal/eng/pressReleases/11/1/index.board?bmode=download&bSeq=&aSeq=363974&ord=1

14 Hall MJ, Levant S, DeFrances CJ. Hospitalization for congestive heart failure: United States, 2000–2010. NCHS data brief. Available at: https://www.cdc.gov/nchs/data/databriefs/db108.pdf.

15 Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. *Eur J Heart Fail* 2014;16:700-8.

16 Lee SE, Lee H-Y, Cho H-J, et al. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean acute heart failure registry (KorAHF). *Korean Circ J* 2017;47:341-53.

17 Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;162:1682-8..

18 Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart

failure (SENIORS). *Eur Heart J* 2005;26:215-25.

19 Hernandez AF, Hammill BG, O'Connor CM, et al. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol* 2009;53:184-92.

20 Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation* 2010;122:585-96.

21 Dobre D, DeJongste MJ, Lucas C, et al. Effectiveness of β-blocker therapy in daily practice patients with advanced chronic heart failure; is there an effect-modification by age? *Br J Clin Pharmacol* 2007;63:356-64.

22 Hamaguchi S, Kinugawa S, Goto D, et al. Predictors of long-term adverse outcomes in elderly patients over 80 years hospitalized with heart failure. *Circ J* 2011;75:2403-10.

23 Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blocker use in patients with reversible airway disease. *Cochrane Database Syst Rev* 2002:CD002992.

24 Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective β-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715-25.

25 Komajda M, Hanon O, Hochadel M, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J* 2008;30:478-86.

26 Murad K, Goff DC, Morgan TM, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. *JACC: Heart Failure* 2015;3:542-50.

Figure legends

Figure 1. Study flow

EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction

Figure 2. Discharge medication profiles.

Prescription of beta-blockers, RAS inhibitors (A), and GDMT (B) according to the age groups in elderly patients with HFrEF.

RAS, renin-angiotensin system; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction

Figure 3. Three-year cumulative survival according to the treatment groups

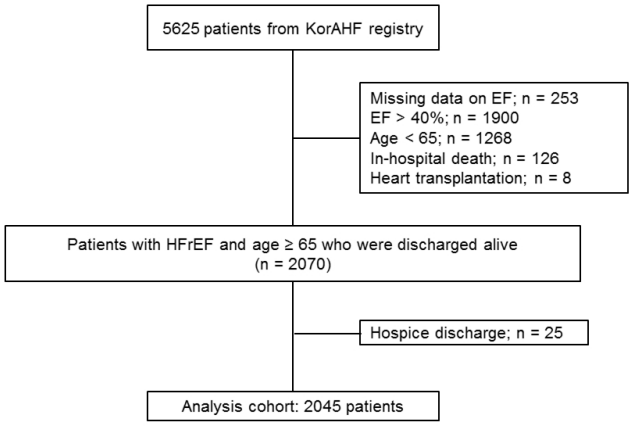
Patients receiving GDMT had lower mortality among the all patients (A), patients aged between 65-79 years (B), and patients aged 80 years or older (C).

BB, beta-blocker; RASi, renin-angiotensin system inhibitor; GDMT, guideline-directed medical therapy

Figure 4. Subgroup analysis.

There was no interaction between the effect of GDMT and diverse subgroups, and GDMT was associated with lower morality across subgroups.

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; GDMT, guideline-directed medical therapy



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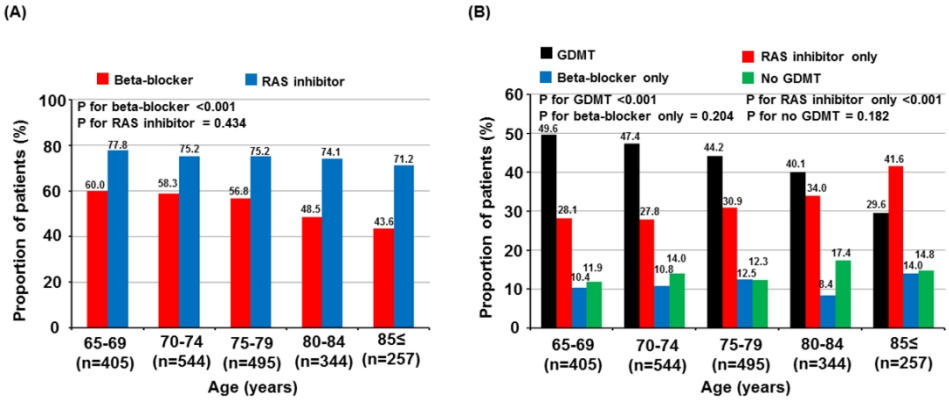

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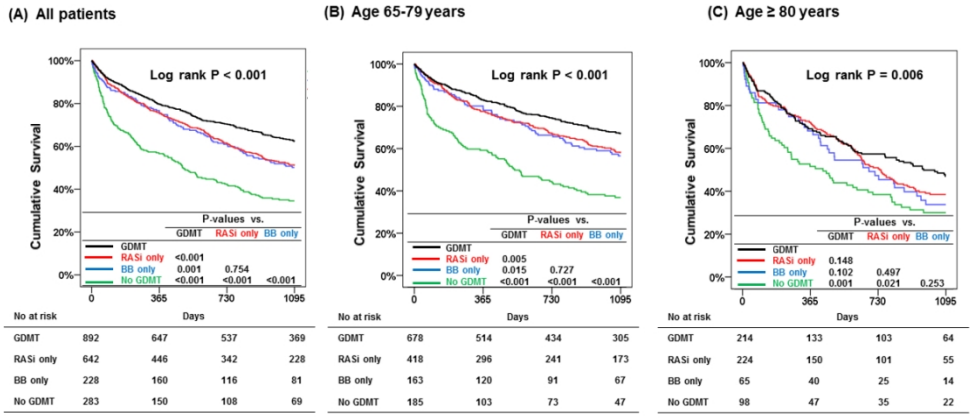

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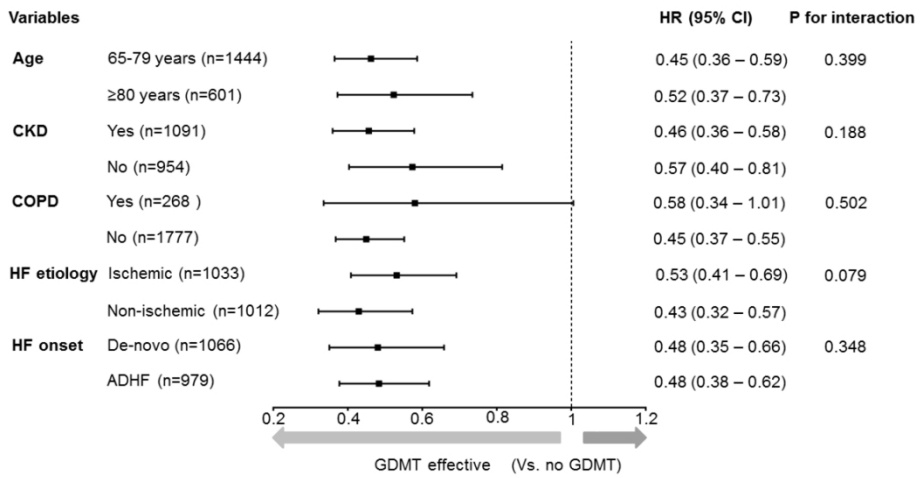

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12,13,8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16, 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15, 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study

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Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study

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ABSTRACT

Objectives and design

Guideline-directed medical therapy (GDMT) with renin-angiotensin system (RAS) inhibitors and beta-blockers has improved survival in patients with heart failure with reduced ejection fraction (HFrEF). Because clinical trials usually do not include very old patients, it is unknown whether the results from clinical trials are applicable to elderly patients with HF. This study was performed to investigate the clinical characteristics of and treatment strategies for elderly patients with HFrEF in a large-prospective cohort.

Setting

The KorAHF registry consecutively enrolled 5,625 patients hospitalized for acute HF from 10 tertiary university hospitals in Korea.

Participants

In this study, 2,045 patients with HFrEF who were aged 65 years or older were included from the KorAHF registry.

Primary outcome measurement

Patient's all-cause mortality data were obtained from the medical record, national insurance data or national death records.

Results

Both beta-blockers and RAS inhibitors were used in 892 (43.8%) patients (GDMT group), beta-blockers only in 228 (11.1%) patients, RAS inhibitors only in 642 (31.5%) patients, and neither beta-blockers nor RAS inhibitors in 283 (13.6%) patients (no GDMT group). With increasing age, the GDMT rate decreased, which was mainly attributed to the decreased

prescription of beta-blockers. In multivariate analysis, GDMT was associated with a 53% reduced risk of all-cause mortality (HR 0.47, 95% CI 0.39-0.57) compared with no GDMT. Use of beta-blockers only (HR, 0.57, 95% CI 0.45-0.73) and RAS inhibitors only (HR 0.58, 95% CI 0.48-0.71) was also associated with reduced risk. In a subgroup of very elderly patients (aged ≥80 years), the GDMT group had the lowest mortality.

Conclusions

GDMT was associated with reduced 3-year all-cause mortality in elderly and very elderly HFrEF patients.

Trial registration

ClinicalTrial.gov NCT01389843

Keywords: heart failure with reduced ejection fraction

Strengths and limitations of this study

- This was a large prospective cohort study that included patients with heart failure with reduced ejection fraction who were aged 65 years or older.
- We could obtain all participants' mortality data from medical record or national death records.
- The registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.

INTRODUCTION

Heart failure (HF) is associated with significant morbidity, mortality, and healthcare burdens.[1] Since the prevalence of HF increases with age, the incidence of elderly patients with HF has been continuously increasing as the aging population increases.[2-4] Elderly patients with HF have worse outcomes: they have more comorbidities, functional and cognitive impairments, and polypharmacy.[5-7] In addition, they are at high risk of re-hospitalization for HF after hospital discharge.[8]

Large clinical trials have shown that guideline-directed medical therapy (GDMT) with renin-angiotensin system (RAS) inhibitors and beta-blockers improved survival in patients with heart failure reduced ejection fraction (HFrEF).[9-11] However, many elderly patients with HF have been excluded from randomized clinical studies because of age, comorbidities, and functional or cognitive impairment, among others.[12] Accordingly, it is unknown whether the results from the clinical trials can be directly applied to elderly patients with HF.

Korea is one of the most rapidly aging societies; and it has become an "aged society" in 2018 and will be a "super-aged society" by year 2026.[13] In 2017, Korea's proportion of individuals aged ≥65 years was 13.8%. Considering that 70% of hospitalizations for HF occurred in patients aged ≥65 years, a better understating of these high-risk patients is critical for proper management.[14] In this study, we investigated the clinical characteristics of and treatment strategies for elderly patients with HFrEF in a large-prospective cohort.

METHODS

Participants and cohort recruitment

The Korean Acute Heart Failure (KorAHF) registry is a prospective multicenter registry designed to reflect the real-world clinical data of Korean patients admitted for acute HF. The study design and primary results of the registry have been published elsewhere [ClinicalTrial.gov NCT01389843].[15, 16] Patients hospitalized for acute HF from 10 tertiary university hospitals in Korea were consecutively enrolled from March 2011 to February 2014. Briefly, patients with signs or symptoms of HF and either lung congestion or objective findings of left ventricle systolic dysfunction or structural heart disease were eligible for enrollment in this registry. To minimize selection bias, we tried to enroll all of the hospitalized patients with acute HF at each hospital. Patients' baseline characteristics, clinical presentation, underlying diseases, vital signs, laboratory tests, treatments, and outcomes were recorded at admission, at discharge, and during the follow-up (30-day, 90-day, 180-day, and 1- to 3-year annually). The mortality data for patients who were lost to follow-up were obtained from the national insurance data or national death records.

In this study, we included patients with HFrEF who were aged 65 years or older. For patients' selection, we excluded patients serially if any of the exclusion criteria was met. The study protocol was approved by the ethics committee at each hospital. Written informed consent was waived by the institutional review board. The study complied with the Declaration of Helsinki.

Patients and public involvement

Patients were not involved in the conception, design or interpretation of this study. The results of this study will be disseminated to patients and healthcare providers through oral

presentations and social media.

Study variables and definition

HFrEF was defined as left ventricular ejection fraction (LVEF) ≤40%. The patients were classified into groups according to the medication prescribed at discharge: the GDMT group (patients who received both beta-blockers and RAS inhibitors), beta-blockers only group, RAS inhibitors only group, and no GDMT group (no beta-blockers or RAS inhibitors). Chronic kidney disease (CKD) was defined as a glomerular filtration rate <60 mL/min/1.73 m^2, and chronic obstructive pulmonary disease (COPD) was defined as a self-reported or physician-confirmed diagnosis of chronic bronchitis, emphysema, or both. The primary outcome was 3-year post-discharge all-cause mortality from index admission.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, whereas categorical variables were presented as counts and their percentages. Differences among continuous variables were analyzed using the one-way ANOVA and those among categorical variables using the χ^2 test. Logistic regression analysis was used to determine the predictors of GDMT prescription. The cumulative event rate was assessed using the Kaplan-Meier method with log-rank analysis. Multivariable Cox regression analysis was used to evaluate the adjusted relative risk of the variables. Multivariable models including age, sex, hypertension, diabetes, previous heart failure history, atrial fibrillation, CKD, cause of heart failure, COPD, and prescription of RAS inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRA), digitalis, and diuretics were chosen according to their clinical relevance and based on the results of previous trials.[3, 11] We evaluated whether there was an interaction between the treatment groups (no GDMT, beta-blockers only, RAS inhibitors only and GDMT) and

subgroups on outcomes. For calculation of P for interaction, we performed Cox regression model and included all variables for defining subgroups (age, CKD, COPD, HF etiology, HF onset), treatment group, and interaction term of each subgroup variables by treatment group as independent variables, in addition to the following covariates: sex, hypertension, diabetes, atrial fibrillation, and prescription of MRA, digitalis and diuretics. To mitigate the impact of potential confounding factors in a registry data, we additional performed the inverse probability of treatment weighting (IPTW). The inferences regarding the rate of all-cause death were conducted with robust standard errors after examining covariate balances among the treatment groups. We used the "Twang" package for R programming for IPTW analysis. Success of IPTW analyses was assessed by calculating standardized differences in the baseline characteristics. All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA) and R v3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria), and a P value of <0.05 was considered statistically significant.

RESULTS

The KorAHF registry includes 5,625 acute HF patients. Of these, we excluded patients with missing LVEF (n=253), those with LVEF >40% (n=1900), age <65 years (n=1268), in-hospital death (n=126), heart transplantation (n=8), and those who were hopelessly discharged (n=25), leaving a total of 2,045 patients available for the final analysis (**figure 1**).

The mean age was 75.9 years and 54.2% were male, 66.7% had hypertension, and 42.0% had diabetes mellitus in all patients. In addition, the mean LVEF was 28.7 ± 7.4%, and most common cause of HFrEF was ischemic cardiomyopathy (50.5%).

Medication prescription pattern according to patients' characteristics

The beta-blocker prescription rate at discharge was 54.8% in all patients and that of RAS inhibitor was 75.0%. With increasing age, the beta-blocker prescription rate decreased (P for trend <0.001), while that of RAS inhibitor remained unchanged (**figure 2A**).

The baseline characteristics of the study population are summarized in **table 1**. Overall, both beta-blockers and RAS inhibitors were used in 892 (43.8%) patients (GDMT group), beta-blockers only in 228 (11.1%) patients, RAS inhibitors only in 642 (31.5%) patients, and neither beta-blockers nor RAS inhibitors in 283 (13.6%) patients (no GDMT group). The beta-blocker prescription rate was lower in patients with COPD (COPD: 45.5%, vs. no COPD: 56.2%, P = 0.01), whereas the prescription of RAS inhibitors was lower in patients with CKD (CKD: 68.7%, vs. no CKD: 82.2%, P <0.001).

Table 1. Baseline characteristics of patients according to treatment strategy

	GDMT (n=892)	Beta blocker only (n=228)	RAS inhibitor only (n=642)	No GDMT (n=283)	P value
Age, years	75.0 ± 6.5	76.2 ± 7.2	76.7 ± 7.1	76.7 ± 6.7	<0.001
Men, n (%)	472 (52.9)	115 (50.7)	369 (57.5)	149 (54.0)	0.211
BMI, kg/m^2	23.0 ± 3.5	22.6 ± 3.5	22.4 ± 3.4	21.9 ± 3.0	<0.001
Medical history					
Previous heart failure, n (%)	414 (46.4)	136 (59.6)	361 (56.2)	167 (59.0)	<0.001
Hypertension, n (%)	609 (68.3)	162 (71.4)	417 (65.0)	174 (63.0)	0.124
Diabetes, n (%)	399 (44.7)	97 (42.7)	242 (37.7)	119 (43.1)	0.050
Chronic kidney disease, n (%)	430 (48.2)	150 (66.1)	320 (49.8)	186 (67.4)	<0.001
Atrial fibrillation, n (%)	281 (31.5)	89 (39.2)	193 (30.1)	81 (29.3)	0.059
COPD, n (%)	92 (10.3)	30 (13.2)	110 (17.1)	36 (13.0)	0.002
Myocardial infarction, n (%)	194 (21.8)	61 (26.9)	146 (22.7)	65 (23.6)	0.433
Cause of heart failure					
Ischemic, n (%)	443 (49.7)	129 (56.8)	311 (48.4)	146 (52.9)	0.132
Dilated, n (%)	222 (24.9)	36 (15.9)	147 (22.9)	50 (18.1)	0.008
Medication on admission					
Beta-blocker, n (%)	316 (35.4)	117 (51.5)	107 (16.7)	53 (19.2)	<0.001
RAS inhibitor, n (%)	380 (42.6)	58 (25.6)	335 (52.2)	72 (26.1)	<0.001
MRA, n (%)	143 (16.0)	47 (20.7)	122 (19.0)	60 (21.7)	0.096
Medication on discharge					
MRA, n (%)	487 (54.6)	95 (41.9)	316 (49.2)	120 (43.5)	<0.001

Loop diuretics, n (%)	714 (80.0)	174 (76.7)	493 (76.8)	189 (68.5)	0.001
Digoxin, n (%)	269 (30.2)	63 (27.8)	193 (30.1)	86 (31.2)	0.865
Systolic BP on discharge, mm Hg	115.0 ± 17.0	115.7 ± 16.4	114.2 ± 16.5	113.0 ± 16.6	0.067
Diastolic BP on discharge, mm Hg	66.1 ± 10.7	67.5 ± 10.7	65.6 ± 11.2	65.2 ± 10.0	0.026
Heart rate on discharge, beats/min	74.6 ± 12.9	78.1 ± 14.4	77.8 ± 14.3	80.6 ± 13.7	<0.001
NYHA functional class on discharge					0.154
I or II, n (%)	792 (88.8)	205 (90.3)	566 (88.2)	250 (90.6)	
III or IV, n (%)	100 (11.2)	22 (9.7)	76 (11.8)	45 (9.4)	
Echocardiographic parameters					
LVEDD, mm	60.3 ± 8.7	57.6 ± 9.6	61.2 ± 8.9	58.8 ± 9.0	<0.001
LVESD, mm	50.3 ± 9.3	47.6 ± 10.0	51.1 ± 9.6	49.1 ± 9.8	<0.001
LVEF, %	28.8 ± 7.3	28.8 ± 7.5	28.5 ± 7.4	28.6 ± 7.7	0.864
Laboratory data on admission					
Hemoglobin, g/dL	12.4 ± 2.0	11.9 ± 2.2	12.2 ± 2.1	11.7 ± 2.2	<0.001
eGFR, ml/min/1.73m^2	63.8 ± 33.8	52.6 ± 32.3	63.2 ± 30.4	53.2 ± 30.1	<0.001
Sodium, mEq/L	138.0 ± 4.4	137.6 ± 4.4	137.3 ± 5.1	137.0 ± 4.6	0.006
Potassium, mEq/L	4.3 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.8	0.001
BNP, pg/mL	1592.9 ± 1489.8	1849.7 ± 1492.0	1724.8 ± 1381.7	1937.1 ± 1920.8	0.223
NT-pro-BNP, pg/mL	10941.1 ± 11006.9	11535.8 ± 10587.7	9978.0 ± 9484.0	14728.7 ± 12514.7	<0.001

GDMT, guideline-directed medical therapy; RAS, renin angiotensin system; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; BNP, brain natriuretic peptide

Five-hundred-ninety-four patients (29.0%) were already taking beta-blockers before the index admission; among them 27.1% discontinued beta-blockers during the index admission and they had lower diastolic blood pressure, higher NYHA functional class and NT-pro-BNP level on admission compared to those who continued beta-blocker (online **supplementary table 1**). When classifying the patients according to beta-blocker use, i.e. continuation (beta blocker use before and after admission), new initiation (new beta-blocker prescription during the index admission), discontinuation (beta-blocker use before, but discontinuation during the index admission), and never use groups (no beta blocker before and after the index admission), there was no difference in survival between patients discontinuation and never use groups, as well as between those in continuation and new initiation groups (online **supplementary figure 1)**. Regarding RAS inhibitors, 846 patients (41.4%) were already taking RAS inhibitors before the index admission. Among them 15.5% discontinued RAS-inhibitor during the index admission and they had lower eGFR level and systolic and diastolic blood pressure, higher NYHA functional class, potassium and NT-pro-BNP level on admission compared to those who continued RAS inhibitors (online **supplementary table 2**). When classifying the patients according to RAS-inhibitor using pattern, patients who received RAS-inhibitors at discharge had better outcomes regardless of previous use than those who did not receive RAS-inhibitors (online **supplementary figure 1).** With increasing age, the proportion of GDMT prescriptions decreased, while that of RAS inhibitors only increased (**figure 2B**). The predictors of GDMT prescription compared to other groups included age 65-79 years, hypertension, diabetes, de-novo onset of heart failure, and concomitant MRA prescription (**table 2**). Underlying COPD, CKD and concomitant use of loop diuretics were inversely associated with the prescription of GDMT.

Table 2. Predictor of prescription of guideline-directed medical therapy compared to other groups

Variable	Odds ratio	95% CI	P value
Age 65-79 (vs. age ≥80 years)	1.52	1.24 – 1.87	<0.001
Male	0.90	0.75 – 1.08	0.240
Hypertension	1.24	1.01 – 1.51	0.036
Diabetes	1.27	1.05 – 1.54	0.014
De novo heart failure (vs. previous heart failure)	1.55	1.29 – 1.86	<0.001
Atrial fibrillation	1.01	0.82 – 1.25	0.911
Chronic kidney disease	0.76	0.63 – 0.92	0.004
Ischemic CMP (vs. non-ischemic)	0.94	0.78 – 1.14	0.546
COPD	0.67	0.50 – 0.88	0.004
Discharge MRA	1.30	1.08 – 1.56	0.007
Discharge digoxin	0.95	0.77 – 1.18	0.634
Discharge loop diuretics	0.76	0.61 – 0.96	0.018

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist

Clinical outcomes

The median follow-up duration was 833 days (interquartile range 240.5 to 1095 days), and 866 (42.3%) patients had died at 3 years. In the Kaplan-Meier survival analysis, patients in the GDMT group had the lowest mortality, whereas those in the no GDMT group had the worst outcomes. Interestingly, there seemed to be no difference in mortality between the beta-blockers only and RAS inhibitors only groups (**figure 3**). Upon further stratification of the patients according to age above or below 80 years, the GDMT group had the lowest

mortality in patients aged above and below 80 years, consistently. In IPTW adjusted population patients in the GDMT group had lower mortality than those in the no GDMT group among the overall patients, patients aged between 65-69 years, and the patients aged 80 years or older (online **supplementary table 3,** online **supplementary figure 2**). In the Cox model after adjustment for significant covariates, GDMT was associated with a 53% reduced risk of all-cause mortality [hazard ratio (HR): 0.47, 95% confidence interval (CI): 0.39-0.57, P <0.001] compared to no GDMT. The beta-blockers only (HR, 0.57, 95% CI 0.45-0.73, P <0.001) and RAS inhibitors only (HR 0.58, 95% CI 0.48-0.71, P<0.001) groups were also associated with reduced risk (**table 3**).

Subgroup analysis

We performed a pre-specified subgroup analysis according to age (65-79 years vs. ≥80 years), CKD, COPD, etiology (ischemic vs. non-ischemic), and HF onset (de-novo HF vs. acute decompensation of chronic HF). There was no significant interaction between medical therapy and any of the subgroups (**figure 4**).

Table 3. Multivariable Cox regression analysis for all-cause mortality

Variable	Hazard ratio	95% CI	P value
Age ≥80 years (vs. age 65-79)	1.60	1.39 – 1.84	<0.001
Male	1.16	1.01 – 1.33	0.039
Hypertension	1.07	0.92 – 1.24	0.392
Diabetes	1.13	0.99 – 1.31	0.080
Previous heart failure (vs. de novo heart failure)	1.39	1.20 – 1.60	<0.001
Atrial fibrillation	0.90	0.77 – 1.07	0.226
Chronic kidney disease	1.50	1.30 – 1.74	<0.001
Ischemic CMP (vs. non-ischemic)	1.29	1.11 – 1.49	<0.001
COPD	1.27	1.04 – 1.53	0.016
Discharge MRA	1.05	0.91 – 1.21	0.499
Discharge digoxin	0.99	0.84 – 1.16	0.885
Discharge loop diuretics	0.90	0.76 – 1.06	0.219
Treatment strategy (vs. no GDMT)			
Beta-blocker only	0.57	0.45 – 0.73	<0.001
RAS inhibitor only	0.58	0.48 – 0.71	<0.001
GDMT	0.47	0.39 – 0.57	<0.001

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; RAS, renin angiotensin system; GDMT, guideline-directed medical therapy

DISCUSSION

The present nationwide multi-center prospective cohort study showed that 1) GDMT was associated with reduced all-cause mortality in elderly patients with HFrEF; 2) prescription of beta-blockers only or RAS inhibitors only was also associated with reduced all-cause mortality compared with no GDMT; and 3) the effect of GDMT also appeared to be effective for reducing all-cause mortality in very elderly patients (age ≥80 years).

GDMT and outcomes in elderly HF patients

Large clinical trials have shown the efficacy of GDMT in patients with HFrEF.[11] However, the patients enrolled in such clinical trials were younger and had fewer comorbidities than real-world elderly patients.[17] Moreover, data from clinical trials supporting the use of GDMT in elderly patients are scarce. The SENIORS study, which included 2,128 patients aged ≥70 years with a history of HF, is considered the representative study conducted in elderly HF patients. It showed that nebivolol reduced the composite of all-cause mortality and rehospitalization for HF, but did not reduce all-cause mortality.[18]

Although observational studies do not provide as high a level of evidence as randomized clinical trials, observational studies may yield real-world evidence.[19, 20] In previous observational studies, the efficacy of beta-blockers in elderly patients has been controversial. In the OPTIMIZE-HF registry, a beta-blocker was not associated with improved survival in patients aged ≥75 years.[19] Dobre et al. reported that the effect of beta-blockers decreased with increasing age, and was not associated with a reduced risk of cardiac death and readmission heart failure in patients aged ≥80 years.[21] Recently, in a subgroup of 237 elderly patients aged ≥80 years in the WET-HF registry, GDMT with beta-blockers and RAS inhibitors did not reduce rates of cardiac death or HF readmission.[22] By contrast, the

present study showed that GDMT was associated with all-cause mortality in elderly HFrEF patients, defined by age ≥65 years. In addition, GDMT was effective in very elderly patients aged ≥80 years. Although the KorAHF and WET-HF studies have included East Asian patients with HF, there are several differences between the 2 studies: KorAHF was larger, especially in terms of the number of patients aged ≥80 years (601 patients in KorAHF vs. 237 patients in WET-HF). As a result, our study was less prone to type II errors, i.e., false negative findings. While WET-HF defined HFrEF as LVEF <45%, the present study enrolled only patients with LVEF ≤40%, which corresponds to the contemporary definition of HFrEF.[11] To our knowledge, this is the first report to show the efficacy of GDMT in very elderly patients with HFrEF.

Prescription of GDMT in elderly patients

The prescription rate of GDMT was 50% in patients aged 65-69 years and 30% in those aged ≥85 years. The decline can be mainly attributed to a decreasing beta-blocker prescription rate. Hamaguchi et al. reported that the prescription rate of beta-blockers was 48% in HFrEF patients aged ≥80 years and that GDMT was applied only in 38% of the patients.[23] In this study, the beta-blocker prescription rate was 55% in all patients and 46% in patients aged ≥80 years. Beta-blockers in very elderly patients may be withheld due to the potential side effects and uncertainty with regard to the benefit for this high-risk group. In addition, 13% of patients had COPD which was associated with a 30% reduced prescription of beta-blockers (beta-blockers in COPD 46% vs. no COPD 56%, P <0.001) but not of RAS inhibitors. Accordingly, COPD was associated with a 33% reduced prescription of GDMT. This finding reflects the possible side effect of beta-blockers, as non-selective beta-blockers may cause bronchoconstriction in patients with COPD. However, given that multiple studies have shown that beta-1 selective beta-blockers can be used safely in patients with asthma and COPD,

beta-1 selective drugs should be considered for patients with COPD.[24, 25]

CKD is very common in patients with HF and is a well-known risk factor in HF patients.[23, 26] In this study, 53% of patients had CKD, and its prevalence increased with age. Since RAS inhibitors can initially aggravate renal function, many physicians withhold RAS inhibitors in patients with CKD. Accordingly, CKD was associated with a 54% reduced prescription of RAS inhibitors (RAS inhibitors in CKD 68% vs. no CKD 83%, P <0.001), resulting in a 24% reduced prescription of GDMT. By contrast, beta-blocker use was not influenced by the presence of CKD. Current guidelines recommend the cautious use of RAS inhibitors in patients with HF and advanced CKD.[11] Our study supports this recommendation, since RAS inhibitor use was associated with a 34% reduced risk of all-cause mortality in patients with CKD.

Limitations

The present study has several limitations. First, owing to the observational nature of the study design, confounding factors may have influenced the study results, despite adjustment for significant covariates. Furthermore, there exists a possibility that unmeasured variables may have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.[27] Third, although the KorAHF registry was designed to enroll all hospitalized HF patients, there exists possibility that some of the patients may not have been enrolled. Fourth, we did not consider dose when defining the GDMT. Although there exists controversy on the relationship between drug dose and outcomes, it should also be investigated in elderly patients.[28] Finally, we do not know whether the patients actually took the prescribed drugs, because many patients had multiple comorbidities and polypharmacy is associated with poor drug compliance.

CONCLUSIONS

Heart failure is common among the elderly, but elderly patients with HF receive less GDMT. Since elderly and very elderly patients with HFrEF appear to benefit from GDMT, physicians should make an effort to prescribe GDMT to these high-risk patients.

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Conflict of Interest Disclosures: The authors declare no conflict of interest

A data sharing statement: Data are housed at the Research of Korea Centers for Disease Control and Prevention and are not available at this time.

Ethics approval: The study protocol was approved by the ethics committee at each 10 tertiary university hospital in Korea.

Patient consent: Written informed consent was waived by the institutional review board at each 10 tertiary hospital in Korea.

REFERENCES

1 Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;6:606-19.

2 Cowie M, Wood D, Coats A, et al. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;20:421-8.

3 Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.

4 Youn J-C, Han S, Ryu K-H. Temporal trends of hospitalized patients with heart failure in Korea. *Korean Circ J* 2017;47:16-24.

5 Murad K, Goff Jr DC, Morgan TM, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. *JACC: Heart Failure* 2015;3:542-50.

6 Shah RU, Tsai V, Klein L, et al. Characteristics and Outcomes of Very Elderly Patients After First Hospitalization for Heart FailureClinical Perspective. *Circ Heart Fail* 2011;4:301-7.

7 Vidán MT, Blaya-Novakova V, Sánchez E, et al. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail* 2016;18:869-75.

8 Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997;157:99-104.

9 The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.

10 Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.

11 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200.

12 Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011;171:550-6.

13 Statistics Korea 2017. Available at: http://kostat.go.kr/portal/eng/pressReleases/11/1/index.board?bmode=download&bSeq=&aSeq=363974&ord=1

14 Hall MJ, Levant S, DeFrances CJ. Hospitalization for congestive heart failure: United States, 2000–2010. NCHS data brief. Available at: https://www.cdc.gov/nchs/data/databriefs/db108.pdf.

15 Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. *Eur J Heart Fail* 2014;16:700-8.

16 Lee SE, Lee H-Y, Cho H-J, et al. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean acute heart failure registry (KorAHF). *Korean Circ J* 2017;47:341-53.

17 Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;162:1682-8..

18 Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart

failure (SENIORS). *Eur Heart J* 2005;26:215-25.

19 Hernandez AF, Hammill BG, O'Connor CM, et al. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol* 2009;53:184-92.

20 Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation* 2010;122:585-96.

21 Dobre D, DeJongste MJ, Lucas C, et al. Effectiveness of β-blocker therapy in daily practice patients with advanced chronic heart failure; is there an effect-modification by age? *Br J Clin Pharmacol* 2007;63:356-64.

22 Akita K, Kohno T, Kohsaka S, et al. Current use of guideline-based medical therapy in elderly patients admitted with acute heart failure with reduced ejection fraction and its impact on event-free survival. *Int J Cardiol* 2017;235:162-8.

23 Hamaguchi S, Kinugawa S, Goto D, et al. Predictors of long-term adverse outcomes in elderly patients over 80 years hospitalized with heart failure. *Circ J* 2011;75:2403-10.

24 Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blocker use in patients with reversible airway disease. *Cochrane Database Syst Rev* 2002:CD002992.

25 Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective β-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715-25.

26 Komajda M, Hanon O, Hochadel M, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J* 2008;30:478-86.

27 Murad K, Goff DC, Morgan TM, et al. Burden of comorbidities and functional and

cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. *JACC: Heart Failure* 2015;3:542-50.

28 Turgeon RD, Kolber MR, Loewen P, et al. Higher versus lower doses of ACE inhibitors, angiotensin-2 receptor blockers and beta-blockers in heart failure with reduced ejection fraction: Systematic review and meta-analysis. *PLoS One* 2019;14:e0212907.

Figure legends

Figure 1. Study flow

EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction

Figure 2. Discharge medication profiles.

Prescription of beta-blockers, RAS inhibitors (A), and GDMT (B) according to the age groups in elderly patients with HFrEF.

RAS, renin-angiotensin system; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction

Figure 3. Three-year cumulative survival according to the treatment groups

Patients receiving GDMT had lower mortality among the all patients (A), patients aged between 65-79 years (B), and patients aged 80 years or older (C).

BB, beta-blocker; RASi, renin-angiotensin system inhibitor; GDMT, guideline-directed medical therapy

Figure 4. Subgroup analysis.

There was no interaction between the effect of GDMT and diverse subgroups, and GDMT was associated with lower morality across subgroups.

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; GDMT, guideline-directed medical therapy

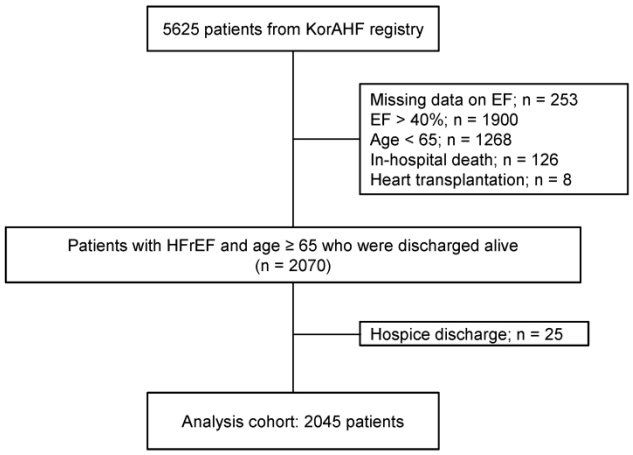
Supplementary figure 1. Cumulative survival according to beta-blocker and RAS inhibitor prescription pattern

BB, beta-blocker; RASi, renin-angiotensin system inhibitor

Supplementary figure 2. Three-year cumulative survival according to the treatment groups in inverse probability treatment weight adjusted population

Patients receiving GDMT had lower mortality among the all patients (A), patients aged between 65-79 years (B), and patients aged 80 years or older (C).

BB, beta-blocker; RASi, renin-angiotensin system inhibitor; GDMT, guideline-directed medical therapy



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EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction

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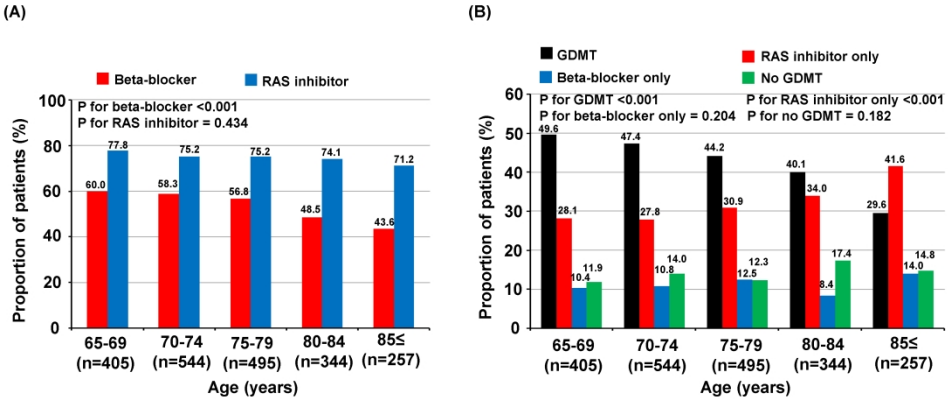

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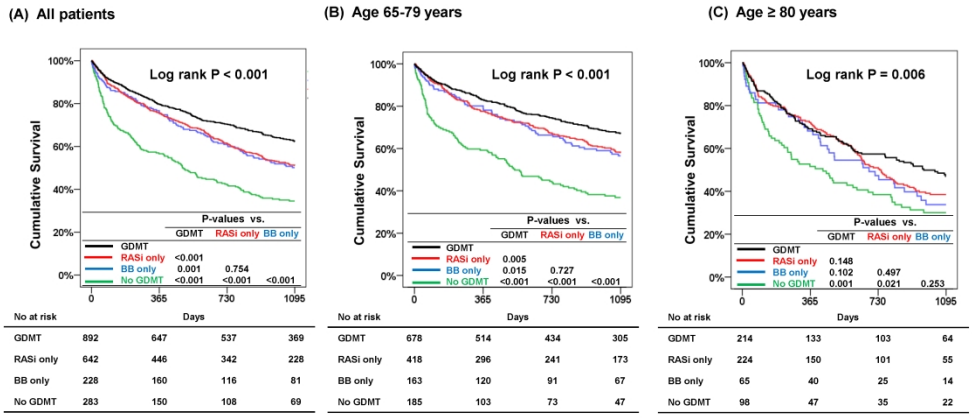

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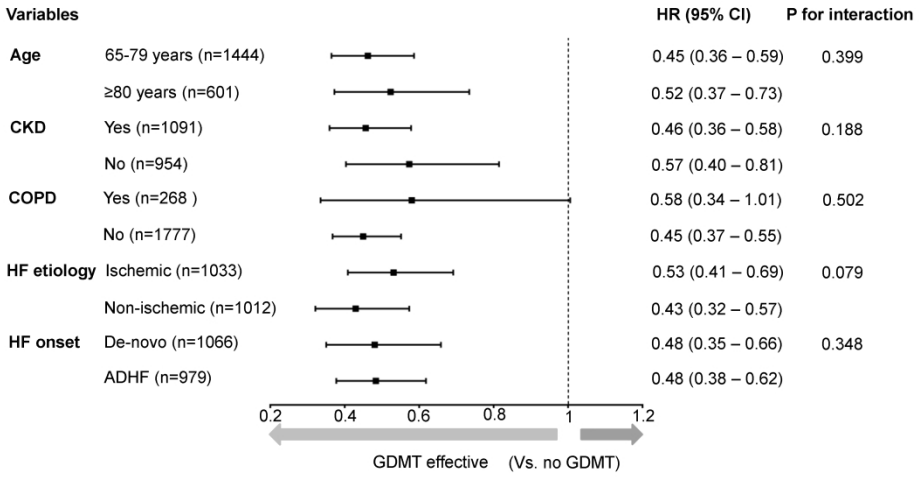

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HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; GDMT, guideline-directed medical therapy

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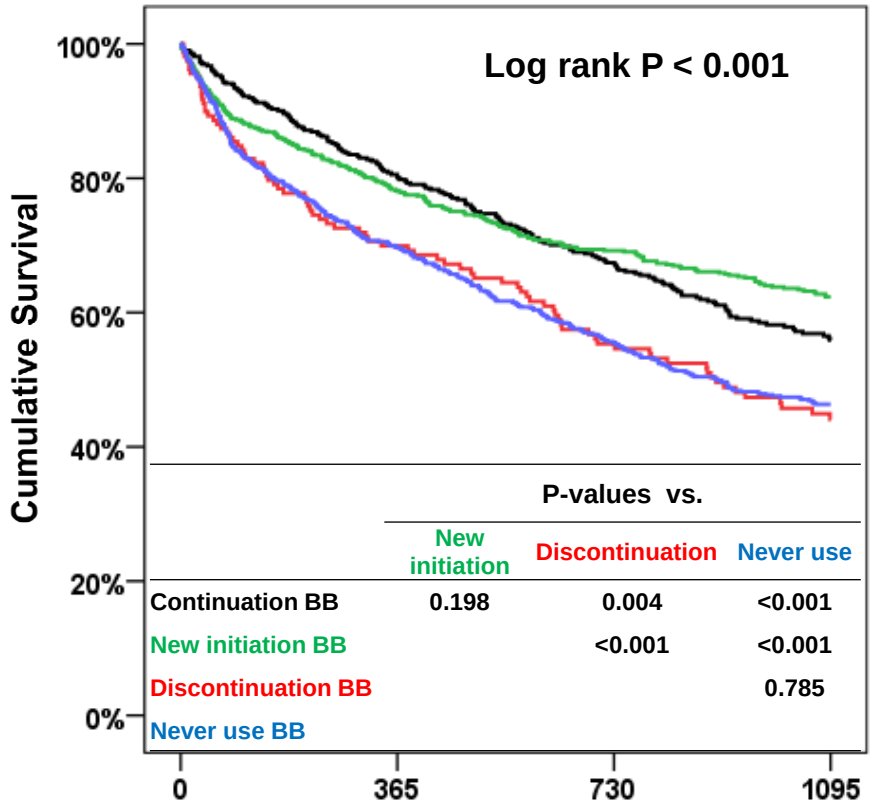
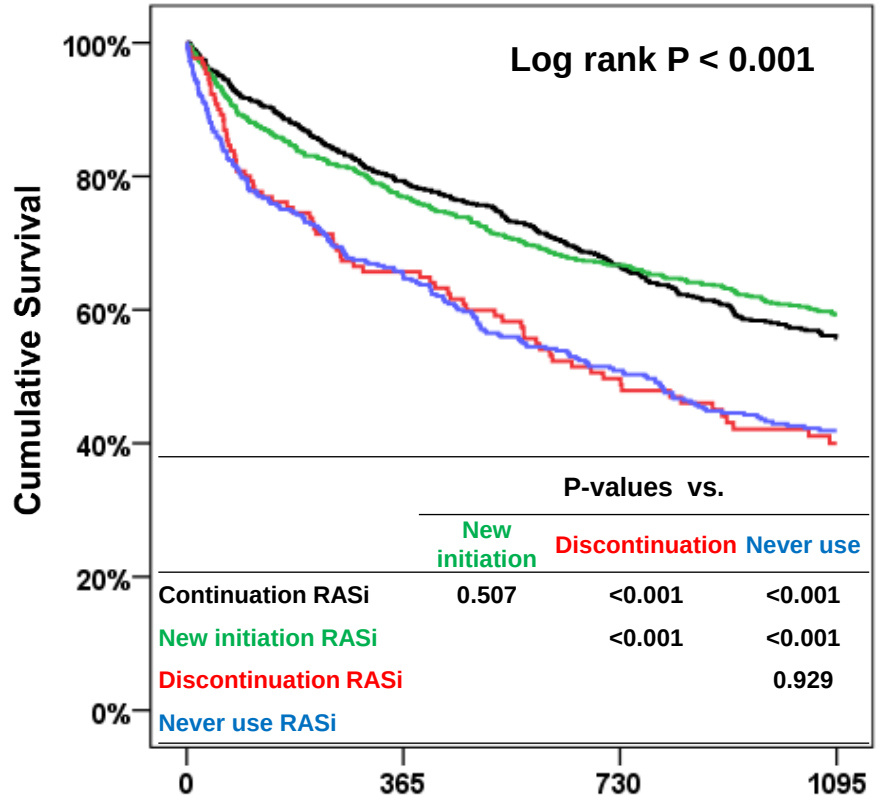
(A) Cumulative survival according to beta-blocker prescription pattern



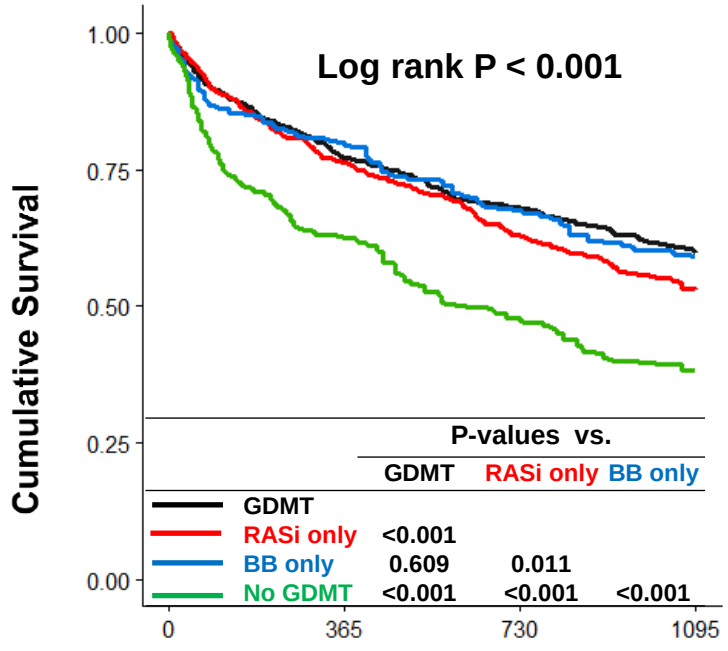
No at risk				
Continuation BB	433	323	251	161
New initiation BB	687	483	402	289
Discontinuation BB	161	102	77	51
Never use BB	764	494	373	246

(B) Cumulative survival according to RAS inhibitor prescription pattern



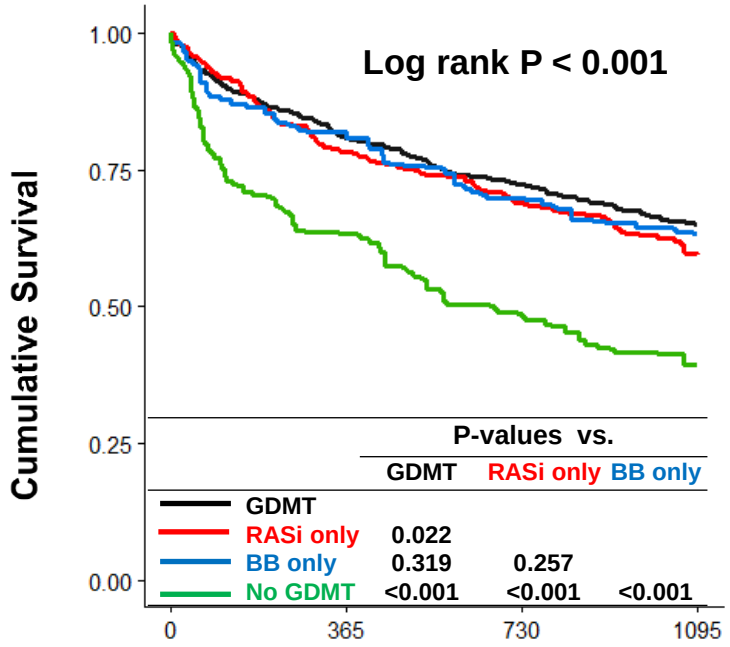
No at risk				
Continuation RASi	715	528	418	278
New initiation RASi	819	565	461	319
Discontinuation RASi	131	80	55	36
Never use RASi	380	230	169	114

(A) All patients



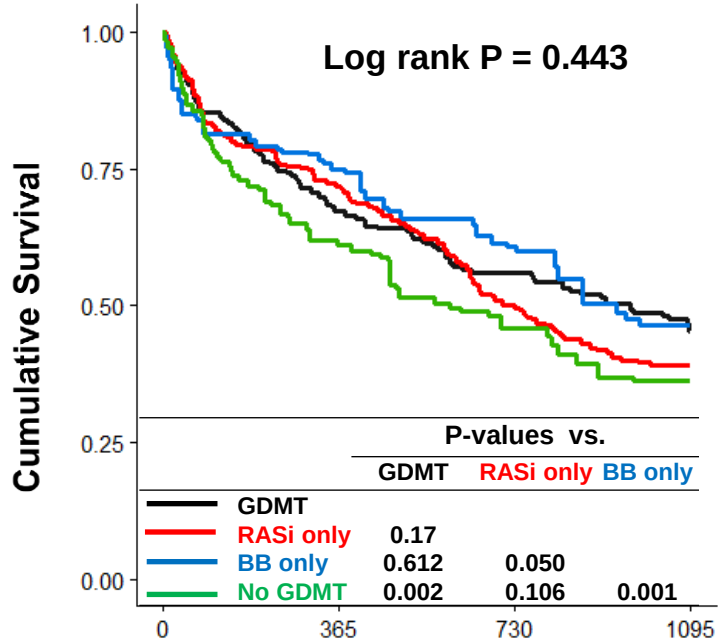
No at risk	Days			
GDMT	1813	1279	1064	729
RASi only	1709	1193	926	633
BB only	1298	936	736	541
No GDMT	1132	654	489	308

(B) Age 65-79 years



No at risk	Days			
GDMT	1326	986	836	586
RASi only	1169	836	689	500
BB only	956	722	583	459
No GDMT	726	423	315	197

(C) Age ≥ 80 years



No at risk	Days			
GDMT	487	293	228	143
RASi only	539	357	237	133
BB only	342	214	154	82
No GDMT	407	231	173	111

Supplementary table 1. Baseline characteristics of patients according to continue or discontinued of beta-blocker during index admission

Variable	Continue beta-blocker (n=433)	Discontinue beta-blocker (n=161)	P value
Age, years	75.3 ± 6.6	76.4 ± 6.9	0.08
Men, n (%)	233 (53.8)	92 (57.1)	0.516
BMI, kg/m^2	23.5 ± 3.6	22.4 ± 3.2	<0.001
Medical history			
Previous heart failure, n (%)	332 (76.7)	116 (72.0)	0.284
Hypertension, n (%)	336 (77.6)	117 (72.7)	0.233
Diabetes, n (%)	213 (49.2)	64 (39.8)	0.042
Atrial fibrillation, n (%)	151 (34.9)	46 (28.6)	0.170
COPD, n (%)	48 (11.1)	21 (13.0)	0.564
Myocardial infarction, n (%)	165 (38.1)	56 (34.8)	0.504
Medication on discharge			
RAS inhibitor, n (%)	316 (73.0)	107 (66.5)	0.127
MRA, n (%)	213 (49.2)	74 (46.0)	0.518
Loop diuretics, n (%)	71 (16.4)	49 (30.4)	<0.001
Digoxin, n (%)	300 (69.3)	116 (72.0)	0.546
Systolic BP on admission, mm Hg	135.5 ± 28.7	131.3 ± 29.0	0.116
Diastolic BP on admission, mm Hg	81.1 ± 18.0	76.8 ± 18.1	0.010
Heart rate on admission, beats/min	89.7 ± 23.8	92.9 ± 27.6	0.172
NYHA functional class III or IV on admission	380 (87.8)	153 (95.0)	0.009

Laboratory data on admission			
eGFR, ml/min/1.73m^2	51.2 ± 25.1	46.7 ± 23.4	0.051
Sodium, mEq/L	137.7 ± 4.2	137.4 ± 5.0	0.454
Potassium, mEq/L	4.5 ± 0.7	4.5 ± 0.7	0.242
BNP, pg/mL	1593.1 ± 1306.1	1926.5 ± 1515.7	0.150
NT-pro-BNP, pg/mL	11545.9 ± 10872.8	14650.1 ± 12629.1	0.036
LVEF, %	29.1 ± 6.9	28.6 ± 7.8	0.483

BMI, body mass index; COPD, chronic obstructive pulmonary disease; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction

Supplementary table 2. Baseline characteristics of patients according to continue or discontinued of RAS inhibitor during index admission

Variable	Continue RAS inhibitor	Discontinue RAS inhibitor	P value
Age, years	75.8 ± 6.7	76.3 ± 6.5	0.481
Men, n (%)	400 (55.9)	70 (53.4)	0.633
BMI, kg/m^2	23.1 ± 3.5	22.9 ± 3.3	0.562
Medical history			
Previous heart failure, n (%)	512 (71.6)	92 (70.2)	0.753
Hypertension, n (%)	543 (75.9)	102 (77.9)	0.738
Diabetes, n (%)	343 (48.0)	70 (53.4)	0.256
Atrial fibrillation, n (%)	235 (32.9)	34 (26.0)	0.127
COPD, n (%)	95 (13.3)	19 (14.5)	0.678
Myocardial infarction, n (%)	220 (30.8)	52 (39.7)	0.053
Medication on discharge			
Beta-blocker, n (%)	380 (53.1)	58 (44.3)	0.071
MRA, n (%)	348 (48.7)	49 (37.4)	0.022
Loop diuretics, n (%)	159 (22.2)	44 (33.6)	0.007
Digoxin, n (%)	483 (67.6)	99 (75.6)	0.081
Systolic BP on admission, mm Hg	134.7 ± 28.6	127.1 ± 31.3	0.006
Diastolic BP on admission, mm Hg	79.8 ± 16.8	73.1 ± 17.3	<0.001
Heart rate on admission, beats/min	91.4 ± 24.6	96.9 ± 22.5	0.018
NYHA functional class III or IV on admission	623 (87.1%)	117 (89.3)	0.567

Laboratory data on admission			
eGFR, ml/min/1.73m^2	53.3 ± 23.6	39.5 ± 20.8	<0.001
Sodium, mEq/L	137.6 ± 4.9	136.8 ± 4.5	0.062
Potassium, mEq/L	4.4 ± 0.7	4.7 ± 0.8	0.001
BNP, pg/mL	1670.8 ± 1502.2	1920.8 ± 2017.2	0.355
NT-pro-BNP, pg/mL	10966.0 ± 10806.0	14939.1 ± 12170.9	0.007
LVEF, %	28.6 ± 7.5	28.6 ± 7.4	0.929

BMI, body mass index; COPD, chronic obstructive pulmonary disease; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction

Online supplementary table 3. Patients characteristics in inverse probability treatment weight adjusted population

	GDMT (n=1813)	Beta blocker only (n=1298)	RAS inhibitor only (n=1709)	No GDMT (n=1132)	Std. Diff.	P value
Age, years	75.5 ± 6.7	75.6 ± 6.8	76.1 ± 7.0	76.7 ± 6.8	0.17	0.07
Men, n (%)	964 (53.2)	757 (58.3)	963 (56.3)	622 (54.9)	0.10	0.26
BMI, kg/m^2	22.7 ± 3.4	22.6 ± 3.5	22.4 ± 3.3	22.4 ± 3.2	0.08	0.34
Medical history						
Previous heart failure, n (%)	905 (49.9)	687 (52.9)	901 (52.8)	656 (58.0)	0.16	0.05
Hypertension, n (%)	1233 (68.0)	870 (67.0)	1108 (64.9)	732 (64.6)	0.07	0.24
Diabetes, n (%)	774 (42.7)	481 (37.0)	650 (38.0)	472 (41.7)	0.11	0.09
Chronic kidney disease, n (%)	933 (51.5)	769 (59.2)	877 (51.3)	674 (59.6)	0.16	0.05
Atrial fibrillation, n (%)	566 (31.2)	448 (34.5)	515 (30.2)	380 (33.6)	0.09	0.32
COPD, n (%)	211 (11.6)	168 (12.9)	247 (14.5)	162 (14.3)	0.08	0.12
Myocardial infarction, n (%)	395 (21.8)	330 (25.4)	384 (22.5)	292 (25.8)	0.10	0.34
Cause of heart failure						
Ischemic, n (%)	920 (50.8)	752 (57.9)	837 (49.0)	615 (54.4)	0.18	0.06
Dilated, n (%)	434 (23.9)	250 (19.2)	387 (22.6)	213 (18.8)	0.12	0.15
Medication on admission						
Beta-blocker, n (%)	561 (31.0)	442 (34.0)	439 (25.7)	259 (22.9)	0.24	0.03
RAS inhibitor, n (%)	727 (40.1)	459 (35.4)	762 (44.6)	409 (36.2)	0.19	0.06
MRA, n (%)	301 (16.6)	277 (21.3)	296 (17.3)	224 (19.8)	0.12	0.15
Medication on discharge						
MRA, n (%)	936 (51.6)	643 (49.6)	839 (49.1)	486 (42.9)	0.17	0.03

Loop diuretics, n (%)	1427 (78.7)	977 (75.2)	1305 (76.4)	794 (70.2)	0.21	0.01
Digoxin, n (%)	547 (30.2)	358 (27.6)	488 (28.5)	361 (31.9)	0.09	0.39
Systolic BP on discharge, mm Hg	114.7 ± 16.8	113.8 ± 16.8	115.0 ± 16.5	112.5 ± 15.4	0.15	0.39
Diastolic BP on discharge, mm Hg	66.1 ± 10.8	66.1 ± 10.1	66.1 ± 10.9	65.0 ± 9.9	0.10	0.20
Heart rate on discharge, beats/min	76.3 ± 13.6	77.8 ± 12.3	77.2 ± 14.2	77.4 ± 13.5	0.10	0.21
NYHA functional class on discharge					0.10	0.23
I or II, n (%)	1598 (88.1)	1148 (88.4)	1496 (87.5)	1028 (90.8)		
III or IV, n (%)	215 (11.9)	150 (11.6)	213 (12.5)	105 (9.2)		
Echocardiographic parameters						
LVEDD, mm	60.2 ± 8.8	59.6 ± 8.7	60.3 ± 8.7	59.3 ± 8.7	0.11	0.40
LVESD, mm	50.3 ± 9.3	49.9 ± 9.3	50.0 ± 9.5	49.4 ± 9.5	0.09	0.26
LVEF, %	28.7 ± 7.3	28.2 ± 7.7	28.9 ± 7.3	29.0 ± 7.2	0.11	0.57
Laboratory data on admission						
Hemoglobin, g/dL	12.3 ± 2.0	12.3 ± 1.9	12.3 ± 2.1	12.1 ± 2.1	0.08	0.49
eGFR, ml/min/1.73m^2	61.6 ± 32.6	58.6 ± 30.1	62.3 ± 30.1	56.5 ± 28.1	0.18	0.07
Sodium, mEq/L	137.8 ± 4.5	138.0 ± 4.2	137.6 ± 4.5	137.4 ± 4.5	0.11	0.78
Potassium, mEq/L	4.4 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.7	0.14	0.46
BNP, pg/mL	1692.2 ± 1528.3	1703.7 ± 1403.4	1731.0 ± 1389.8	1732.8 ± 1858.4	0.03	0.81
NT-pro-BNP, pg/mL	11650.7 ± 11236.4	10810.0 ± 10121.4	10549.1 ± 10321.2	12307.0 ± 10979.5	0.16	0.10

GDMT, guideline-directed medical therapy; RAS, renin angiotensin system; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; BNP, brain natriuretic peptide

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12,13,8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16, 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15, 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study

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Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study

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ABSTRACT

Objectives and design

Guideline-directed medical therapy (GDMT) with renin-angiotensin system (RAS) inhibitors and beta-blockers has improved survival in patients with heart failure with reduced ejection fraction (HFrEF). As clinical trials usually do not include very old patients, it is unknown whether the results from clinical trials are applicable to elderly patients with HF. This study was performed to investigate the clinical characteristics and treatment strategies for elderly patients with HFrEF in a large-prospective cohort.

Setting

The KorAHF registry consecutively enrolled 5,625 patients hospitalized for acute HF from 10 tertiary university hospitals in Korea.

Participants

In this study, 2,045 patients with HFrEF who were aged 65 years or older were included from the KorAHF registry.

Primary outcome measurement

All-cause mortality data were obtained from medical records, national insurance data, or national death records.

Results

Both beta-blockers and RAS inhibitors were used in 892 (43.8%) patients (GDMT group), beta-blockers only in 228 (11.1%) patients, RAS inhibitors only in 642 (31.5%) patients, and neither beta-blockers nor RAS inhibitors in 283 (13.6%) patients (no GDMT group). With increasing age, the GDMT rate decreased, which was mainly attributed to the decreased

prescription of beta-blockers. In multivariate analysis, GDMT was associated with a 53% reduced risk of all-cause mortality (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.39-0.57) compared with no GDMT. Use of beta-blockers only (HR, 0.57, 95% CI 0.45-0.73) and RAS inhibitors only (HR 0.58, 95% CI 0.48-0.71) was also associated with reduced risk. In a subgroup of very elderly patients (aged ≥80 years), the GDMT group had the lowest mortality.

Conclusions

GDMT was associated with reduced 3-year all-cause mortality in elderly and very elderly HFrEF patients.

Trial registration

ClinicalTrial.gov NCT01389843

Keywords: heart failure with reduced ejection fraction

Strengths and limitations of this study

- This was a large prospective cohort study that included patients with heart failure with reduced ejection fraction who were aged 65 years or older.
- We obtained all participants' mortality data from medical or national death records.
- The registry could not capture all comorbidities including functional or cognitive impairments, an important prognostic factor for elderly patients.

INTRODUCTION

Heart failure (HF) is associated with significant morbidity, mortality, and healthcare burdens.[1] Since the prevalence of HF increases with age, the incidence of elderly patients with HF has been continuously increasing as the aging population increases.[2-4] Elderly patients with HF have worsened outcomes: they have more comorbidities, functional and cognitive impairments, and polypharmacy.[5-7] In addition, they are at high risk of re-hospitalization for HF after hospital discharge.[8]

Large clinical trials have shown that guideline-directed medical therapy (GDMT) with renin-angiotensin system (RAS) inhibitors and beta-blockers improved survival in patients with heart failure with reduced ejection fraction (HFrEF).[9-11] However, many elderly patients with HF have been excluded from randomized clinical studies due to age, comorbidities, or functional or cognitive impairments, among others.[12] Accordingly, it is unknown whether the results from clinical trials can be directly applied to elderly patients with HF.

Korea is one of the most rapidly aging societies. In 2018, it has become an "aged society" and will be a "super-aged society" by 2026.[13] In 2017, Korea's proportion of individuals aged ≥65 years was 13.8%. Considering that 70% of hospitalizations for HF occurred in patients aged ≥65 years, a better understating of these high-risk patients is critical for proper management.[14] In this study, we investigated the clinical characteristics and treatment strategies for elderly patients with HFrEF in a large-prospective cohort.

METHODS

Participants and cohort recruitment

The Korean Acute Heart Failure (KorAHF) registry is a prospective multicenter registry designed to reflect the real-world clinical data of Korean patients admitted for acute HF. The study design and primary results of the registry have been published elsewhere [ClinicalTrial.gov NCT01389843].[15, 16] Patients hospitalized for acute HF from 10 tertiary university hospitals in Korea were consecutively enrolled from March 2011 to February 2014. Briefly, patients with signs or symptoms of HF and either lung congestion or objective findings of left ventricle systolic dysfunction or structural heart disease were eligible for enrollment in this registry. To minimize selection bias, we tried to enroll all hospitalized patients with acute HF at each hospital. Patients' baseline characteristics, clinical presentation, underlying diseases, vital signs, laboratory tests, treatments, and outcomes were recorded at admission, and discharge, and during follow-up (30-day, 90-day, 180-day, and 1- to 3-year annually). The mortality data for patients who were lost to follow-up were obtained from the national insurance data or national death records.

In this study, we included patients with HFrEF who were aged 65 years or older. For patient selection, we serially excluded patients if any of the exclusion criteria was met. The study protocol was approved by the ethics committee at each hospital. Written informed consent was waived by the institutional review board. The study complied with the Declaration of Helsinki.

Patients and public involvement

Patients were not involved in the conception, design or interpretation of this study. The results of this study will be disseminated to patients and healthcare providers through oral presentations and social media.

Study variables and definition

HFrEF was defined as a left ventricular ejection fraction (LVEF) of ≤40%. The patients were classified into groups according to the medication prescribed at discharge: the GDMT group (patients who received both beta-blockers and RAS inhibitors), beta-blockers only group, RAS inhibitors only group, and no GDMT group (no beta-blockers or RAS inhibitors). Chronic kidney disease (CKD) was defined as a glomerular filtration rate of <60 mL/min/1.73 m^2, and chronic obstructive pulmonary disease (COPD) was defined as a self-reported or physician-confirmed diagnosis of chronic bronchitis, emphysema, or both. The primary outcome was 3-year post-discharge all-cause mortality from index admission.

Statistical analysis

Continuous variables were presented as a mean ± standard deviation, whereas categorical variables were presented as counts and their percentages. Differences among continuous variables were analyzed using a one-way ANOVA and those among categorical variables using the χ^2 test. Logistic regression analysis was used to determine the predictors of GDMT prescription. We converted the odds ratios from logistic regression analysis into relative risks because of the high prevalence of GDMT.[17] The cumulative event rate was assessed using the Kaplan-Meier method with log-rank analysis. Multivariable Cox regression analysis was used to evaluate the adjusted relative risk of the variables. Multivariable models including age, sex, hypertension, diabetes, previous heart failure history, atrial fibrillation, CKD, cause of heart failure, COPD, treatment strategy (no GDMT, beta-blockers only, RAS inhibitors only and GDMT), and prescription of mineralocorticoid receptor antagonists (MRA), digitalis, and diuretics were chosen according to their clinical relevance and based on the results of previous trials.[3, 11] Furthermore, we performed a pre-specified subgroup analysis including age, CKD, COPD, HF etiology, and HF onset, and produced forest plots of the hazard ratio of

medical therapy (i.e. GDMT, beta-blockers only, RAS inhibitors only) compared with no GDMT. We evaluated whether there was an interaction between treatment strategy and the subgroups on all-cause mortality. For the calculation of P for interaction, Cox regression models were used which included the indicator variables for treatment strategy, subgrouping variables, and interaction term of the treatment strategy-by-subgrouping variable of interest (age, CKD, COPD, HF etiology or HF onset), as independent variables. The following covariates were also included in the interaction models: sex, hypertension, diabetes, atrial fibrillation, and prescription of MRA, digitalis and diuretics. To mitigate the impact of potential confounding factors in the registry data, we additionally performed the inverse probability of treatment weighting (IPTW). The inferences regarding the rate of all-cause death were conducted with robust standard errors after examining covariate balances among treatment groups. We used the "Twang" package for R programming for IPTW analysis. Success of IPTW analyses was assessed by calculating the standardized differences in baseline characteristics. All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA) and R v3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria). A P value <0.05 was considered statistically significant.

RESULTS

The KorAHF registry includes 5,625 acute HF patients. Of these, we excluded patients with missing LVEF (n=253), those with LVEF >40% (n=1900), <65 years in age (n=1268), in-hospital death (n=126), heart transplantation (n=8), and those who were hopelessly discharged (n=25), leaving a total of 2,045 patients available for the final analysis (**figure 1**).

Overall, the mean age was 75.9 years, 54.2% were male, 66.7% had hypertension, and 42.0% had diabetes mellitus. In addition, the mean LVEF was 28.7 ± 7.4%, and the most common cause of HFrEF was ischemic cardiomyopathy (50.5%).

Medication prescription pattern according to patients' characteristics

The beta-blocker prescription rate at discharge was 54.8% in all patients and that of RAS inhibitors was 75.0%. With increasing age, the beta-blocker prescription rate decreased (P for trend <0.001), while that of RAS inhibitors remained unchanged (**figure 2A**).

The baseline characteristics of the study population are summarized in **table 1**. Overall, both beta-blockers and RAS inhibitors were used in 892 (43.8%) patients (GDMT group), beta-blockers only in 228 (11.1%) patients, RAS inhibitors only in 642 (31.5%) patients, and neither beta-blockers nor RAS inhibitors in 283 (13.6%) patients (no GDMT group). The beta-blocker prescription rate was lower in patients with COPD (COPD: 45.5%, vs. no COPD: 56.2%, P = 0.01), whereas the prescription of RAS inhibitors was lower in patients with CKD (CKD: 68.7%, vs. no CKD: 82.2%, P <0.001).

Table 1. Baseline characteristics of patients according to treatment strategy

	GDMT (n=892)	Beta blocker only (n=228)	RAS inhibitor only (n=642)	No GDMT (n=283)	P value
Age, years	75.0 ± 6.5	76.2 ± 7.2	76.7 ± 7.1	76.7 ± 6.7	<0.001
Men, n (%)	472 (52.9)	115 (50.7)	369 (57.5)	149 (54.0)	0.211
BMI, kg/m^2	23.0 ± 3.5	22.6 ± 3.5	22.4 ± 3.4	21.9 ± 3.0	<0.001
Medical history					
Previous heart failure, n (%)	414 (46.4)	136 (59.6)	361 (56.2)	167 (59.0)	<0.001
Hypertension, n (%)	609 (68.3)	162 (71.4)	417 (65.0)	174 (63.0)	0.124
Diabetes, n (%)	399 (44.7)	97 (42.7)	242 (37.7)	119 (43.1)	0.050
Chronic kidney disease, n (%)	430 (48.2)	150 (66.1)	320 (49.8)	186 (67.4)	<0.001
Atrial fibrillation, n (%)	281 (31.5)	89 (39.2)	193 (30.1)	81 (29.3)	0.059
COPD, n (%)	92 (10.3)	30 (13.2)	110 (17.1)	36 (13.0)	0.002
Myocardial infarction, n (%)	194 (21.8)	61 (26.9)	146 (22.7)	65 (23.6)	0.433
Cause of heart failure					
Ischemic, n (%)	443 (49.7)	129 (56.8)	311 (48.4)	146 (52.9)	0.132
Dilated, n (%)	222 (24.9)	36 (15.9)	147 (22.9)	50 (18.1)	0.008
Medication on admission					
Beta-blocker, n (%)	316 (35.4)	117 (51.5)	107 (16.7)	53 (19.2)	<0.001
RAS inhibitor, n (%)	380 (42.6)	58 (25.6)	335 (52.2)	72 (26.1)	<0.001
MRA, n (%)	143 (16.0)	47 (20.7)	122 (19.0)	60 (21.7)	0.096
Medication on discharge					
MRA, n (%)	487 (54.6)	95 (41.9)	316 (49.2)	120 (43.5)	<0.001

Loop diuretics, n (%)	714 (80.0)	174 (76.7)	493 (76.8)	189 (68.5)	0.001
Digoxin, n (%)	269 (30.2)	63 (27.8)	193 (30.1)	86 (31.2)	0.865
Systolic BP on discharge, mm Hg	115.0 ± 17.0	115.7 ± 16.4	114.2 ± 16.5	113.0 ± 16.6	0.067
Diastolic BP on discharge, mm Hg	66.1 ± 10.7	67.5 ± 10.7	65.6 ± 11.2	65.2 ± 10.0	0.026
Heart rate on discharge, beats/min	74.6 ± 12.9	78.1 ± 14.4	77.8 ± 14.3	80.6 ± 13.7	<0.001
NYHA functional class on discharge					0.154
I or II, n (%)	792 (88.8)	205 (90.3)	566 (88.2)	250 (90.6)	
III or IV, n (%)	100 (11.2)	22 (9.7)	76 (11.8)	45 (9.4)	
Echocardiographic parameters					
LVEDD, mm	60.3 ± 8.7	57.6 ± 9.6	61.2 ± 8.9	58.8 ± 9.0	<0.001
LVESD, mm	50.3 ± 9.3	47.6 ± 10.0	51.1 ± 9.6	49.1 ± 9.8	<0.001
LVEF, %	28.8 ± 7.3	28.8 ± 7.5	28.5 ± 7.4	28.6 ± 7.7	0.864
Laboratory data on admission					
Hemoglobin, g/dL	12.4 ± 2.0	11.9 ± 2.2	12.2 ± 2.1	11.7 ± 2.2	<0.001
eGFR, ml/min/1.73m^2	63.8 ± 33.8	52.6 ± 32.3	63.2 ± 30.4	53.2 ± 30.1	<0.001
Sodium, mEq/L	138.0 ± 4.4	137.6 ± 4.4	137.3 ± 5.1	137.0 ± 4.6	0.006
Potassium, mEq/L	4.3 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.8	0.001
BNP, pg/mL	1592.9 ± 1489.8	1849.7 ± 1492.0	1724.8 ± 1381.7	1937.1 ± 1920.8	0.223
NT-pro-BNP, pg/mL	10941.1 ± 11006.9	11535.8 ± 10587.7	9978.0 ± 9484.0	14728.7 ± 12514.7	<0.001

GDMT, guideline-directed medical therapy; RAS, renin angiotensin system; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; BNP, brain natriuretic peptide

Five hundred ninety-four patients (29.0%) were already taking beta-blockers before index admission; among them, 27.1% discontinued beta-blockers during index admission and had lower diastolic blood pressure and higher NYHA functional class and NT-pro-BNP levels on admission compared to those who continued beta-blockers (online **supplementary table 1**). When classifying patients according to beta-blocker use [continuation (beta-blocker use before and after admission), new initiation (new beta-blocker prescription during index admission), discontinuation (beta-blocker use before, but discontinuation during index admission), and never use groups (no beta blocker before and after index admission)], there was no difference in survival between patient discontinuation and the never use groups, as well as between those in continuation and new initiation groups (online **supplementary figure 1)**. Regarding RAS inhibitors, 846 patients (41.4%) were already taking RAS inhibitors before index admission. Among them, 15.5% discontinued RAS inhibitors during index admission and had lower eGFR levels and systolic and diastolic blood pressure, and higher NYHA functional class, potassium, and NT-pro-BNP levels on admission compared to those who continued RAS inhibitors (online **supplementary table 2**). When classifying the patients according to RAS inhibitor usage patterns, patients who received RAS inhibitors at discharge had better outcomes regardless of previous use than those who did not receive RAS inhibitors (online **supplementary figure 1).** With increasing age, the proportion of GDMT prescriptions decreased, while that of RAS inhibitors only increased (**figure 2B**). The predictors of GDMT prescription compared to any of the other three treatment groups included age 65-79 years, hypertension, diabetes, *de novo* onset of heart failure, and concomitant MRA prescription (**table 2**). Underlying COPD, CKD, and concomitant use of loop diuretics were inversely associated with the prescription of GDMT.

Table 2. Predictors of prescription of guideline-directed medical therapy compared to any of the other three treatment groups

Variable	Relative risk	95% CI	P value
Age 65-79 (vs. age ≥80 years)	1.28	1.14 – 1.43	<0.001
Male	0.94	0.85 – 1.04	0.240
Hypertension	1.13	1.01 – 1.25	0.036
Diabetes	1.14	1.03 – 1.26	0.014
De novo heart failure (vs. previous heart failure)	1.28	1.16 – 1.40	<0.001
Atrial fibrillation	1.01	0.89 – 1.13	0.911
Chronic kidney disease	0.86	0.77 – 0.96	0.004
Ischemic CMP (vs. non-ischemic)	0.97	0.86 – 1.07	0.546
COPD	0.79	0.65 – 0.93	0.004
Discharge MRA	1.16	1.05 – 1.28	0.007
Discharge digoxin	0.97	0.86 – 1.09	0.634
Discharge loop diuretics	0.84	0.72 – 0.98	0.018

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist

Clinical outcomes

The median follow-up duration was 833 days (interquartile range: 240.5 to 1095 days), and 866 (42.3%) patients had died at 3 years. In the Kaplan-Meier survival analysis, patients in the GDMT group had the lowest mortality, whereas those in the no GDMT group had the worst outcomes. Interestingly, there seemed to be no difference in mortality between the

beta-blockers only and RAS inhibitors only groups (**figure 3**). Upon further stratification of the patients according to age above or below 80 years, the GDMT group had the lowest mortality in patients aged above and below 80 years, consistently. In IPTW adjusted population patients in the GDMT group had lower mortality than those in the no GDMT group among the overall patients, patients aged between 65-69 years, and patients aged 80 years or older (online **supplementary table 3,** online **supplementary figure 2**). In the Cox model after adjustment for significant covariates, GDMT was associated with a 53% reduced risk of all-cause mortality [hazard ratio (HR): 0.47, 95% confidence interval (CI): 0.39-0.57, P <0.001] compared to no GDMT. The beta-blockers (HR, 0.57, 95% CI 0.45-0.73, P <0.001) or RAS inhibitors (HR 0.58, 95% CI 0.48-0.71, P<0.001) only groups were also associated with reduced risk (**table 3**).

Subgroup analysis

We performed a pre-specified subgroup analysis according to age (65-79 years vs. ≥80 years), CKD, COPD, etiology (ischemic vs. non-ischemic), and HF onset (*de novo* HF vs. acute decompensation of chronic HF). There was no significant interaction between medical therapy and any subgroup (**figure 4**).

Table 3. Multivariable Cox regression analysis for all-cause mortality

Variable	Hazard ratio	95% CI	P value
Age ≥80 years (vs. age 65-79)	1.60	1.39 – 1.84	<0.001
Male	1.16	1.01 – 1.33	0.039
Hypertension	1.07	0.92 – 1.24	0.392
Diabetes	1.13	0.99 – 1.31	0.080
Previous heart failure (vs. de novo heart failure)	1.39	1.20 – 1.60	<0.001
Atrial fibrillation	0.90	0.77 – 1.07	0.226
Chronic kidney disease	1.50	1.30 – 1.74	<0.001
Ischemic CMP (vs. non-ischemic)	1.29	1.11 – 1.49	<0.001
COPD	1.27	1.04 – 1.53	0.016
Discharge MRA	1.05	0.91 – 1.21	0.499
Discharge digoxin	0.99	0.84 – 1.16	0.885
Discharge loop diuretics	0.90	0.76 – 1.06	0.219
Treatment strategy (vs. no GDMT)			
Beta-blocker only	0.57	0.45 – 0.73	<0.001
RAS inhibitor only	0.58	0.48 – 0.71	<0.001
GDMT	0.47	0.39 – 0.57	<0.001

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; RAS, renin angiotensin system; GDMT, guideline-directed medical therapy

DISCUSSION

The present nationwide multi-center prospective cohort study showed: 1) GDMT was associated with reduced all-cause mortality in elderly patients with HFrEF; 2) prescription of beta-blockers or RAS inhibitors only was also associated with reduced all-cause mortality compared with no GDMT; and 3) the effect of GDMT also appeared to be effective for reducing all-cause mortality in very elderly patients (age ≥80 years).

GDMT and outcomes in elderly HF patients

Large clinical trials have shown the efficacy of GDMT in patients with HFrEF.[11] However, the patients enrolled in such clinical trials were younger and had fewer comorbidities than real-world elderly patients.[18] Moreover, data from clinical trials supporting the use of GDMT in elderly patients are scarce. The SENIORS study, which included 2,128 patients aged ≥70 years with a history of HF, is considered the representative study conducted in elderly HF patients. It showed that nebivolol reduced the composite of all-cause mortality and rehospitalization for HF but did not reduce all-cause mortality.[19]

Although observational studies do not provide as high a level of evidence as randomized clinical trials, they may yield real-world evidence.[20, 21] In previous observational studies, the efficacy of beta-blockers in elderly patients has been controversial. In the OPTIMIZE-HF registry, a beta-blocker was not associated with improved survival in patients aged ≥75 years.[20] Dobre et al. reported that the effect of beta-blockers decreased with increasing age, and was not associated with a reduced risk of cardiac death and readmission heart failure in patients aged ≥80 years.[22] Recently, in a subgroup of 237 elderly patients aged ≥80 years in the WET-HF registry, GDMT with beta-blockers and RAS inhibitors did not reduce the rates of cardiac death or HF readmission.[23] By contrast, the

present study showed that GDMT was associated with all-cause mortality in elderly (≥65 years) HFrEF patients. In addition, GDMT was effective in very elderly patients (≥80 years). Although the KorAHF and WET-HF studies have included East Asian patients with HF, there are several differences between the studies: KorAHF was larger, especially in terms of the number of patients aged ≥80 years (601 patients in KorAHF vs. 237 patients in WET-HF). As a result, our study was less prone to type II errors, such as false negative findings. While WET-HF defined HFrEF as LVEF <45%, the present study enrolled only patients with LVEF ≤40%, which corresponds to the contemporary definition of HFrEF.[11] To our knowledge, this is the first report to show the efficacy of GDMT in very elderly patients with HFrEF.

Prescription of GDMT in elderly patients

The prescription rate of GDMT was 50% in patients aged 65-69 years and 30% in those aged ≥85 years. The decline can be mainly attributed to a decreasing beta-blocker prescription rate. Hamaguchi et al. reported that the prescription rate of beta-blockers was 48% in HFrEF patients aged ≥80 years and that GDMT was applied only in 38% of these patients.[24] In this study, the beta-blocker prescription rate was 55% in all patients and 46% in patients aged ≥80 years. Beta-blockers in very elderly patients may be withheld due to the potential side effects and uncertainty with regard to the benefits for this high-risk group. In addition, 13% of patients had COPD which was associated with a 30% reduced prescription rate of beta-blockers (beta-blockers in COPD 46% vs. no COPD 56%, P <0.001) but not of RAS inhibitors. Accordingly, COPD was associated with a 33% reduced prescription rate of GDMT. This finding reflects the possible side effect of beta-blockers, as non-selective beta-blockers may cause bronchoconstriction in patients with COPD. However, given that multiple studies have shown that beta-1 selective beta-blockers can be used safely in patients with asthma and COPD, beta-1 selective drugs should be considered for patients with

COPD.[25, 26]

CKD is very common in patients with HF and is a well-known risk factor in HF patients.[24, 27] In this study, 53% of patients had CKD, and its prevalence increased with age. Since RAS inhibitors can initially aggravate renal function, many physicians withhold RAS inhibitors in patients with CKD. Accordingly, CKD was associated with a 54% reduced prescription rate of RAS inhibitors (RAS inhibitors in CKD: 68% vs. no CKD: 83%, P <0.001), resulting in a 24% reduced prescription rate of GDMT. By contrast, beta-blocker usage was not influenced by the presence of CKD. Current guidelines recommend the cautious use of RAS inhibitors in patients with HF and advanced CKD.[11] Our study supports this recommendation, since RAS inhibitor use was associated with a 34% reduced risk of all-cause mortality in patients with CKD.

Limitations

The present study has several limitations. First, owing to the observational nature of the study design, confounding factors may have influenced the study results, despite adjustment for significant covariates. Furthermore, there exists a possibility that unmeasured variables may have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairments, which are an important prognostic factor for elderly patients.[28] Third, we performed the IPTW analysis to mitigate the impact of compounding factors but there exists the possibility that variables included in the IPTW analysis had not been sufficiently categorized for producing balanced groups. Fourth, although the KorAHF registry was designed to enroll all hospitalized HF patients, there exists the possibility that some of the patients may not have been enrolled. Fourth, we did not consider the dosage when defining GDMT. Although there exists controversy on the relationship between drug dosage and outcomes, it should also be investigated in elderly patients.[29] Finally, we do not

know whether the patients actually took the prescribed drugs, as many patients had multiple comorbidities and polypharmacy is known to be associated with poor drug compliance.

CONCLUSIONS

Heart failure is common among the elderly, but elderly patients with HF receive less GDMT. The present study suggests that GDMT may be effective in elderly and very elderly patients with HFrEF and physicians should make an effort to prescribe GDMT to these high-risk patients.

Contributors: SWW, PJJ and CDJ: substantial contributions to the conception or design of the work, acquisition, analysis and interpretation of data. PHA, CHJ, LHY, KKH, YBS, KSM, BSH, JES, KJJ, CMC, CSC and OBH: substantial contributions to the conception or design of the work and acquisition of data.

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Conflict of Interest Disclosures: The authors declare no conflict of interest

A data sharing statement: Data are housed at the Research of Korea Centers for Disease Control and Prevention and are not available at this time.

Ethics approval: The study protocol was approved by the ethics committee at each 10 tertiary university hospital in Korea.

Patient consent: Written informed consent was waived by the institutional review board at each 10 tertiary hospital in Korea.

REFERENCES

1 Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;6:606-19.

2 Cowie M, Wood D, Coats A, et al. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;20:421-8.

3 Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.

4 Youn J-C, Han S, Ryu K-H. Temporal trends of hospitalized patients with heart failure in Korea. *Korean Circ J* 2017;47:16-24.

5 Murad K, Goff Jr DC, Morgan TM, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. *JACC: Heart Failure* 2015;3:542-50.

6 Shah RU, Tsai V, Klein L, et al. Characteristics and Outcomes of Very Elderly Patients After First Hospitalization for Heart FailureClinical Perspective. *Circ Heart Fail* 2011;4:301-7.

7 Vidán MT, Blaya-Novakova V, Sánchez E, et al. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail* 2016;18:869-75.

8 Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997;157:99-104.

9 The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.

10 Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.

11 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200.

12 Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011;171:550-6.

13 Statistics Korea 2017. Available at: http://kostat.go.kr/portal/eng/pressReleases/11/1/index.board?bmode=download&bSeq=&aSeq=363974&ord=1

14 Hall MJ, Levant S, DeFrances CJ. Hospitalization for congestive heart failure: United States, 2000–2010. NCHS data brief. Available at: https://www.cdc.gov/nchs/data/databriefs/db108.pdf.

15 Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. *Eur J Heart Fail* 2014;16:700-8.

16 Lee SE, Lee H-Y, Cho H-J, et al. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean acute heart failure registry (KorAHF). *Korean Circ J* 2017;47:341-53.

17 Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.

18 Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;162:1682-8.

19 Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215-25.

20 Hernandez AF, Hammill BG, O'Connor CM, et al. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol* 2009;53:184-92.

21 Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation* 2010;122:585-96.

22 Dobre D, DeJongste MJ, Lucas C, et al. Effectiveness of β-blocker therapy in daily practice patients with advanced chronic heart failure; is there an effect-modification by age? *Br J Clin Pharmacol* 2007;63:356-64.

23 Akita K, Kohno T, Kohsaka S, et al. Current use of guideline-based medical therapy in elderly patients admitted with acute heart failure with reduced ejection fraction and its impact on event-free survival. *Int J Cardiol* 2017;235:162-8.

24 Hamaguchi S, Kinugawa S, Goto D, et al. Predictors of long-term adverse outcomes in elderly patients over 80 years hospitalized with heart failure. *Circ J* 2011;75:2403-10.

25 Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blocker use in patients with reversible airway disease. *Cochrane Database Syst Rev* 2002:CD002992.

26 Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective β-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715-25.

27 Komajda M, Hanon O, Hochadel M, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J*

2008;30:478-86.

28 Murad K, Goff DC, Morgan TM, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. *JACC: Heart Failure* 2015;3:542-50.

29 Turgeon RD, Kolber MR, Loewen P, et al. Higher versus lower doses of ACE inhibitors, angiotensin-2 receptor blockers and beta-blockers in heart failure with reduced ejection fraction: Systematic review and meta-analysis. *PLoS One* 2019;14:e0212907.

Figure legends

Figure 1. Study flow

EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction

Figure 2. Discharge medication profiles.

Prescription of beta-blockers, RAS inhibitors (A), and GDMT (B) in elderly patients with HFrEF according to age group.

RAS, renin-angiotensin system; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction

Figure 3. Three-year cumulative survival according to the treatment groups.

Patients receiving GDMT had lower mortality among all patients (A), patients aged between 65-79 years (B), and patients aged 80 years or older (C).

BB, beta-blocker; RASi, renin-angiotensin system inhibitor; GDMT, guideline-directed medical therapy

Figure 4. Subgroup analysis.

The hazard ratios (HRs) of medical therapy (i.e. GDMT, beta-blockers only, RAS inhibitors only) compared with no GDMT for all-cause mortality in subgroups were calculated using multivariate Cox regression analysis. The forest plots demonstrate the HRs of GDMT vs. no

GDMT from the results. There was no significant interaction between the treatment strategy (no GDMT, beta-blockers only, RAS inhibitors only and GDMT) and diverse subgroups, and GDMT was associated with lower morality across subgroups.

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; GDMT, guideline-directed medical therapy

*The P for interaction indicates whether treatment strategy interacts with the subgrouping variable. It was calculated from multivariable Cox regression analysis which included the variables for treatment strategy, subgrouping variables, interaction term of the treatment strategy-by-subgrouping variable, sex, hypertension, diabetes, atrial fibrillation, and prescription of mineralocorticoid receptor antagonists, digitalis and diuretics.

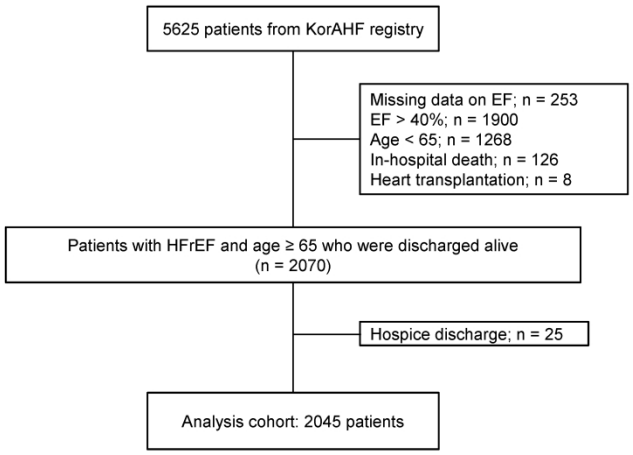
Supplementary figure 1. Cumulative survival according to beta-blocker and RAS inhibitor prescription pattern

BB, beta-blocker; RASi, renin-angiotensin system inhibitor

Supplementary figure 2. Three-year cumulative survival according to treatment group in an inverse probability treatment weight adjusted population

Patients receiving GDMT had lower mortality among all patients (A), patients aged between 65-79 years (B), and patients aged 80 years or older (C).

BB, beta-blocker; RASi, renin-angiotensin system inhibitor; GDMT, guideline-directed medical therapy



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EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction

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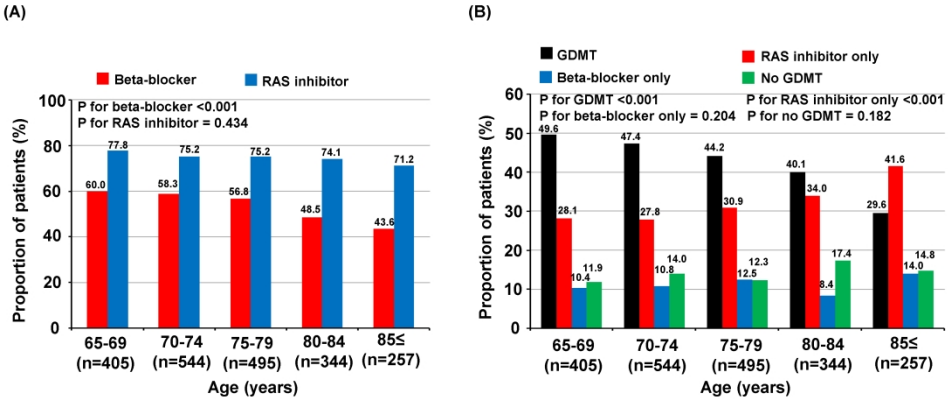

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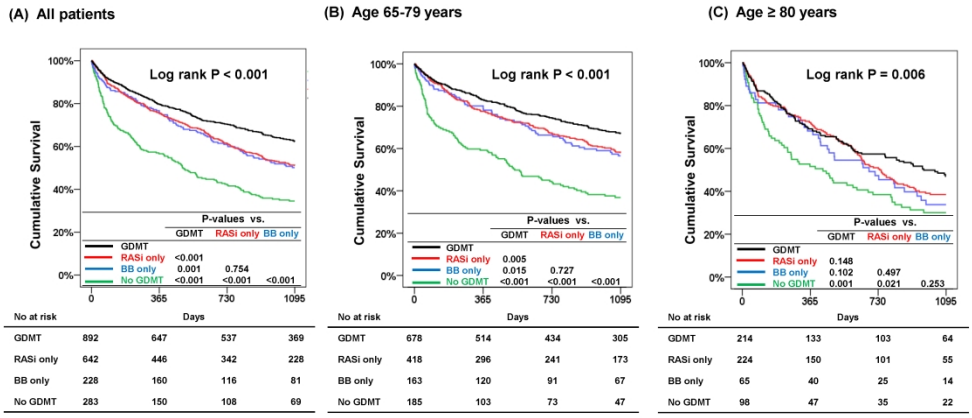

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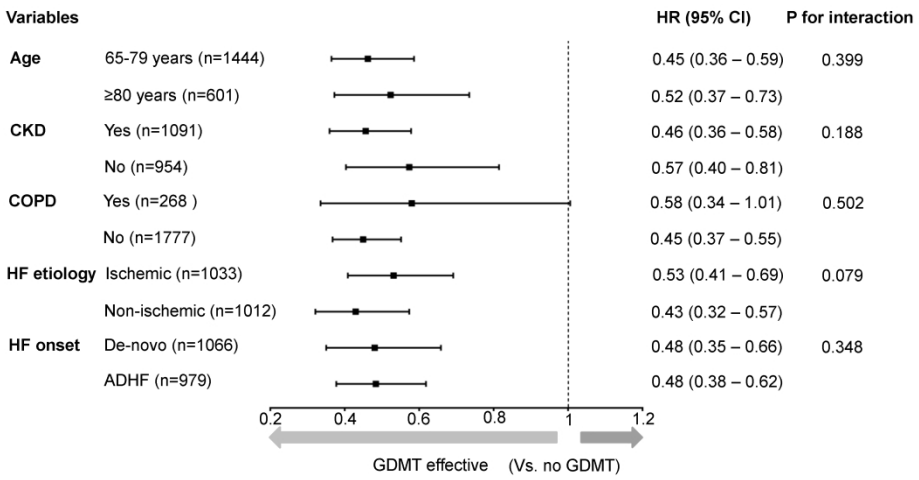

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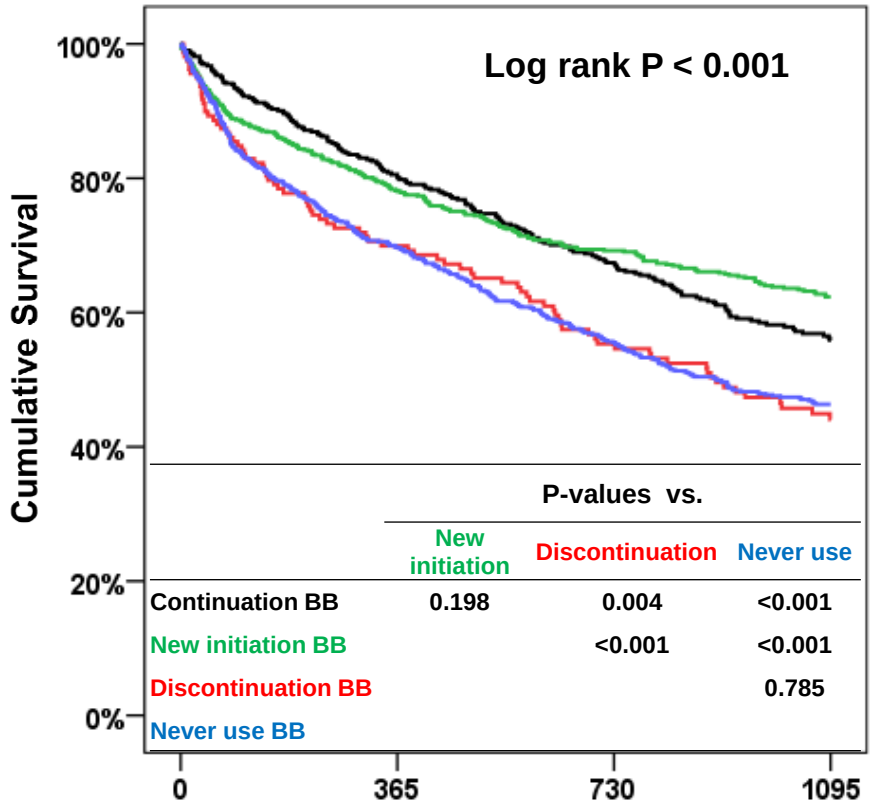
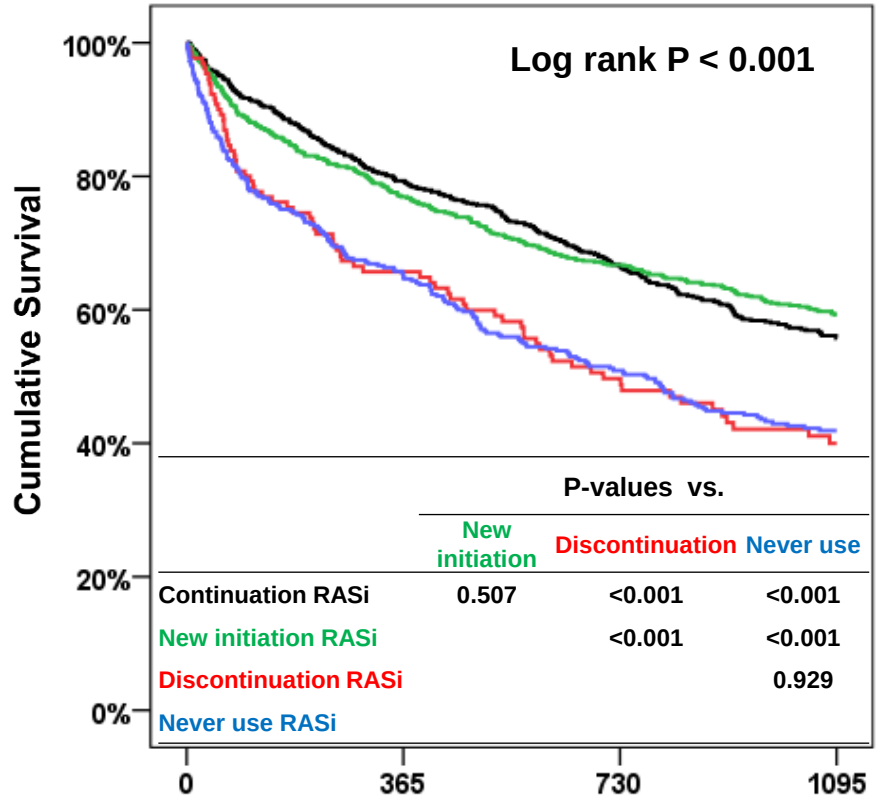
(A) Cumulative survival according to beta-blocker prescription pattern



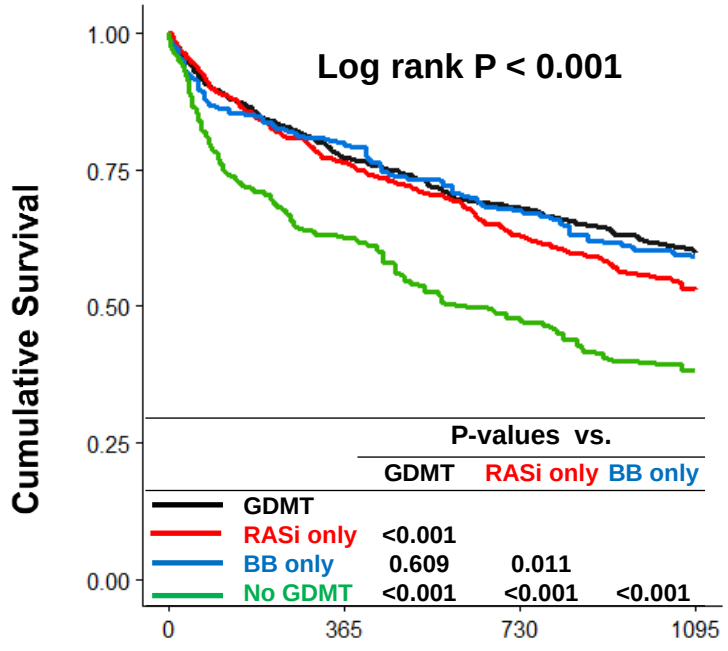
No at risk				
Continuation BB	433	323	251	161
New initiation BB	687	483	402	289
Discontinuation BB	161	102	77	51
Never use BB	764	494	373	246

(B) Cumulative survival according to RAS inhibitor prescription pattern



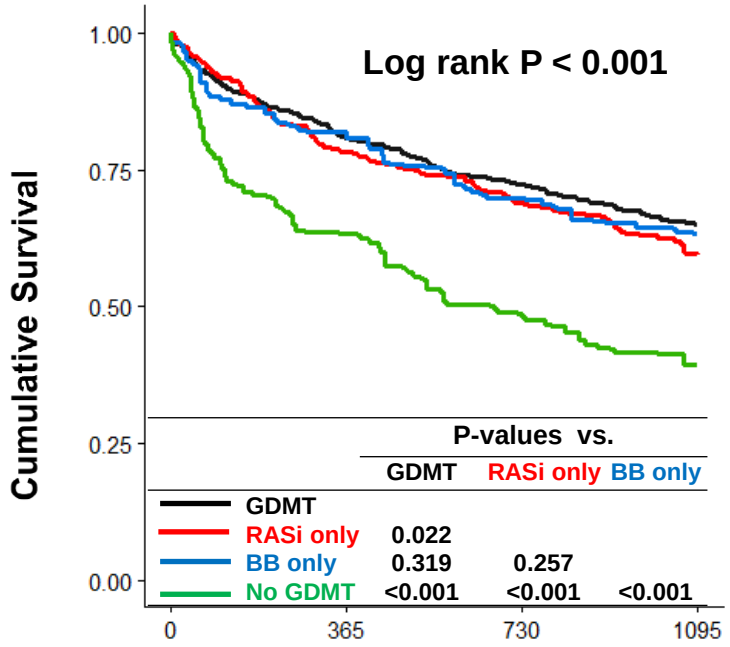
No at risk				
Continuation RASi	715	528	418	278
New initiation RASi	819	565	461	319
Discontinuation RASi	131	80	55	36
Never use RASi	380	230	169	114

(A) All patients



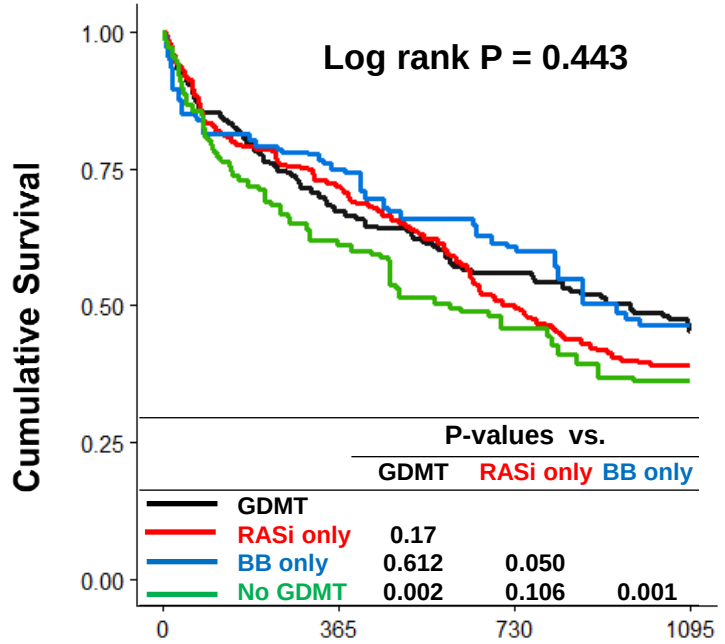
No at risk	Days			
GDMT	1813	1279	1064	729
RASi only	1709	1193	926	633
BB only	1298	936	736	541
No GDMT	1132	654	489	308

(B) Age 65-79 years



No at risk	Days			
GDMT	1326	986	836	586
RASi only	1169	836	689	500
BB only	956	722	583	459
No GDMT	726	423	315	197

(C) Age ≥ 80 years



No at risk	Days			
GDMT	487	293	228	143
RASi only	539	357	237	133
BB only	342	214	154	82
No GDMT	407	231	173	111

Supplementary table 1. Baseline characteristics of patients according to continue or discontinued of beta-blocker during index admission

Variable	Continue beta-blocker (n=433)	Discontinue beta-blocker (n=161)	P value
Age, years	75.3 ± 6.6	76.4 ± 6.9	0.08
Men, n (%)	233 (53.8)	92 (57.1)	0.516
BMI, kg/m^2	23.5 ± 3.6	22.4 ± 3.2	<0.001
Medical history			
Previous heart failure, n (%)	332 (76.7)	116 (72.0)	0.284
Hypertension, n (%)	336 (77.6)	117 (72.7)	0.233
Diabetes, n (%)	213 (49.2)	64 (39.8)	0.042
Atrial fibrillation, n (%)	151 (34.9)	46 (28.6)	0.170
COPD, n (%)	48 (11.1)	21 (13.0)	0.564
Myocardial infarction, n (%)	165 (38.1)	56 (34.8)	0.504
Medication on discharge			
RAS inhibitor, n (%)	316 (73.0)	107 (66.5)	0.127
MRA, n (%)	213 (49.2)	74 (46.0)	0.518
Loop diuretics, n (%)	71 (16.4)	49 (30.4)	<0.001
Digoxin, n (%)	300 (69.3)	116 (72.0)	0.546
Systolic BP on admission, mm Hg	135.5 ± 28.7	131.3 ± 29.0	0.116
Diastolic BP on admission, mm Hg	81.1 ± 18.0	76.8 ± 18.1	0.010
Heart rate on admission, beats/min	89.7 ± 23.8	92.9 ± 27.6	0.172
NYHA functional class III or IV on admission	380 (87.8)	153 (95.0)	0.009

Laboratory data on admission			
eGFR, ml/min/1.73m^2	51.2 ± 25.1	46.7 ± 23.4	0.051
Sodium, mEq/L	137.7 ± 4.2	137.4 ± 5.0	0.454
Potassium, mEq/L	4.5 ± 0.7	4.5 ± 0.7	0.242
BNP, pg/mL	1593.1 ± 1306.1	1926.5 ± 1515.7	0.150
NT-pro-BNP, pg/mL	11545.9 ± 10872.8	14650.1 ± 12629.1	0.036
LVEF, %	29.1 ± 6.9	28.6 ± 7.8	0.483

BMI, body mass index; COPD, chronic obstructive pulmonary disease; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction

Supplementary table 2. Baseline characteristics of patients according to continue or discontinued of RAS inhibitor during index admission

Variable	Continue RAS inhibitor	Discontinue RAS inhibitor	P value
Age, years	75.8 ± 6.7	76.3 ± 6.5	0.481
Men, n (%)	400 (55.9)	70 (53.4)	0.633
BMI, kg/m^2	23.1 ± 3.5	22.9 ± 3.3	0.562
Medical history			
Previous heart failure, n (%)	512 (71.6)	92 (70.2)	0.753
Hypertension, n (%)	543 (75.9)	102 (77.9)	0.738
Diabetes, n (%)	343 (48.0)	70 (53.4)	0.256
Atrial fibrillation, n (%)	235 (32.9)	34 (26.0)	0.127
COPD, n (%)	95 (13.3)	19 (14.5)	0.678
Myocardial infarction, n (%)	220 (30.8)	52 (39.7)	0.053
Medication on discharge			
Beta-blocker, n (%)	380 (53.1)	58 (44.3)	0.071
MRA, n (%)	348 (48.7)	49 (37.4)	0.022
Loop diuretics, n (%)	159 (22.2)	44 (33.6)	0.007
Digoxin, n (%)	483 (67.6)	99 (75.6)	0.081
Systolic BP on admission, mm Hg	134.7 ± 28.6	127.1 ± 31.3	0.006
Diastolic BP on admission, mm Hg	79.8 ± 16.8	73.1 ± 17.3	<0.001
Heart rate on admission, beats/min	91.4 ± 24.6	96.9 ± 22.5	0.018
NYHA functional class III or IV on admission	623 (87.1%)	117 (89.3)	0.567

Laboratory data on admission			
eGFR, ml/min/1.73m^2	53.3 ± 23.6	39.5 ± 20.8	<0.001
Sodium, mEq/L	137.6 ± 4.9	136.8 ± 4.5	0.062
Potassium, mEq/L	4.4 ± 0.7	4.7 ± 0.8	0.001
BNP, pg/mL	1670.8 ± 1502.2	1920.8 ± 2017.2	0.355
NT-pro-BNP, pg/mL	10966.0 ± 10806.0	14939.1 ± 12170.9	0.007
LVEF, %	28.6 ± 7.5	28.6 ± 7.4	0.929

BMI, body mass index; COPD, chronic obstructive pulmonary disease; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction

Online supplementary table 3. Patients characteristics in inverse probability treatment weight adjusted population

	GDMT (n=1813)	Beta blocker only (n=1298)	RAS inhibitor only (n=1709)	No GDMT (n=1132)	Std. Diff.	P value
Age, years	75.5 ± 6.7	75.6 ± 6.8	76.1 ± 7.0	76.7 ± 6.8	0.17	0.07
Men, n (%)	964 (53.2)	757 (58.3)	963 (56.3)	622 (54.9)	0.10	0.26
BMI, kg/m^2	22.7 ± 3.4	22.6 ± 3.5	22.4 ± 3.3	22.4 ± 3.2	0.08	0.34
Medical history						
Previous heart failure, n (%)	905 (49.9)	687 (52.9)	901 (52.8)	656 (58.0)	0.16	0.05
Hypertension, n (%)	1233 (68.0)	870 (67.0)	1108 (64.9)	732 (64.6)	0.07	0.24
Diabetes, n (%)	774 (42.7)	481 (37.0)	650 (38.0)	472 (41.7)	0.11	0.09
Chronic kidney disease, n (%)	933 (51.5)	769 (59.2)	877 (51.3)	674 (59.6)	0.16	0.05
Atrial fibrillation, n (%)	566 (31.2)	448 (34.5)	515 (30.2)	380 (33.6)	0.09	0.32
COPD, n (%)	211 (11.6)	168 (12.9)	247 (14.5)	162 (14.3)	0.08	0.12
Myocardial infarction, n (%)	395 (21.8)	330 (25.4)	384 (22.5)	292 (25.8)	0.10	0.34
Cause of heart failure						
Ischemic, n (%)	920 (50.8)	752 (57.9)	837 (49.0)	615 (54.4)	0.18	0.06
Dilated, n (%)	434 (23.9)	250 (19.2)	387 (22.6)	213 (18.8)	0.12	0.15
Medication on admission						
Beta-blocker, n (%)	561 (31.0)	442 (34.0)	439 (25.7)	259 (22.9)	0.24	0.03
RAS inhibitor, n (%)	727 (40.1)	459 (35.4)	762 (44.6)	409 (36.2)	0.19	0.06
MRA, n (%)	301 (16.6)	277 (21.3)	296 (17.3)	224 (19.8)	0.12	0.15
Medication on discharge						
MRA, n (%)	936 (51.6)	643 (49.6)	839 (49.1)	486 (42.9)	0.17	0.03

Loop diuretics, n (%)	1427 (78.7)	977 (75.2)	1305 (76.4)	794 (70.2)	0.21	0.01
Digoxin, n (%)	547 (30.2)	358 (27.6)	488 (28.5)	361 (31.9)	0.09	0.39
Systolic BP on discharge, mm Hg	114.7 ± 16.8	113.8 ± 16.8	115.0 ± 16.5	112.5 ± 15.4	0.15	0.39
Diastolic BP on discharge, mm Hg	66.1 ± 10.8	66.1 ± 10.1	66.1 ± 10.9	65.0 ± 9.9	0.10	0.20
Heart rate on discharge, beats/min	76.3 ± 13.6	77.8 ± 12.3	77.2 ± 14.2	77.4 ± 13.5	0.10	0.21
NYHA functional class on discharge					0.10	0.23
I or II, n (%)	1598 (88.1)	1148 (88.4)	1496 (87.5)	1028 (90.8)		
III or IV, n (%)	215 (11.9)	150 (11.6)	213 (12.5)	105 (9.2)		
Echocardiographic parameters						
LVEDD, mm	60.2 ± 8.8	59.6 ± 8.7	60.3 ± 8.7	59.3 ± 8.7	0.11	0.40
LVESD, mm	50.3 ± 9.3	49.9 ± 9.3	50.0 ± 9.5	49.4 ± 9.5	0.09	0.26
LVEF, %	28.7 ± 7.3	28.2 ± 7.7	28.9 ± 7.3	29.0 ± 7.2	0.11	0.57
Laboratory data on admission						
Hemoglobin, g/dL	12.3 ± 2.0	12.3 ± 1.9	12.3 ± 2.1	12.1 ± 2.1	0.08	0.49
eGFR, ml/min/1.73m^2	61.6 ± 32.6	58.6 ± 30.1	62.3 ± 30.1	56.5 ± 28.1	0.18	0.07
Sodium, mEq/L	137.8 ± 4.5	138.0 ± 4.2	137.6 ± 4.5	137.4 ± 4.5	0.11	0.78
Potassium, mEq/L	4.4 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.7	0.14	0.46
BNP, pg/mL	1692.2 ± 1528.3	1703.7 ± 1403.4	1731.0 ± 1389.8	1732.8 ± 1858.4	0.03	0.81
NT-pro-BNP, pg/mL	11650.7 ± 11236.4	10810.0 ± 10121.4	10549.1 ± 10321.2	12307.0 ± 10979.5	0.16	0.10

GDMT, guideline-directed medical therapy; RAS, renin angiotensin system; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; BNP, brain natriuretic peptide

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12,13,8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16, 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15, 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study

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Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study

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ABSTRACT

Objectives and design

Guideline-directed medical therapy (GDMT) with renin-angiotensin system (RAS) inhibitors and beta-blockers has improved survival in patients with heart failure with reduced ejection fraction (HFrEF). As clinical trials usually do not include very old patients, it is unknown whether the results from clinical trials are applicable to elderly patients with HF. This study was performed to investigate the clinical characteristics and treatment strategies for elderly patients with HFrEF in a large-prospective cohort.

Setting

The KorAHF registry consecutively enrolled 5,625 patients hospitalized for acute HF from 10 tertiary university hospitals in Korea.

Participants

In this study, 2,045 patients with HFrEF who were aged 65 years or older were included from the KorAHF registry.

Primary outcome measurement

All-cause mortality data were obtained from medical records, national insurance data, or national death records.

Results

Both beta-blockers and RAS inhibitors were used in 892 (43.8%) patients (GDMT group), beta-blockers only in 228 (11.1%) patients, RAS inhibitors only in 642 (31.5%) patients, and neither beta-blockers nor RAS inhibitors in 283 (13.6%) patients (no GDMT group). With increasing age, the GDMT rate decreased, which was mainly attributed to the decreased

prescription of beta-blockers. In multivariate analysis, GDMT was associated with a 53% reduced risk of all-cause mortality (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.39-0.57) compared with no GDMT. Use of beta-blockers only (HR, 0.57, 95% CI 0.45-0.73) and RAS inhibitors only (HR 0.58, 95% CI 0.48-0.71) was also associated with reduced risk. In a subgroup of very elderly patients (aged ≥80 years), the GDMT group had the lowest mortality.

Conclusions

GDMT was associated with reduced 3-year all-cause mortality in elderly and very elderly HFrEF patients.

Trial registration

ClinicalTrial.gov NCT01389843

Keywords: heart failure with reduced ejection fraction

Strengths and limitations of this study

- This was a large prospective cohort study that included patients with heart failure with reduced ejection fraction who were aged 65 years or older.
- We obtained all participants' mortality data from medical or national death records.
- The registry could not capture all comorbidities including functional or cognitive impairments, an important prognostic factor for elderly patients.

INTRODUCTION

Heart failure (HF) is associated with significant morbidity, mortality, and healthcare burdens.[1] Since the prevalence of HF increases with age, the incidence of elderly patients with HF has been continuously increasing as the aging population increases.[2-4] Elderly patients with HF have worsened outcomes: they have more comorbidities, functional and cognitive impairments, and polypharmacy.[5-7] In addition, they are at high risk of re-hospitalization for HF after hospital discharge.[8]

Large clinical trials have shown that guideline-directed medical therapy (GDMT) with renin-angiotensin system (RAS) inhibitors and beta-blockers improved survival in patients with heart failure with reduced ejection fraction (HFrEF).[9-11] However, many elderly patients with HF have been excluded from randomized clinical studies due to age, comorbidities, or functional or cognitive impairments, among others.[12] Accordingly, it is unknown whether the results from clinical trials can be directly applied to elderly patients with HF.

Korea is one of the most rapidly aging societies. In 2018, it has become an "aged society" and will be a "super-aged society" by 2026.[13] In 2017, Korea's proportion of individuals aged ≥65 years was 13.8%. Considering that 70% of hospitalizations for HF occurred in patients aged ≥65 years, a better understating of these high-risk patients is critical for proper management.[14] In this study, we investigated the clinical characteristics and treatment strategies for elderly patients with HFrEF in a large-prospective cohort.

METHODS

Participants and cohort recruitment

The Korean Acute Heart Failure (KorAHF) registry is a prospective multicenter registry designed to reflect the real-world clinical data of Korean patients admitted for acute HF. The study design and primary results of the registry have been published elsewhere [ClinicalTrial.gov NCT01389843].[15, 16] Patients hospitalized for acute HF from 10 tertiary university hospitals in Korea were consecutively enrolled from March 2011 to February 2014. Briefly, patients with signs or symptoms of HF and either lung congestion or objective findings of left ventricle systolic dysfunction or structural heart disease were eligible for enrollment in this registry. To minimize selection bias, we tried to enroll all hospitalized patients with acute HF at each hospital. Patients' baseline characteristics, clinical presentation, underlying diseases, vital signs, laboratory tests, treatments, and outcomes were recorded at admission, and discharge, and during follow-up (30-day, 90-day, 180-day, and 1- to 3-year annually). The mortality data for patients who were lost to follow-up were obtained from the national insurance data or national death records.

In this study, we included patients with HFrEF who were aged 65 years or older. For patient selection, we serially excluded patients if any of the exclusion criteria was met. The study protocol was approved by the ethics committee at each hospital. Written informed consent was waived by the institutional review board. The study complied with the Declaration of Helsinki.

Patients and public involvement

Patients were not involved in the conception, design or interpretation of this study. The results of this study will be disseminated to patients and healthcare providers through oral presentations and social media.

Study variables and definition

HFrEF was defined as a left ventricular ejection fraction (LVEF) of ≤40%. The patients were classified into groups according to the medication prescribed at discharge: the GDMT group (patients who received both beta-blockers and RAS inhibitors), beta-blockers only group, RAS inhibitors only group, and no GDMT group (no beta-blockers or RAS inhibitors). Chronic kidney disease (CKD) was defined as a glomerular filtration rate of <60 mL/min/1.73 m^2, and chronic obstructive pulmonary disease (COPD) was defined as a self-reported or physician-confirmed diagnosis of chronic bronchitis, emphysema, or both. The primary outcome was 3-year post-discharge all-cause mortality from index admission.

Statistical analysis

Continuous variables were presented as a mean ± standard deviation, whereas categorical variables were presented as counts and their percentages. Differences among continuous variables were analyzed using a one-way ANOVA and those among categorical variables using the χ^2 test. Logistic regression analysis was used to determine the predictors of GDMT prescription. We converted the odds ratios from logistic regression analysis into risk ratios because of the high prevalence of GDMT.[17] The cumulative event rate was assessed using the Kaplan-Meier method with log-rank analysis. Multivariable Cox regression analysis was used to evaluate the adjusted relative risk of the variables. Multivariable models including age, sex, hypertension, diabetes, previous heart failure history, atrial fibrillation, CKD, cause of heart failure, COPD, treatment strategy (no GDMT, beta-blockers only, RAS inhibitors only and GDMT), and prescription of mineralocorticoid receptor antagonists (MRA), digitalis, and diuretics were chosen according to their clinical relevance and based on the results of previous trials.[3, 11] Furthermore, we performed a pre-specified subgroup analysis including age, CKD, COPD, HF etiology, and HF onset, and produced forest plots of the hazard ratio of

medical therapy (i.e. GDMT, beta-blockers only, RAS inhibitors only) compared with no GDMT. We evaluated whether there was an interaction between treatment strategy and the subgroups on all-cause mortality. For the calculation of P for interaction, Cox regression models were used which included the indicator variables for treatment strategy, subgrouping variables, and interaction term of the treatment strategy-by-subgrouping variable of interest (age, CKD, COPD, HF etiology or HF onset), as independent variables. The following covariates were also included in the interaction models: sex, hypertension, diabetes, atrial fibrillation, and prescription of MRA, digitalis and diuretics. To mitigate the impact of potential confounding factors in the registry data, we additionally performed the inverse probability of treatment weighting (IPTW). The inferences regarding the rate of all-cause death were conducted with robust standard errors after examining covariate balances among treatment groups. We used the "Twang" package for R programming for IPTW analysis. Success of IPTW analyses was assessed by calculating the standardized differences in baseline characteristics. All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA) and R v3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria). A P value <0.05 was considered statistically significant.

RESULTS

The KorAHF registry includes 5,625 acute HF patients. Of these, we excluded patients with missing LVEF (n=253), those with LVEF >40% (n=1900), <65 years in age (n=1268), in-hospital death (n=126), heart transplantation (n=8), and those who were hopelessly discharged (n=25), leaving a total of 2,045 patients available for the final analysis (**figure 1**).

Overall, the mean age was 75.9 years, 54.2% were male, 66.7% had hypertension, and 42.0% had diabetes mellitus. In addition, the mean LVEF was 28.7 ± 7.4%, and the most common cause of HFrEF was ischemic cardiomyopathy (50.5%).

Medication prescription pattern according to patients' characteristics

The beta-blocker prescription rate at discharge was 54.8% in all patients and that of RAS inhibitors was 75.0%. With increasing age, the beta-blocker prescription rate decreased (P for trend <0.001), while that of RAS inhibitors remained unchanged (**figure 2A**).

The baseline characteristics of the study population are summarized in **table 1**. Overall, both beta-blockers and RAS inhibitors were used in 892 (43.8%) patients (GDMT group), beta-blockers only in 228 (11.1%) patients, RAS inhibitors only in 642 (31.5%) patients, and neither beta-blockers nor RAS inhibitors in 283 (13.6%) patients (no GDMT group). The beta-blocker prescription rate was lower in patients with COPD (COPD: 45.5%, vs. no COPD: 56.2%, P = 0.01), whereas the prescription of RAS inhibitors was lower in patients with CKD (CKD: 68.7%, vs. no CKD: 82.2%, P <0.001).

Table 1. Baseline characteristics of patients according to treatment strategy

	GDMT (n=892)	Beta blocker only (n=228)	RAS inhibitor only (n=642)	No GDMT (n=283)	P value
Age, years	75.0 ± 6.5	76.2 ± 7.2	76.7 ± 7.1	76.7 ± 6.7	<0.001
Men, n (%)	472 (52.9)	115 (50.7)	369 (57.5)	149 (54.0)	0.211
BMI, kg/m^2	23.0 ± 3.5	22.6 ± 3.5	22.4 ± 3.4	21.9 ± 3.0	<0.001
Medical history					
Previous heart failure, n (%)	414 (46.4)	136 (59.6)	361 (56.2)	167 (59.0)	<0.001
Hypertension, n (%)	609 (68.3)	162 (71.4)	417 (65.0)	174 (63.0)	0.124
Diabetes, n (%)	399 (44.7)	97 (42.7)	242 (37.7)	119 (43.1)	0.050
Chronic kidney disease, n (%)	430 (48.2)	150 (66.1)	320 (49.8)	186 (67.4)	<0.001
Atrial fibrillation, n (%)	281 (31.5)	89 (39.2)	193 (30.1)	81 (29.3)	0.059
COPD, n (%)	92 (10.3)	30 (13.2)	110 (17.1)	36 (13.0)	0.002
Myocardial infarction, n (%)	194 (21.8)	61 (26.9)	146 (22.7)	65 (23.6)	0.433
Cause of heart failure					
Ischemic, n (%)	443 (49.7)	129 (56.8)	311 (48.4)	146 (52.9)	0.132
Dilated, n (%)	222 (24.9)	36 (15.9)	147 (22.9)	50 (18.1)	0.008
Medication on admission					
Beta-blocker, n (%)	316 (35.4)	117 (51.5)	107 (16.7)	53 (19.2)	<0.001
RAS inhibitor, n (%)	380 (42.6)	58 (25.6)	335 (52.2)	72 (26.1)	<0.001
MRA, n (%)	143 (16.0)	47 (20.7)	122 (19.0)	60 (21.7)	0.096
Medication on discharge					
MRA, n (%)	487 (54.6)	95 (41.9)	316 (49.2)	120 (43.5)	<0.001

Loop diuretics, n (%)	714 (80.0)	174 (76.7)	493 (76.8)	189 (68.5)	0.001
Digoxin, n (%)	269 (30.2)	63 (27.8)	193 (30.1)	86 (31.2)	0.865
Systolic BP on discharge, mm Hg	115.0 ± 17.0	115.7 ± 16.4	114.2 ± 16.5	113.0 ± 16.6	0.067
Diastolic BP on discharge, mm Hg	66.1 ± 10.7	67.5 ± 10.7	65.6 ± 11.2	65.2 ± 10.0	0.026
Heart rate on discharge, beats/min	74.6 ± 12.9	78.1 ± 14.4	77.8 ± 14.3	80.6 ± 13.7	<0.001
NYHA functional class on discharge					0.154
I or II, n (%)	792 (88.8)	205 (90.3)	566 (88.2)	250 (90.6)	
III or IV, n (%)	100 (11.2)	22 (9.7)	76 (11.8)	45 (9.4)	
Echocardiographic parameters					
LVEDD, mm	60.3 ± 8.7	57.6 ± 9.6	61.2 ± 8.9	58.8 ± 9.0	<0.001
LVESD, mm	50.3 ± 9.3	47.6 ± 10.0	51.1 ± 9.6	49.1 ± 9.8	<0.001
LVEF, %	28.8 ± 7.3	28.8 ± 7.5	28.5 ± 7.4	28.6 ± 7.7	0.864
Laboratory data on admission					
Hemoglobin, g/dL	12.4 ± 2.0	11.9 ± 2.2	12.2 ± 2.1	11.7 ± 2.2	<0.001
eGFR, ml/min/1.73m^2	63.8 ± 33.8	52.6 ± 32.3	63.2 ± 30.4	53.2 ± 30.1	<0.001
Sodium, mEq/L	138.0 ± 4.4	137.6 ± 4.4	137.3 ± 5.1	137.0 ± 4.6	0.006
Potassium, mEq/L	4.3 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.8	0.001
BNP, pg/mL	1592.9 ± 1489.8	1849.7 ± 1492.0	1724.8 ± 1381.7	1937.1 ± 1920.8	0.223
NT-pro-BNP, pg/mL	10941.1 ± 11006.9	11535.8 ± 10587.7	9978.0 ± 9484.0	14728.7 ± 12514.7	<0.001

GDMT, guideline-directed medical therapy; RAS, renin angiotensin system; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; BNP, brain natriuretic peptide

Five hundred ninety-four patients (29.0%) were already taking beta-blockers before index admission; among them, 27.1% discontinued beta-blockers during index admission and had lower diastolic blood pressure and higher NYHA functional class and NT-pro-BNP levels on admission compared to those who continued beta-blockers (online **supplementary table 1**). When classifying patients according to beta-blocker use [continuation (beta-blocker use before and after admission), new initiation (new beta-blocker prescription during index admission), discontinuation (beta-blocker use before, but discontinuation during index admission), and never use groups (no beta blocker before and after index admission)], there was no difference in survival between patient discontinuation and the never use groups, as well as between those in continuation and new initiation groups (online **supplementary figure 1)**. Regarding RAS inhibitors, 846 patients (41.4%) were already taking RAS inhibitors before index admission. Among them, 15.5% discontinued RAS inhibitors during index admission and had lower eGFR levels and systolic and diastolic blood pressure, and higher NYHA functional class, potassium, and NT-pro-BNP levels on admission compared to those who continued RAS inhibitors (online **supplementary table 2**). When classifying the patients according to RAS inhibitor usage patterns, patients who received RAS inhibitors at discharge had better outcomes regardless of previous use than those who did not receive RAS inhibitors (online **supplementary figure 1).** With increasing age, the proportion of GDMT prescriptions decreased, while that of RAS inhibitors only increased (**figure 2B**). The predictors of GDMT prescription compared to any of the other three treatment groups included age 65-79 years, hypertension, diabetes, *de novo* onset of heart failure, and concomitant MRA prescription (**table 2**). Underlying COPD, CKD, and concomitant use of loop diuretics were inversely associated with the prescription of GDMT.

Table 2. Predictors of prescription of guideline-directed medical therapy compared to any of the other three treatment groups

Variable	Risk ratio	95% CI	P value
Age 65-79 (vs. age ≥80 years)	1.28	1.14 – 1.43	<0.001
Male	0.94	0.85 – 1.04	0.240
Hypertension	1.13	1.01 – 1.25	0.036
Diabetes	1.14	1.03 – 1.26	0.014
De novo heart failure (vs. previous heart failure)	1.28	1.16 – 1.40	<0.001
Atrial fibrillation	1.01	0.89 – 1.13	0.911
Chronic kidney disease	0.86	0.77 – 0.96	0.004
Ischemic CMP (vs. non-ischemic)	0.97	0.86 – 1.07	0.546
COPD	0.79	0.65 – 0.93	0.004
Discharge MRA	1.16	1.05 – 1.28	0.007
Discharge digoxin	0.97	0.86 – 1.09	0.634
Discharge loop diuretics	0.84	0.72 – 0.98	0.018

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist

Clinical outcomes

The median follow-up duration was 833 days (interquartile range: 240.5 to 1095 days), and 866 (42.3%) patients had died at 3 years. In the Kaplan-Meier survival analysis, patients in the GDMT group had the lowest mortality, whereas those in the no GDMT group had the worst outcomes. Interestingly, there seemed to be no difference in mortality between the beta-blockers only and RAS inhibitors only groups (**figure 3**). Upon further stratification of

the patients according to age above or below 80 years, the GDMT group had the lowest mortality in patients aged above and below 80 years, consistently. In IPTW adjusted population patients in the GDMT group had lower mortality than those in the no GDMT group among the overall patients, patients aged between 65-69 years, and patients aged 80 years or older (online **supplementary table 3,** online **supplementary figure 2**). In the Cox model after adjustment for significant covariates, GDMT was associated with a 53% reduced risk of all-cause mortality [hazard ratio (HR): 0.47, 95% confidence interval (CI): 0.39-0.57, P <0.001] compared to no GDMT. The beta-blockers (HR, 0.57, 95% CI 0.45-0.73, P <0.001) or RAS inhibitors (HR 0.58, 95% CI 0.48-0.71, P<0.001) only groups were also associated with reduced risk (**table 3**).

Subgroup analysis

We performed a pre-specified subgroup analysis according to age (65-79 years vs. ≥80 years), CKD, COPD, etiology (ischemic vs. non-ischemic), and HF onset (*de novo* HF vs. acute decompensation of chronic HF). There was no significant interaction between medical therapy and any subgroup (**figure 4**).

Table 3. Multivariable Cox regression analysis for all-cause mortality

Variable	Hazard ratio	95% CI	P value
Age ≥80 years (vs. age 65-79)	1.60	1.39 – 1.84	<0.001
Male	1.16	1.01 – 1.33	0.039
Hypertension	1.07	0.92 – 1.24	0.392
Diabetes	1.13	0.99 – 1.31	0.080
Previous heart failure (vs. de novo heart failure)	1.39	1.20 – 1.60	<0.001
Atrial fibrillation	0.90	0.77 – 1.07	0.226
Chronic kidney disease	1.50	1.30 – 1.74	<0.001
Ischemic CMP (vs. non-ischemic)	1.29	1.11 – 1.49	<0.001
COPD	1.27	1.04 – 1.53	0.016
Discharge MRA	1.05	0.91 – 1.21	0.499
Discharge digoxin	0.99	0.84 – 1.16	0.885
Discharge loop diuretics	0.90	0.76 – 1.06	0.219
Treatment strategy (vs. no GDMT)			
Beta-blocker only	0.57	0.45 – 0.73	<0.001
RAS inhibitor only	0.58	0.48 – 0.71	<0.001
GDMT	0.47	0.39 – 0.57	<0.001

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; RAS, renin angiotensin system; GDMT, guideline-directed medical therapy

DISCUSSION

The present nationwide multi-center prospective cohort study showed: 1) GDMT was associated with reduced all-cause mortality in elderly patients with HFrEF; 2) prescription of beta-blockers or RAS inhibitors only was also associated with reduced all-cause mortality compared with no GDMT; and 3) the effect of GDMT also appeared to be effective for reducing all-cause mortality in very elderly patients (age ≥80 years).

GDMT and outcomes in elderly HF patients

Large clinical trials have shown the efficacy of GDMT in patients with HFrEF.[11] However, the patients enrolled in such clinical trials were younger and had fewer comorbidities than real-world elderly patients.[18] Moreover, data from clinical trials supporting the use of GDMT in elderly patients are scarce. The SENIORS study, which included 2,128 patients aged ≥70 years with a history of HF, is considered the representative study conducted in elderly HF patients. It showed that nebivolol reduced the composite of all-cause mortality and rehospitalization for HF but did not reduce all-cause mortality.[19]

Although observational studies do not provide as high a level of evidence as randomized clinical trials, they may yield real-world evidence.[20, 21] In previous observational studies, the efficacy of beta-blockers in elderly patients has been controversial. In the OPTIMIZE-HF registry, a beta-blocker was not associated with improved survival in patients aged ≥75 years.[20] Dobre et al. reported that the effect of beta-blockers decreased with increasing age, and was not associated with a reduced risk of cardiac death and readmission heart failure in patients aged ≥80 years.[22] Recently, in a subgroup of 237 elderly patients aged ≥80 years in the WET-HF registry, GDMT with beta-blockers and RAS inhibitors did not reduce the rates of cardiac death or HF readmission.[23] By contrast, the

present study showed that GDMT was associated with all-cause mortality in elderly (≥65 years) HFrEF patients. In addition, GDMT was effective in very elderly patients (≥80 years). Although the KorAHF and WET-HF studies have included East Asian patients with HF, there are several differences between the studies: KorAHF was larger, especially in terms of the number of patients aged ≥80 years (601 patients in KorAHF vs. 237 patients in WET-HF). As a result, our study was less prone to type II errors, such as false negative findings. While WET-HF defined HFrEF as LVEF <45%, the present study enrolled only patients with LVEF ≤40%, which corresponds to the contemporary definition of HFrEF.[11] To our knowledge, this is the first report to show the efficacy of GDMT in very elderly patients with HFrEF.

Prescription of GDMT in elderly patients

The prescription rate of GDMT was 50% in patients aged 65-69 years and 30% in those aged ≥85 years. The decline can be mainly attributed to a decreasing beta-blocker prescription rate. Hamaguchi et al. reported that the prescription rate of beta-blockers was 48% in HFrEF patients aged ≥80 years and that GDMT was applied only in 38% of these patients.[24] In this study, the beta-blocker prescription rate was 55% in all patients and 46% in patients aged ≥80 years. Beta-blockers in very elderly patients may be withheld due to the potential side effects and uncertainty with regard to the benefits for this high-risk group. In addition, 13% of patients had COPD which was associated with a 30% reduced prescription rate of beta-blockers (beta-blockers in COPD 46% vs. no COPD 56%, P <0.001) but not of RAS inhibitors. Accordingly, COPD was associated with a 33% reduced prescription rate of GDMT. This finding reflects the possible side effect of beta-blockers, as non-selective beta-blockers may cause bronchoconstriction in patients with COPD. However, given that multiple studies have shown that beta-1 selective beta-blockers can be used safely in patients with asthma and COPD, beta-1 selective drugs should be considered for patients with

COPD.[25, 26]

CKD is very common in patients with HF and is a well-known risk factor in HF patients.[24, 27] In this study, 53% of patients had CKD, and its prevalence increased with age. Since RAS inhibitors can initially aggravate renal function, many physicians withhold RAS inhibitors in patients with CKD. Accordingly, CKD was associated with a 54% reduced prescription rate of RAS inhibitors (RAS inhibitors in CKD: 68% vs. no CKD: 83%, P <0.001), resulting in a 24% reduced prescription rate of GDMT. By contrast, beta-blocker usage was not influenced by the presence of CKD. Current guidelines recommend the cautious use of RAS inhibitors in patients with HF and advanced CKD.[11] Our study supports this recommendation, since RAS inhibitor use was associated with a 34% reduced risk of all-cause mortality in patients with CKD.

Limitations

The present study has several limitations. First, owing to the observational nature of the study design, confounding factors may have influenced the study results, despite adjustment for significant covariates. Furthermore, there exists a possibility that unmeasured variables may have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairments, which are an important prognostic factor for elderly patients.[28] Third, we performed the IPTW analysis to mitigate the impact of compounding factors but there exists the possibility that variables included in the IPTW analysis had not been sufficiently categorized for producing balanced groups. Fourth, although the KorAHF registry was designed to enroll all hospitalized HF patients, there exists the possibility that some of the patients may not have been enrolled. Fourth, we did not consider the dosage when defining GDMT. Although there exists controversy on the relationship between drug dosage and outcomes, it should also be investigated in elderly patients.[29] Finally, we do not

know whether the patients actually took the prescribed drugs, as many patients had multiple comorbidities and polypharmacy is known to be associated with poor drug compliance.

CONCLUSIONS

Heart failure is common among the elderly, but elderly patients with HF receive less GDMT. The present study suggests that GDMT may be effective in elderly and very elderly patients with HFrEF and physicians should make an effort to prescribe GDMT to these high-risk patients.

Contributors: SWW, PJJ and CDJ: substantial contributions to the conception or design of the work, acquisition, analysis and interpretation of data. PHA, CHJ, LHY, KKH, YBS, KSM, BSH, JES, KJJ, CMC, CSC and OBH: substantial contributions to the conception or design of the work and acquisition of data.

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Conflict of Interest Disclosures: The authors declare no conflict of interest

A data sharing statement: Data are housed at the Research of Korea Centers for Disease Control and Prevention and are not available at this time.

Ethics approval: The study protocol was approved by the ethics committee at each participating tertiary university hospital in Korea (IRB of Seoul National University Bundang Hospital, IRB number B1104 125 014; IRB of Seoul National University Hospital, IRB number 1102-072-352; IRB of Yonsei University Severance Hospital, IRB number 4-2011-0075; IRB of Kyungpook National University Hospital, IRB number 2011-04-016; IRB of Asan Medical Center, IRB number 2011-0204; IRB of Seoul St Mary's Hospital, IRB number KC110IMI0172; IRB of Chonnam National University Hospital, IRB number CHUN-2011-061; IRB of Chungbuk National University Hospital, IRB number 2011-03-008; IRB of Samsung Medical Center, IRB number 2013-040017; IRB of Wonju Severance Christian Hospital, IRB number CR311003).

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Patient consent: Written informed consent was waived by the institutional review board at each participating tertiary hospital in Korea.

REFERENCES

1 Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;6:606-19.

2 Cowie M, Wood D, Coats A, et al. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;20:421-8.

3 Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.

4 Youn J-C, Han S, Ryu K-H. Temporal trends of hospitalized patients with heart failure in Korea. *Korean Circ J* 2017;47:16-24.

5 Murad K, Goff Jr DC, Morgan TM, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. *JACC: Heart Failure* 2015;3:542-50.

6 Shah RU, Tsai V, Klein L, et al. Characteristics and Outcomes of Very Elderly Patients After First Hospitalization for Heart FailureClinical Perspective. *Circ Heart Fail* 2011;4:301-7.

7 Vidán MT, Blaya-Novakova V, Sánchez E, et al. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail* 2016;18:869-75.

8 Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997;157:99-104.

9 The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.

10 Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.

11 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200.

12 Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011;171:550-6.

13 Statistics Korea 2017. Available at: http://kostat.go.kr/portal/eng/pressReleases/11/1/index.board?bmode=download&bSeq=&aSeq=363974&ord=1

14 Hall MJ, Levant S, DeFrances CJ. Hospitalization for congestive heart failure: United States, 2000–2010. NCHS data brief. Available at: https://www.cdc.gov/nchs/data/databriefs/db108.pdf.

15 Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. *Eur J Heart Fail* 2014;16:700-8.

16 Lee SE, Lee H-Y, Cho H-J, et al. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean acute heart failure registry (KorAHF). *Korean Circ J* 2017;47:341-53.

17 Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.

18 Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;162:1682-8.

19 Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215-25.

20 Hernandez AF, Hammill BG, O'Connor CM, et al. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol* 2009;53:184-92.

21 Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation* 2010;122:585-96.

22 Dobre D, DeJongste MJ, Lucas C, et al. Effectiveness of β-blocker therapy in daily practice patients with advanced chronic heart failure; is there an effect-modification by age? *Br J Clin Pharmacol* 2007;63:356-64.

23 Akita K, Kohno T, Kohsaka S, et al. Current use of guideline-based medical therapy in elderly patients admitted with acute heart failure with reduced ejection fraction and its impact on event-free survival. *Int J Cardiol* 2017;235:162-8.

24 Hamaguchi S, Kinugawa S, Goto D, et al. Predictors of long-term adverse outcomes in elderly patients over 80 years hospitalized with heart failure. *Circ J* 2011;75:2403-10.

25 Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blocker use in patients with reversible airway disease. *Cochrane Database Syst Rev* 2002:CD002992.

26 Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective β-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715-25.

27 Komajda M, Hanon O, Hochadel M, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J*

2008;30:478-86.

28 Murad K, Goff DC, Morgan TM, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. *JACC: Heart Failure* 2015;3:542-50.

29 Turgeon RD, Kolber MR, Loewen P, et al. Higher versus lower doses of ACE inhibitors, angiotensin-2 receptor blockers and beta-blockers in heart failure with reduced ejection fraction: Systematic review and meta-analysis. *PLoS One* 2019;14:e0212907.

Figure legends

Figure 1. Study flow

EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction

Figure 2. Discharge medication profiles.

Prescription of beta-blockers, RAS inhibitors (A), and GDMT (B) in elderly patients with HFrEF according to age group.

RAS, renin-angiotensin system; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction

Figure 3. Three-year cumulative survival according to the treatment groups.

Patients receiving GDMT had lower mortality among all patients (A), patients aged between 65-79 years (B), and patients aged 80 years or older (C).

BB, beta-blocker; RASi, renin-angiotensin system inhibitor; GDMT, guideline-directed medical therapy

Figure 4. Subgroup analysis.

The hazard ratios (HRs) of medical therapy (i.e. GDMT, beta-blockers only, RAS inhibitors only) compared with no GDMT for all-cause mortality in subgroups were calculated using multivariate Cox regression analysis. The forest plots demonstrate the HRs of GDMT vs. no

GDMT from the results. There was no significant interaction between the treatment strategy (no GDMT, beta-blockers only, RAS inhibitors only and GDMT) and diverse subgroups, and GDMT was associated with lower morality across subgroups.

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; GDMT, guideline-directed medical therapy

*The P for interaction indicates whether treatment strategy interacts with the subgrouping variable. It was calculated from multivariable Cox regression analysis which included the variables for treatment strategy, subgrouping variables, interaction term of the treatment strategy-by-subgrouping variable, sex, hypertension, diabetes, atrial fibrillation, and prescription of mineralocorticoid receptor antagonists, digitalis and diuretics.

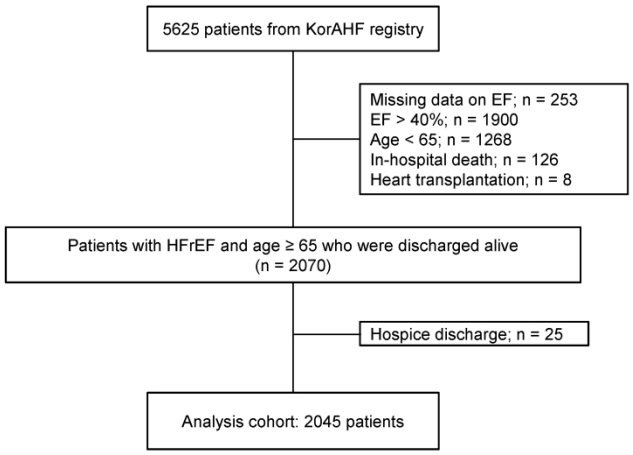
Supplementary figure 1. Cumulative survival according to beta-blocker and RAS inhibitor prescription pattern

BB, beta-blocker; RASi, renin-angiotensin system inhibitor

Supplementary figure 2. Three-year cumulative survival according to treatment group in an inverse probability treatment weight adjusted population

Patients receiving GDMT had lower mortality among all patients (A), patients aged between 65-79 years (B), and patients aged 80 years or older (C).

BB, beta-blocker; RASi, renin-angiotensin system inhibitor; GDMT, guideline-directed medical therapy



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EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction

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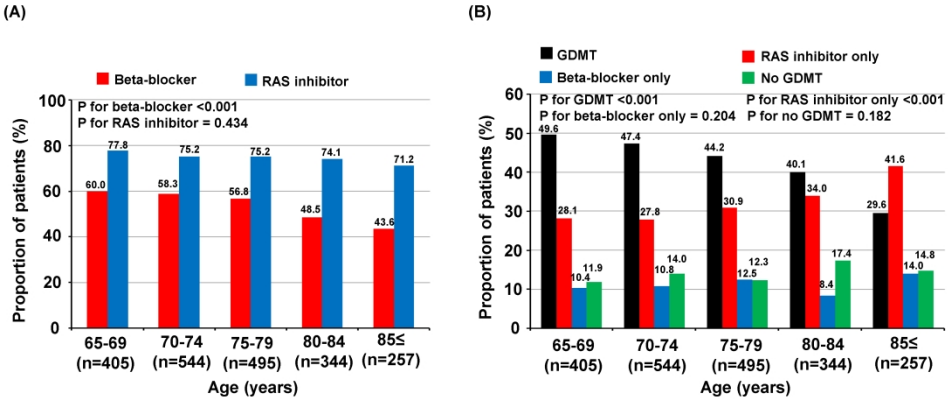

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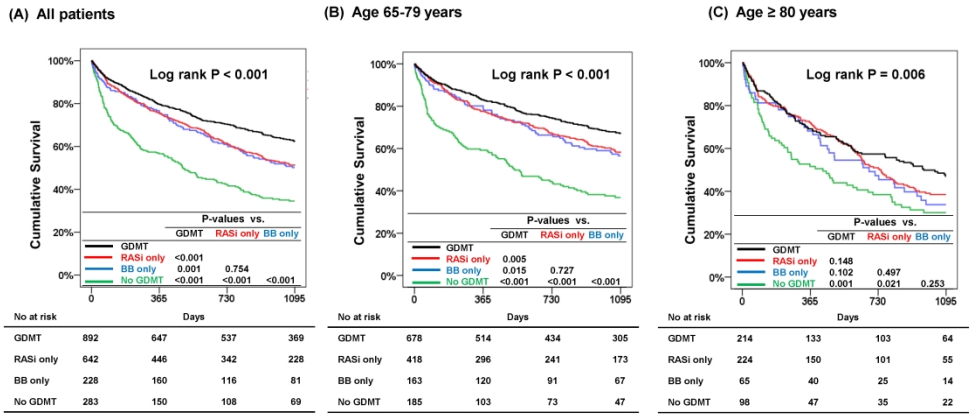

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Patients receiving GDMT had lower mortality among the all patients (A), patients aged between 65-79 years (B), and patients aged 80 years or older (C).
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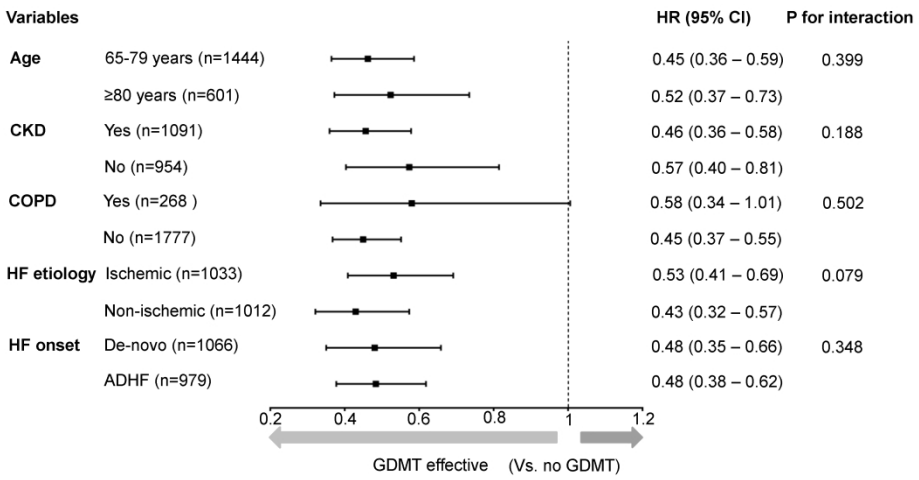

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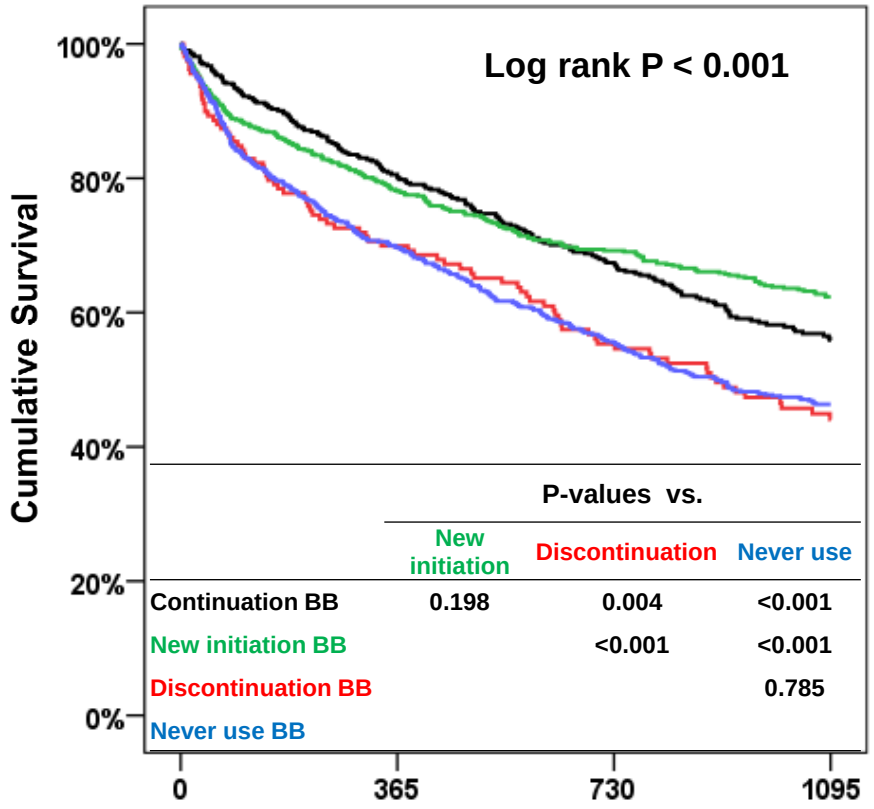
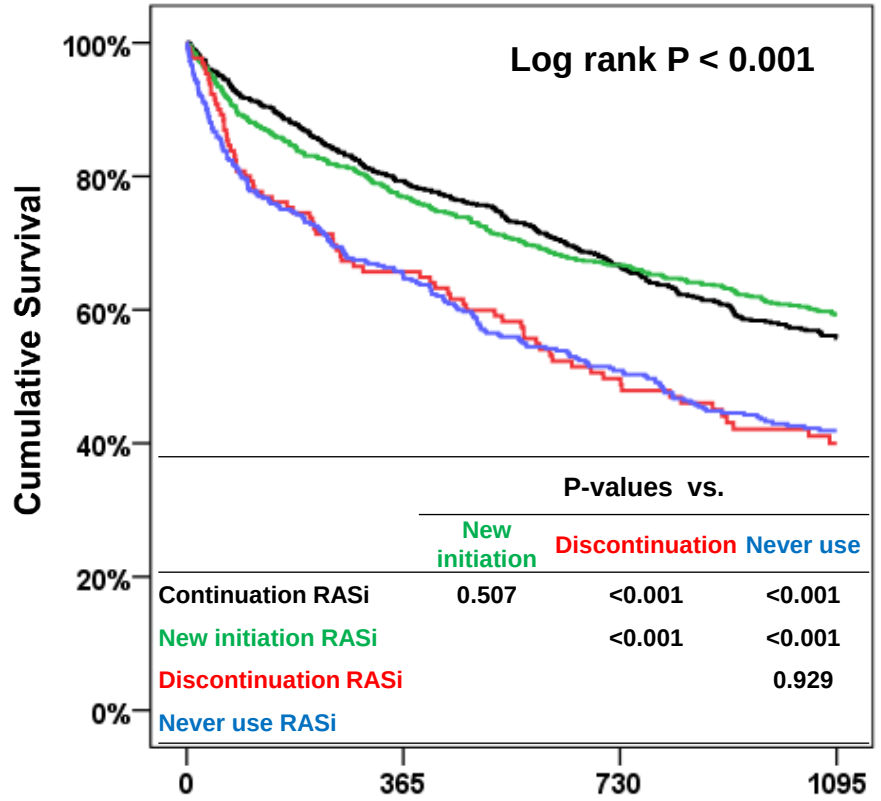
(A) Cumulative survival according to beta-blocker prescription pattern



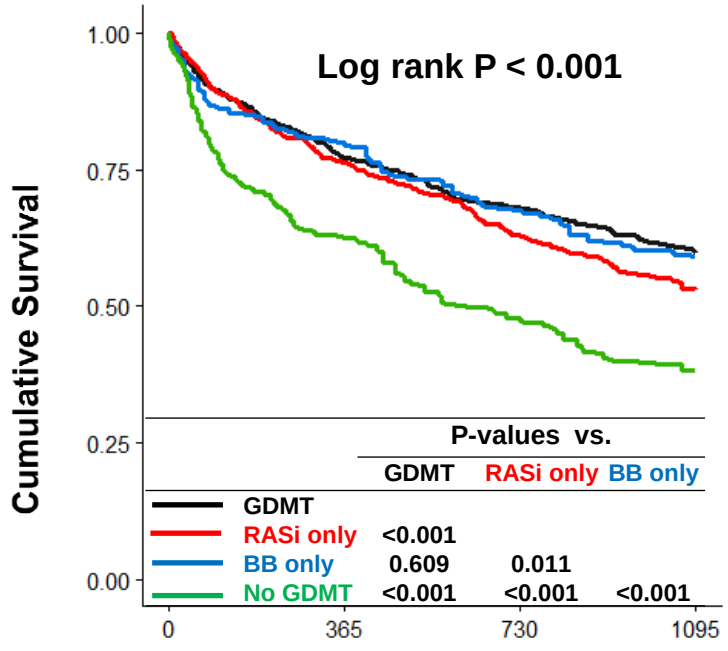
No at risk				
Continuation BB	433	323	251	161
New initiation BB	687	483	402	289
Discontinuation BB	161	102	77	51
Never use BB	764	494	373	246

(B) Cumulative survival according to RAS inhibitor prescription pattern



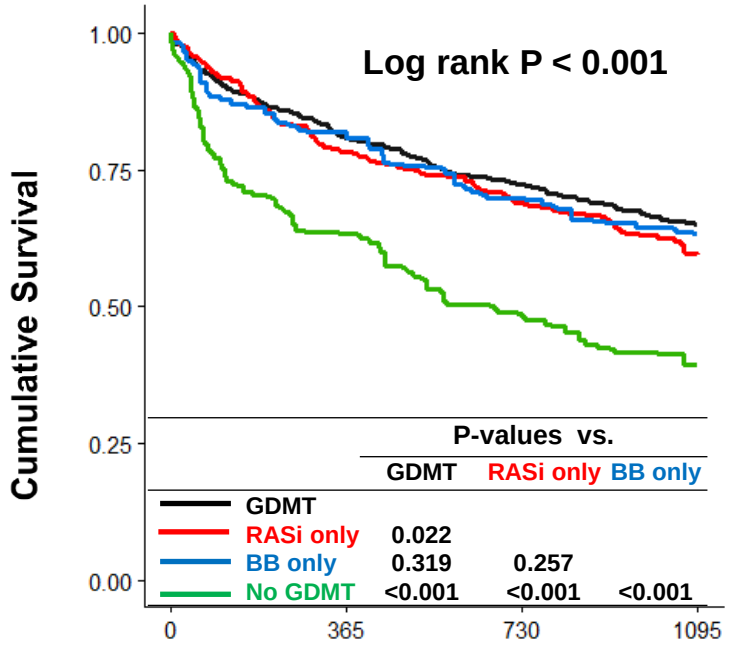
No at risk				
Continuation RASi	715	528	418	278
New initiation RASi	819	565	461	319
Discontinuation RASi	131	80	55	36
Never use RASi	380	230	169	114

(A) All patients



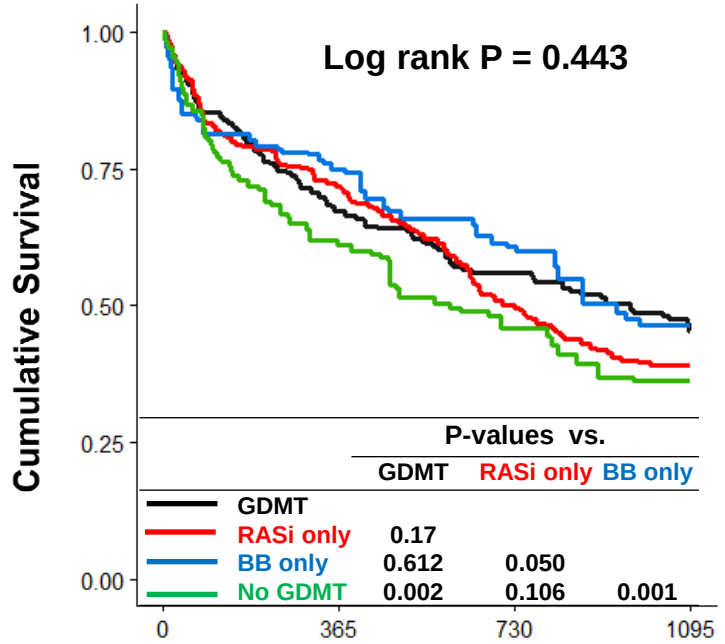
No at risk	Days			
GDMT	1813	1279	1064	729
RASi only	1709	1193	926	633
BB only	1298	936	736	541
No GDMT	1132	654	489	308

(B) Age 65-79 years



No at risk	Days			
GDMT	1326	986	836	586
RASi only	1169	836	689	500
BB only	956	722	583	459
No GDMT	726	423	315	197

(C) Age ≥ 80 years



No at risk	Days			
GDMT	487	293	228	143
RASi only	539	357	237	133
BB only	342	214	154	82
No GDMT	407	231	173	111

Supplementary table 1. Baseline characteristics of patients according to continue or discontinued of beta-blocker during index admission

Variable	Continue beta-blocker (n=433)	Discontinue beta-blocker (n=161)	P value
Age, years	75.3 ± 6.6	76.4 ± 6.9	0.08
Men, n (%)	233 (53.8)	92 (57.1)	0.516
BMI, kg/m^2	23.5 ± 3.6	22.4 ± 3.2	<0.001
Medical history			
Previous heart failure, n (%)	332 (76.7)	116 (72.0)	0.284
Hypertension, n (%)	336 (77.6)	117 (72.7)	0.233
Diabetes, n (%)	213 (49.2)	64 (39.8)	0.042
Atrial fibrillation, n (%)	151 (34.9)	46 (28.6)	0.170
COPD, n (%)	48 (11.1)	21 (13.0)	0.564
Myocardial infarction, n (%)	165 (38.1)	56 (34.8)	0.504
Medication on discharge			
RAS inhibitor, n (%)	316 (73.0)	107 (66.5)	0.127
MRA, n (%)	213 (49.2)	74 (46.0)	0.518
Loop diuretics, n (%)	71 (16.4)	49 (30.4)	<0.001
Digoxin, n (%)	300 (69.3)	116 (72.0)	0.546
Systolic BP on admission, mm Hg	135.5 ± 28.7	131.3 ± 29.0	0.116
Diastolic BP on admission, mm Hg	81.1 ± 18.0	76.8 ± 18.1	0.010
Heart rate on admission, beats/min	89.7 ± 23.8	92.9 ± 27.6	0.172
NYHA functional class III or IV on admission	380 (87.8)	153 (95.0)	0.009

Laboratory data on admission			
eGFR, ml/min/1.73m^2	51.2 ± 25.1	46.7 ± 23.4	0.051
Sodium, mEq/L	137.7 ± 4.2	137.4 ± 5.0	0.454
Potassium, mEq/L	4.5 ± 0.7	4.5 ± 0.7	0.242
BNP, pg/mL	1593.1 ± 1306.1	1926.5 ± 1515.7	0.150
NT-pro-BNP, pg/mL	11545.9 ± 10872.8	14650.1 ± 12629.1	0.036
LVEF, %	29.1 ± 6.9	28.6 ± 7.8	0.483

BMI, body mass index; COPD, chronic obstructive pulmonary disease; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction

Supplementary table 2. Baseline characteristics of patients according to continue or discontinued of RAS inhibitor during index admission

Variable	Continue RAS inhibitor	Discontinue RAS inhibitor	P value
Age, years	75.8 ± 6.7	76.3 ± 6.5	0.481
Men, n (%)	400 (55.9)	70 (53.4)	0.633
BMI, kg/m^2	23.1 ± 3.5	22.9 ± 3.3	0.562
Medical history			
Previous heart failure, n (%)	512 (71.6)	92 (70.2)	0.753
Hypertension, n (%)	543 (75.9)	102 (77.9)	0.738
Diabetes, n (%)	343 (48.0)	70 (53.4)	0.256
Atrial fibrillation, n (%)	235 (32.9)	34 (26.0)	0.127
COPD, n (%)	95 (13.3)	19 (14.5)	0.678
Myocardial infarction, n (%)	220 (30.8)	52 (39.7)	0.053
Medication on discharge			
Beta-blocker, n (%)	380 (53.1)	58 (44.3)	0.071
MRA, n (%)	348 (48.7)	49 (37.4)	0.022
Loop diuretics, n (%)	159 (22.2)	44 (33.6)	0.007
Digoxin, n (%)	483 (67.6)	99 (75.6)	0.081
Systolic BP on admission, mm Hg	134.7 ± 28.6	127.1 ± 31.3	0.006
Diastolic BP on admission, mm Hg	79.8 ± 16.8	73.1 ± 17.3	<0.001
Heart rate on admission, beats/min	91.4 ± 24.6	96.9 ± 22.5	0.018
NYHA functional class III or IV on admission	623 (87.1%)	117 (89.3)	0.567

Laboratory data on admission			
eGFR, ml/min/1.73m^2	53.3 ± 23.6	39.5 ± 20.8	<0.001
Sodium, mEq/L	137.6 ± 4.9	136.8 ± 4.5	0.062
Potassium, mEq/L	4.4 ± 0.7	4.7 ± 0.8	0.001
BNP, pg/mL	1670.8 ± 1502.2	1920.8 ± 2017.2	0.355
NT-pro-BNP, pg/mL	10966.0 ± 10806.0	14939.1 ± 12170.9	0.007
LVEF, %	28.6 ± 7.5	28.6 ± 7.4	0.929

BMI, body mass index; COPD, chronic obstructive pulmonary disease; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction

Online supplementary table 3. Patients characteristics in inverse probability treatment weight adjusted population

	GDMT (n=1813)	Beta blocker only (n=1298)	RAS inhibitor only (n=1709)	No GDMT (n=1132)	Std. Diff.	P value
Age, years	75.5 ± 6.7	75.6 ± 6.8	76.1 ± 7.0	76.7 ± 6.8	0.17	0.07
Men, n (%)	964 (53.2)	757 (58.3)	963 (56.3)	622 (54.9)	0.10	0.26
BMI, kg/m^2	22.7 ± 3.4	22.6 ± 3.5	22.4 ± 3.3	22.4 ± 3.2	0.08	0.34
Medical history						
Previous heart failure, n (%)	905 (49.9)	687 (52.9)	901 (52.8)	656 (58.0)	0.16	0.05
Hypertension, n (%)	1233 (68.0)	870 (67.0)	1108 (64.9)	732 (64.6)	0.07	0.24
Diabetes, n (%)	774 (42.7)	481 (37.0)	650 (38.0)	472 (41.7)	0.11	0.09
Chronic kidney disease, n (%)	933 (51.5)	769 (59.2)	877 (51.3)	674 (59.6)	0.16	0.05
Atrial fibrillation, n (%)	566 (31.2)	448 (34.5)	515 (30.2)	380 (33.6)	0.09	0.32
COPD, n (%)	211 (11.6)	168 (12.9)	247 (14.5)	162 (14.3)	0.08	0.12
Myocardial infarction, n (%)	395 (21.8)	330 (25.4)	384 (22.5)	292 (25.8)	0.10	0.34
Cause of heart failure						
Ischemic, n (%)	920 (50.8)	752 (57.9)	837 (49.0)	615 (54.4)	0.18	0.06
Dilated, n (%)	434 (23.9)	250 (19.2)	387 (22.6)	213 (18.8)	0.12	0.15
Medication on admission						
Beta-blocker, n (%)	561 (31.0)	442 (34.0)	439 (25.7)	259 (22.9)	0.24	0.03
RAS inhibitor, n (%)	727 (40.1)	459 (35.4)	762 (44.6)	409 (36.2)	0.19	0.06
MRA, n (%)	301 (16.6)	277 (21.3)	296 (17.3)	224 (19.8)	0.12	0.15
Medication on discharge						
MRA, n (%)	936 (51.6)	643 (49.6)	839 (49.1)	486 (42.9)	0.17	0.03

Loop diuretics, n (%)	1427 (78.7)	977 (75.2)	1305 (76.4)	794 (70.2)	0.21	0.01
Digoxin, n (%)	547 (30.2)	358 (27.6)	488 (28.5)	361 (31.9)	0.09	0.39
Systolic BP on discharge, mm Hg	114.7 ± 16.8	113.8 ± 16.8	115.0 ± 16.5	112.5 ± 15.4	0.15	0.39
Diastolic BP on discharge, mm Hg	66.1 ± 10.8	66.1 ± 10.1	66.1 ± 10.9	65.0 ± 9.9	0.10	0.20
Heart rate on discharge, beats/min	76.3 ± 13.6	77.8 ± 12.3	77.2 ± 14.2	77.4 ± 13.5	0.10	0.21
NYHA functional class on discharge					0.10	0.23
I or II, n (%)	1598 (88.1)	1148 (88.4)	1496 (87.5)	1028 (90.8)		
III or IV, n (%)	215 (11.9)	150 (11.6)	213 (12.5)	105 (9.2)		
Echocardiographic parameters						
LVEDD, mm	60.2 ± 8.8	59.6 ± 8.7	60.3 ± 8.7	59.3 ± 8.7	0.11	0.40
LVESD, mm	50.3 ± 9.3	49.9 ± 9.3	50.0 ± 9.5	49.4 ± 9.5	0.09	0.26
LVEF, %	28.7 ± 7.3	28.2 ± 7.7	28.9 ± 7.3	29.0 ± 7.2	0.11	0.57
Laboratory data on admission						
Hemoglobin, g/dL	12.3 ± 2.0	12.3 ± 1.9	12.3 ± 2.1	12.1 ± 2.1	0.08	0.49
eGFR, ml/min/1.73m^2	61.6 ± 32.6	58.6 ± 30.1	62.3 ± 30.1	56.5 ± 28.1	0.18	0.07
Sodium, mEq/L	137.8 ± 4.5	138.0 ± 4.2	137.6 ± 4.5	137.4 ± 4.5	0.11	0.78
Potassium, mEq/L	4.4 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.7	0.14	0.46
BNP, pg/mL	1692.2 ± 1528.3	1703.7 ± 1403.4	1731.0 ± 1389.8	1732.8 ± 1858.4	0.03	0.81
NT-pro-BNP, pg/mL	11650.7 ± 11236.4	10810.0 ± 10121.4	10549.1 ± 10321.2	12307.0 ± 10979.5	0.16	0.10

GDMT, guideline-directed medical therapy; RAS, renin angiotensin system; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; BNP, brain natriuretic peptide

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12,13,8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16, 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15, 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.