Clinical Research in Cardiology (2021) 110:1392–1403
https://doi.org/10.1007/s00392-020-01689-8

ORIGINAL PAPER

Response to beta-blockers and natriuretic peptide level in acute heart failure: analysis of data from the Korean acute heart failure registry

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Received: 21 March 2020 / Accepted: 8 June 2020 / Published online: 25 June 2020

Abstract

Background To investigate the effect of beta-blockers according to NP levels and HF phenotypes because natriuretic peptide (NP) level can be used to risk-stratify HF patients regardless of left ventricular ejection fraction (LVEF).

Methods Of 5,625 patients in the Korean acute heart failure registry, we included patients with LVEF and NP levels. HF phenotypes were defined as HF with reduced ejection fraction (HFrEF) (EF ≤ 40%), HF with midrange ejection fraction (HFmrEF) (40% < EF < 50%), and HF with preserved EF (HFpEF) (EF ≥ 50%). Patients were further stratified by NP tertiles. Primary outcome was 5-year all-cause mortality according to beta-blocker use at discharge.

Results Both B-type NP (BNP) ($r = -0.279$, $P < 0.001$) and N-terminal pro-BNP ($r = -0.186$, $P < 0.001$) levels correlated inversely with LVEF. During a median follow-up duration of 961 days, 1560 (35.3%) patients died. In HFrEF, patients taking beta-blockers showed better survival regardless of NP levels. Regarding HFmrEF, there was no mortality difference between those taking and not taking beta-blockers. In HFpEF, beta-blocker use demonstrated lower mortality in those in the 3rd NP tertile (log-rank $P = 0.041$) but not in those in the 1st and 2nd NP tertiles (log-rank $P > 0.05$). After adjusting covariates, the use of beta-blockers was associated with a 38%-reduced mortality (hazard ratio: 0.62; 95% confidence interval: 0.39–0.98; $P = 0.040$) in HFpEF patients in the 3rd NP tertile but not in those in 1st and 2nd tertiles.

Chan Soon Park and Jin Joo Park contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-020-01689-8) contains supplementary material, which is available to authorized users.

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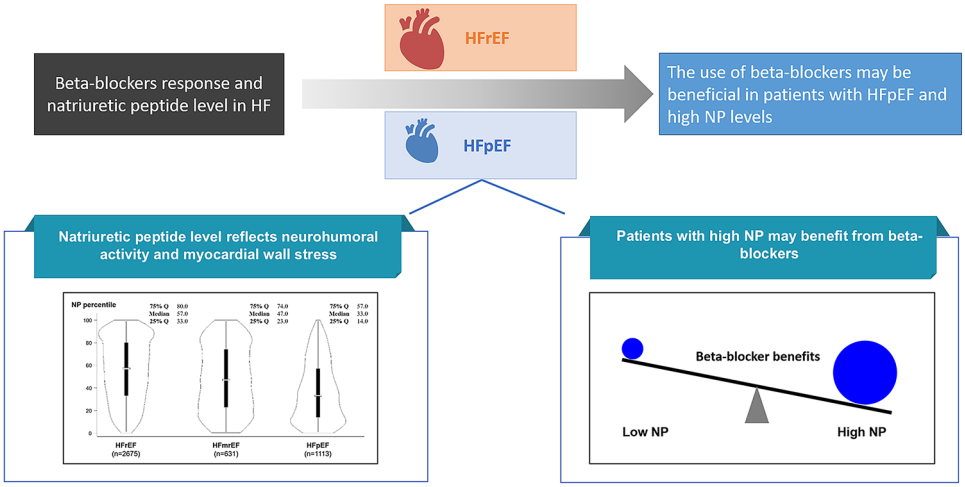
Conclusions We confirm that the use of beta-blockers is beneficial in patients with HFrEF. Furthermore, we extend the benefits of beta-blockers to patients with HFpEF and high NP levels.

Clinical Trial Registration ClinicalTrial.gov identifier: NCT01389843 URL: https://clinicaltrials.gov/ct2/show/NCT01389843

Graphic abstract



Keywords Beta-blockers · Heart failure · Natriuretic peptide · Mortality

Introduction

Current guidelines for the management of patients with heart failure (HF) rely heavily on the classification of patients by left ventricular ejection fraction (LVEF). Depending on the level of LVEF, HF is classified into HF with reduced ejection fraction (HFrEF), midrange ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) [1, 2]. Although l these groups have deleterious prognoses [3, 4], their response to medical treatment varies between the groups. Because multiple studies have shown that beta-blockers enhance survival in patients with HFrEF [5–7], current HF practice guidelines recommend their use unless they are contraindicated [1, 2]. In addition, a recent meta-analysis demonstrated that beta-blockers had beneficial effects on patients with HFmrEF [8]. By contrast, beta-blockers failed to show improvement of survival in patients with HFpEF [8, 9].

Neurohumoral activation plays a pivotal role in the development and progression of HF [10, 11], and various drugs targeting neurohumoral pathways, such as beta-blockers, have been used in the management of patients with HF. Natriuretic peptide (NP) is a discerning marker of neurohumoral activity and myocardial wall stress [12], and it has been used for diagnosis and risk prediction in patients with HF regardless of LVEF [13–15]. Because patients with HFpEF have lower NP levels than those with HFrEF [16], the effect of beta-blockers may be attenuated in HFpEF.

Considering that NP level reflects the degree of neurohumoral activation and myocardial wall stress, we hypothesised that patients with high NP may benefit from beta-blockers regardless of HF types. To explore this hypothesis, we analysed the effect of beta-blockers on survival stratified by LVEF and NP level in a large, prospective, multicenter cohort of patients with acute HF (AHF).

Methods

Study population and data collection

The Korean acute heart failure (KorAHF) registry is a prospective, nationwide, multicenter cohort study, and the design and preliminary results have been published elsewhere [ClinicalTrial.gov identifier: NCT01389843] [17, 18]. Between March 2011 and December 2014, 5625 consecutive patients hospitalised for AHF in 10 tertiary university hospitals in the Republic of Korea were enrolled in this registry. Patients who had signs or symptoms of HF and pulmonary congestion, objective findings of left ventricular systolic dysfunction, or structural heart disease were included in this study. We excluded patients with HF who were hospitalized due to other medical condition, such as cancer treatment. Then, the patients were classified into de novo (new-onset acute HF in a patient without previously known cardiac dysfunction) or acute decompensation of chronic HF and

the aggravating factors for acute decompensation were also recorded.

All patients were scheduled to undergo follow-up at least 5 years after the index hospitalisation. The mortality data of patients who were lost to follow-up were collected from the National Insurance data or National Death Records. The institutional review board or ethics committee at each participating institute approved the study protocol and waived the need for written informed consent; this study complied with the Declaration of Helsinki principles. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Study variables and definitions

Based on the echocardiography findings in the index AHF hospitalisation, patients were classified into those with HFrEF (LVEF of ≤ 40%), HF with midrange ejection fraction (HFmrEF) (40% < LVEF < 50%), and HFpEF (LVEF ≥ 50%). Natriuretic peptide (NP) levels at admission, and those at discharge, and the change of NP levels during hospitalization proved their independent predictive values [19]. We stratified according to the tertiles of natriuretic (NP) levels at admission because the majority of patients had NP levels measured at admission. The thresholds for the 2nd and 3rd tertiles, respectively, were 600 pg/ml and 1379 pg/ml for B-type natriuretic peptide (BNP), and 3020 pg/ml and 8535 pg/ml for N-terminal proBNP (NT-proBNP). Medication history of beta-blocker, renin–angiotensin system inhibitor, mineralocorticoid receptor antagonist, loop diuretic, and thiazide was collected at discharge. Regarding beta-blocker prescription during admission, 28% patients were already on beta-blockers at admission. The prescription rates reached a peak during hospitalization with 61%, but declined to 53% by the discharge, inferring that physicians attempt to initiate guideline-directed medical therapy but must discontinue some drugs due to intolerability [20]. The primary outcome was the 5-year all-cause post-discharge mortality according to beta-blocker use.

Statistical analysis

Data were presented as numbers and frequencies for categorical variables and as means ± standard deviations or medians with interquartile intervals for continuous variables. For comparison between groups, the χ^2 test (or Fisher's exact test when any expected cell count was <5 for a 2 × 2 table) was used for categorical variables and the unpaired Student's *t* test for continuous variables. For analysing continuous variables between more than two groups, we used one-way analysis of variance. The chronological trend of the clinical outcomes was expressed as Kaplan–Meier estimates and compared according to beta-blocker use. The log-rank test was performed for the comparison of the differences in the clinical outcomes. A multivariable Cox proportional hazard regression model was used to determine the independent predictors of all-cause 5-year mortality.

To estimate the sensitivity, we performed the inverse-probability treatment-weighted (IPTW) analyses to account for confounders in patients with HFrEF, HFmrEF, HFpEF, and for the respective NP tertiles. The following variables were included for matching: age, sex, body mass index, previous history of heart failure, hypertension, diabetes mellitus, ischemic heart disease, valvular heart disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, cerebrovascular disease, atrial fibrillation, New York Heart Association functional class, laboratory results of initial hemoglobin, sodium, potassium, blood urea nitrogen and creatinine, renin-angiotensin system inhibitors (RAS-inhibitors) at discharge, mineralocorticoid receptor antagonists (MRA) at discharge, and NP percentiles. The use of RAS-inhibitors was not balanced in matched cohorts of HFrEF and HFmrEF. In HFpEF, all variables were well balanced.

Two-sided *P* values of < 0.05 were considered statistically significant. The statistical tests were performed using IBM SPSS version 23 (SPSS Inc., Chicago, IL, USA) and R programming version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org).

Results

Demographic and clinical characteristics

Of 5625 patients from KorAHF cohort, baseline echocardiography was performed in 5103 patients. Based on LVEF, patients were divided into HFrEF ($n = 3088$), HFmrEF ($n = 730$), and HFpEF groups ($n = 1285$). Patients who died during the index admission ($n = 202$) or those who did not have baseline NP measurements ($n = 482$) were excluded from this study; therefore, the data of 4419 patients were available. In this analysis cohort, 2675 (60.5%), 631 (14.3%), and 1113 (25.2%) patients had HFrEF, HFmrEF, and HFpEF, respectively (Fig. 1).

Table 1 demonstrates the clinical characteristics of patients according to HF types and NP tertiles. In brief, patients with high NP levels were older, showed female preponderance and lower body mass index, and had a more frequent previous history of chronic kidney disease in all HF types. Overall clinical characteristics of patients according to NP tertiles and HF phenotypes are separately presented in Supplementary Table 1 and Supplementary table 2.

There was a significant inverse relationship between LVEF and BNP ($r = 0.279$, $P < 0.001$) and between LVEF and NTproBNP ($r = -0.186$, $P < 0.001$) (Supplementary Fig. 1A). Therefore, patients with HFrEF showed highest

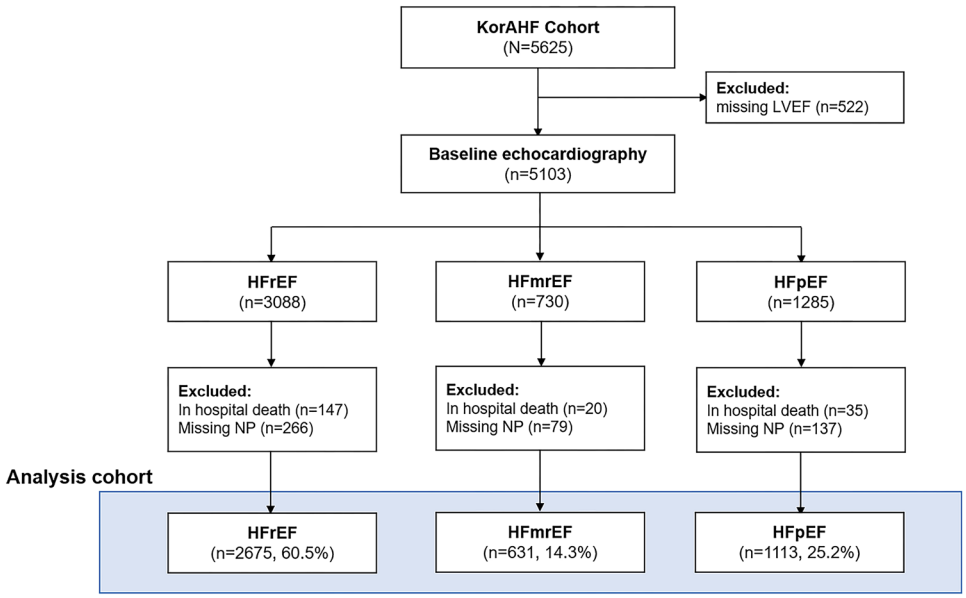


Fig. 1 Study population and relationship between LVEF and NP. Flow chart of the study. *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LVEF* left ventricular ejection fraction, *NP* natriuretic peptide

NP levels while those with HFpEF showed lowest NP levels (BNP median: 1009 pg/mL vs. 784 pg/mL vs. 578 pg/mL, $P<0.001$; NT-proBNP median: 5722 pg/mL vs. 4556 pg/mL vs. 2661 pg/mL, $P<0.001$) (Supplementary Fig. 1B).

Clinical outcomes of beta-blocker use according to LVEF and NP

During the 5-year follow-up (median follow-up duration, 961 days; interquartile interval, 328–1346 days), 1560 patients (35.3%) died. The deceased had more unfavorable characteristics such as older age, higher incidence of previous heart failure, hypertension, diabetes mellitus, ischemic heart disease, valvular heart disease, COPD, chronic kidney disease, cerebrovascular accident, and atrial fibrillation, higher New York Heart Association functional class, and higher NP level, and included less patients prescribed with beta-blockers and RAS-inhibitors (Supplementary table 3).

When stratifying according to the HF types, the 5-year mortality did not differ between patients with HFrEF (938 died/mortality 35.1%), HFmrEF (222 died/mortality 35.2%), and HFpEF (400 died/mortality 35.9%) (log-rank $P=0.913$). When patients were grouped by NP tertiles, patients in higher NP tertiles had higher mortality across all HF types (Supplementary Fig. 1).

For HFrEF, patients taking beta-blockers showed better survival than did those not taking beta-blockers regardless of NP levels (Fig. 2a). For HFmrEF, the mortality did not differ between patients taking and not taking beta-blockers (log-rank $P=0.118$). For HFpEF, there was no difference in mortality between patients taking beta-blockers or not (log-rank $P=0.079$), either. However, when HFpEF patients were stratified according to NP levels, among patients in the 3rd NP-tertile those taking beta-blockers had lower mortality than those not taking beta-blockers (log-rank $P=0.041$).

In Cox-proportional hazard regression analysis with adjustment for significant covariates, the use of beta-blockers was associated with a 26%-reduced mortality in all HFrEF patients (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.65–0.85, $P<0.001$). The beneficial effect of beta-blockers was consistent for HFrEF patients in all three NP tertiles. For HFpEF, use of beta-blockers was associated with a 38% reduced mortality only in those in the 3rd NP tertile (HR 0.62, 95% CI 0.39–0.98, $P=0.040$), but not in those in the 1st and 2nd NP tertiles (1st NP tertile: HR 0.83, 95% CI 0.59–1.15, $P=0.262$; 2nd NP tertile: HR 1.00, 95% CI 0.69–1.45, $P=0.995$). For HFmrEF, the use of beta-blockers was not associated with improved clinical outcomes.

Similar results were observed in the IPTW cohort (Fig. 2b); for HFpEF, only those in the 3rd NP tertile taking beta-blockers, had better survival than those not taking beta-blockers (HR 0.64, 95% CI 0.45–0.89, $P=0.033$).

Subgroup analysis

We performed exploratory analyses for the subgroups that included age, sex, HF onset (de-novo versus acute decompensated HF), hypertension, diabetes mellitus, ischemic heart disease, chronic kidney disease, atrial fibrillation, and HF types (Fig. 3). There was no significant interaction of beta-blocker effect within each subgroup except for sex, hypertension, and HF types.

Table 1 Clinical characteristics of patients according to HF phenotypes and NP tertiles

	HFrEF ($n=2675$)				HFmrEF ($n=631$)				HFpEF ($n=1113$)			
	1st tertile ($n=699$)	2nd tertile ($n=944$)	3rd tertile ($n=1032$)	*P* value	1st tertile ($n=237$)	2nd tertile ($n=195$)	3rd tertile ($n=199$)	*P* value	1st tertile ($n=583$)	2nd tertile ($n=344$)	3rd tertile ($n=186$)	*P* value
Demographic data												
Age (years)	64 (53–73)	69 (56–77)	72 (62–79)	< 0.001	72 (62–78)	75 (68–80)	75 (66–82)	0.007	74 (64–80)	76 (69–82)	77 (70–83)	0.003
Men (%)	477 (68.2)	575 (60.9)	537 (52.0)	< 0.001	141 (59.5)	83 (42.6)	79 (39.7)	< 0.001	245 (42.0)	112 (32.6)	59 (31.7)	0.003
BMI (kg/m^2)	23.9 (21.5–26.3)	22.9 (20.9–25.3)	22.1 (19.8–24.4)	< 0.001	23.9 (21.5–25.8)	23.4 (21.3–25.4)	21.6 (20.0–24.1)	< 0.001	24.1 (22.0–27.0)	23.1 (20.3–25.7)	22.8 (20.0–25.1)	< 0.001
De novo HF (%)	410 (58.7)	487 (51.6)	493 (47.8)	< 0.001	145 (61.2)	121 (62.1)	105 (52.8)	0.111	353 (60.7)	208 (60.5)	104 (55.9)	0.495
Past medical History (%)												
Hypertension	331 (47.4)	512 (54.2)	626 (60.7)	< 0.001	133 (56.1)	129 (66.2)	147 (73.9)	0.001	366 (62.8)	237 (68.9)	126 (67.7)	0.130
Diabetes mellitus	224 (32.0)	333 (35.3)	417 (40.4)	0.001	63 (26.6)	78 (40.0)	79 (39.7)	0.003	182 (31.2)	106 (30.8)	52 (28.0)	0.697
Ischemic heart disease	154 (22.1)	266 (28.2)	352 (34.1)	< 0.001	59 (24.9)	57 (29.2)	69 (34.7)	0.082	118 (20.2)	67 (19.5)	51 (27.4)	0.073
Valvular heart disease	64 (9.2)	68 (7.2)	96 (9.3)	0.193	36 (15.2)	24 (12.3)	24 (12.1)	0.559	160 (27.4)	73 (21.2)	49 (26.3)	0.103
COPD	68 (9.7)	109 (11.5)	103 (10.0)	0.398	31 (13.1)	12 (6.2)	16 (8.0)	0.035	82 (14.1)	47 (13.7)	21 (11.3)	0.623
Chronic kidney disease	29 (4.1)	84 (8.9)	259 (25.1)	< 0.001	16 (6.8)	23 (11.8)	58 (29.1)	< 0.001	37 (6.3)	38 (11.0)	47 (25.3)	< 0.001
Cerebrovascular disease	74 (10.6)	119 (12.6)	191 (18.5)	< 0.001	30 (12.7)	35 (17.9)	34 (17.1)	0.269	75 (12.9)	68 (19.8)	36 (19.4)	0.009
Atrial fibrillation	157 (22.5)	234 (24.8)	229 (22.2)	0.343	74 (31.2)	67 (34.4)	45 (22.6)	0.029	214 (36.8)	137 (39.8)	57 (30.6)	0.112
NYHA functional class at admission (%)												
II	157 (22.5)	120 (12.7)	93 (9.0)	< 0.001	61 (25.7)	25 (12.8)	14 (7.0)	< 0.001	140 (24.0)	44 (12.8)	16 (8.6)	< 0.001
III	281 (40.2)	338 (35.8)	373 (36.1)		92 (38.8)	69 (35.4)	60 (30.2)		231 (39.6)	119 (34.6)	60 (32.3)	
IV	261 (37.3)	486 (51.5)	566 (54.8)		84 (35.4)	101 (51.8)	125 (62.8)		212 (36.4)	181 (52.6)	110 (59.1)	
NYHA functional class at discharge (%)												
I	153 (23.2)	160 (17.3)	137 (13.6)	< 0.001	45 (20.5)	29 (15.5)	27 (14.1)	0.009	113 (20.0)	64 (18.7)	22 (12.0)	0.038
II	467 (70.8)	665 (72.0)	727 (72.4)		160 (72.7)	131 (70.1)	136 (70.8)		383 (67.7)	239 (69.9)	135 (73.4)	
III	26 (3.9)	56 (6.1)	86 (8.6)		10 (4.5)	24 (12.8)	18 (9.4)		39 (6.9)	30 (8.8)	13 (7.1)	
IV	14 (2.1)	42 (4.6)	54 (5.4)		5 (2.3)	3 (1.6)	11 (5.7)		31 (5.5)	9 (2.6)	14 (7.6)	

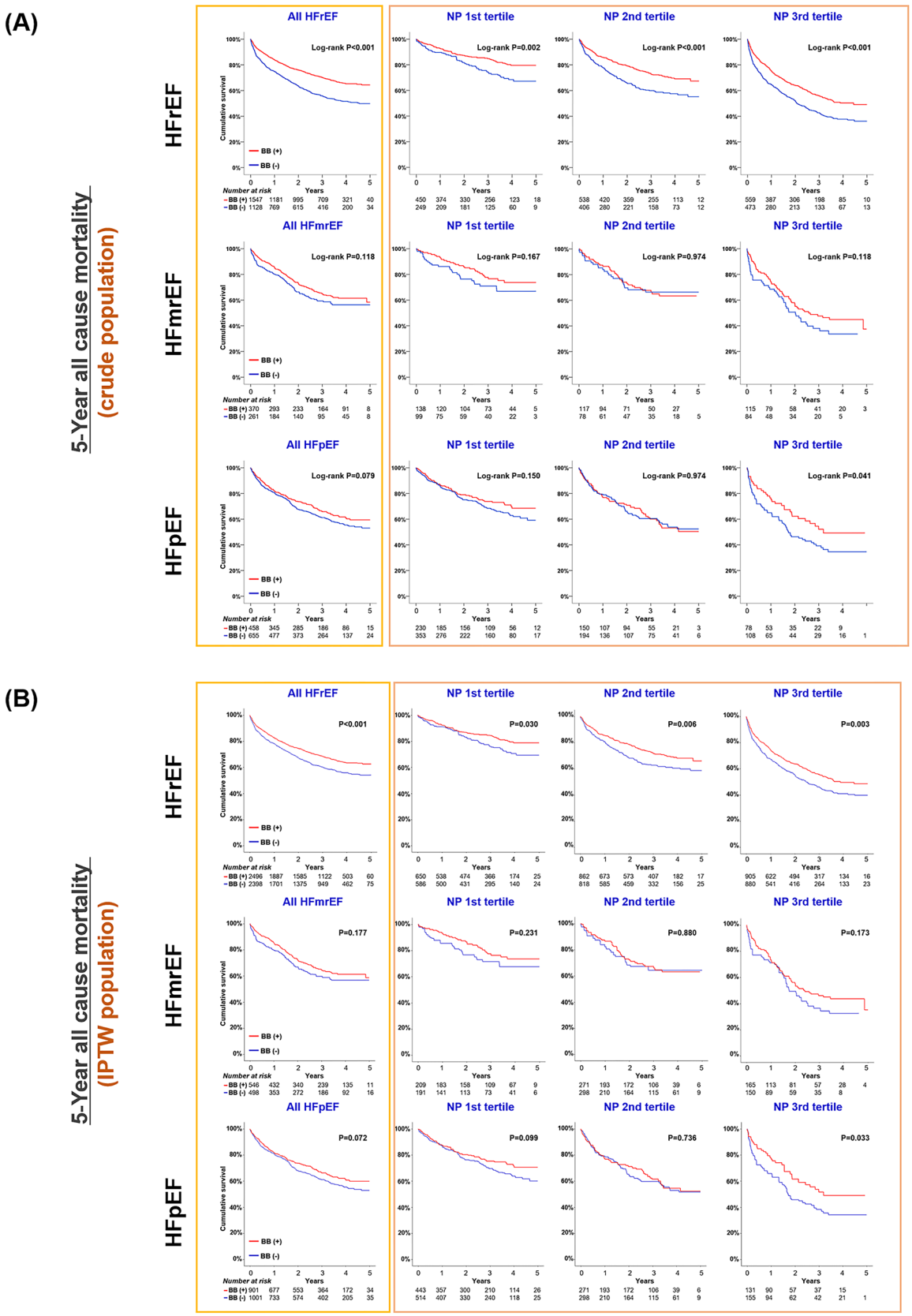
Table 1 (continued)

	HFrEF ($n=2675$)				HFmrEF ($n=631$)				HFpEF ($n=1113$)			
	1st tertile ($n=699$)	2nd tertile ($n=944$)	3rd tertile ($n=1032$)	*P* value	1st tertile ($n=237$)	2nd tertile ($n=195$)	3rd tertile ($n=199$)	*P* value	1st tertile ($n=583$)	2nd tertile ($n=344$)	3rd tertile ($n=186$)	*P* value
Physical exam at admission												
SBP (mmHg)	124 (108–142)	125 (108–149)	130 (110–150)	0.001	130 (112–153)	139 (120–157)	146 (117–168)	0.001	130 (115–152)	140 (117–160)	138 (117–160)	0.007
DBP (mmHg)	77 (66–90)	80 (69–91)	80 (69–92)	0.005	78 (67–90)	80 (70–94)	80 (70–92)	0.128	74 (65–88)	79 (66–91)	76 (64–90)	0.122
HR (beats per min)	89 (74–107)	96 (80–112)	96 (80–112)	< 0.001	85 (70–103)	92(78–111)	89 (72–109)	0.026	80 (68–96)	88 (71–109)	88 (70–101)	< 0.001
Physical exam at discharge												
SBP (mmHg)	110 (100–120)	110 (100–120)	112 (100–127)	< 0.001	115 (101–126)	115 (106–130)	120 (106–135)	0.060	115 (105–130)	116 (103–130)	120 (105–133)	0.091
DBP (mmHg)	68 (60–74)	66 (60–72)	67 (60–74)	0.127	68 (60–74)	68 (60–74)	65 (60–76)	0.815	67 (60–74)	68 (59–74)	64 (60–71)	0.299
HR (beats per min)	74 (66–85)	76 (66–86)	78 (70–88)	< 0.001	72 (63–82)	76 (67–85)	74 (66–84)	0.062	72 (65–82)	74 (66–84)	74 (67–85)	0.087
Laboratory findings												
Hemoglobin (mg/dL)	13.5 (12.2–15.0)	13.1 (11.7–14.5)	11.8 (10.5–13.5)	< 0.001	12.9 (11.2–14.4)	12.3 (10.4–13.8)	10.7 (9.6–12.2)	< 0.001	12.1 (10.7–13.7)	12.1 (10.5–13.4)	11.3 (9.9–12.6)	< 0.001
Sodium (mmol/L)	139 (137–141)	138 (136–141)	137 (134–140)	< 0.001	139 (137–141)	139 (136–141)	137 (135–140)	0.002	139 (136–141)	138 (135–141)	137 (134–140)	< 0.001
Potassium (mmol/L)	4.2 (4.0–4.5)	4.3 (4.0–4.7)	4.5 (4.0–4.9)	< 0.001	4.2 (3.8–4.5)	4.3 (3.9–4.7)	4.4 (4.0–5.0)	< 0.001	4.2 (3.9–4.5)	4.2 (3.9–4.7)	4.5 (4.0–5.0)	< 0.001
BUN (mg/dL)	17.8 (14.0–23.1)	20.6 (15.9–27.0)	27.8 (19.8–41.5)	< 0.001	18.1 (15.0–23.2)	20.0 (15.8–26.4)	29.3 (20.0–43.2)	< 0.001	17.8 (13.8–24.1)	21.0 (15.0–29.0)	30.1 (19.3–45.3)	< 0.001
Creatinine (mg/dL)	1.0 (0.8–1.2)	1.1 (0.8–1.4)	1.4 (1.0–2.1)	< 0.001	1.0 (0.8–1.3)	1.0 (0.8–1.2)	1.6 (1.0–2.7)	< 0.001	0.9 (0.7–12.0)	1.0 (0.8–1.4)	1.5 (1.0–2.3)	< 0.001
BNP (pg/mL)	402.0 (246.0–507.5)	957.0 (745.5–1122.0)	2441.5 (1785.3–3517.5)	< 0.001	334.0 (132.5–456.5)	839.0 (721.0–1020.0)	2252.5 (1703.0–3127.0)	< 0.001	288.5 (139.3–485.0)	832.5 (696.3–1073.8)	2070.1 (1597.8–2673.3)	< 0.001
NT-proBNP (pg/mL)	1682.5 (923.5–2344.5)	4910.0 (3866.0–6499.0)	18,575.0 (12,258.3–32,243.8)	< 0.001	1541.0 (682.0–2228.0)	5256.0 (4069.5–6266.8)	17,918.0 (11,748.5–30,762.8)	< 0.001	1193.5 (574.8–1974.3)	4712.0 (3822.5–6226.5)	13,523.0 (10,575.5–22,142.8)	< 0.001
Echocardiography												
LAD (mm)	47.5 (41.6–53.0)	48.2 (43.0–53.8)	47.0 (42.0–53.0)	0.011	47.3 (41.9–55.0)	48.2 (43.0–55.0)	46.0 (39.1–52.8)	0.042	49.0 (42.0–56.5)	50.0 (44.0–56.0)	50.0 (43.8–56.0)	0.840
LVEDD (mm)	62 (57–68)	62 (57–68)	60 (55–66)	< 0.001	54 (48–57)	53 (49–58)	55 (50–58)	0.787	50 (45–54)	50 (44–54)	49 (45–55)	0.077

Table 1 (continued)

	HFrEF ($n=2675$)				HFmrEF ($n=631$)				HFpEF ($n=1113$)			
	1st tertile ($n=699$)	2nd tertile ($n=944$)	3rd tertile ($n=1032$)	*P* value	1st tertile ($n=237$)	2nd tertile ($n=195$)	3rd tertile ($n=199$)	*P* value	1st tertile ($n=583$)	2nd tertile ($n=344$)	3rd tertile ($n=186$)	*P* value
E/e'	17.0 (13.0–23.8)	20.6 (15.2–26.8)	21.3 (16.4–29.4)	< 0.001	14.6 (11.0–20.9)	19.4 (13.7–26.2)	19.1 (14.8–28.2)	< 0.001	15.3 (11.2–21.2)	18.0 (13.0–24.8)	19.7 (14.3–26.0)	< 0.001
LVEF (%)	29.0 (22.0–34.0)	27.0 (21.0–33.0)	27.0 (21.0–33.0)	0.002	45.0 (43.0–47.0)	45.0 (42.0–47.0)	44 (42–46)	0.052	60.0 (55.0–65.0)	58.0 (54.0–63.0)	56.0 (52.8–62.0)	0.001
Medications at discharge (%)												
Beta-blocker	450 (64.4)	538 (57.0)	559 (54.2)	< 0.001	138 (58.2)	117 (60.0)	115 (57.8)	0.894	230 (39.5)	150 (43.6)	78 (41.9)	0.450
RAS-inhibitor	574 (82.1)	748 (79.2)	743 (72.0)	< 0.001	172 (72.6)	128 (65.6)	136 (68.3)	0.289	311 (53.3)	198 (57.6)	113 (60.8)	0.157
MRA	401 (57.4)	556 (58.9)	457 (44.3)	< 0.001	91 (38.4)	89 (45.6)	73 (36.7)	0.154	220 (37.7)	143 (41.6)	63 (33.9)	0.204
Loop diuretics	550 (78.7)	763 (80.8)	790 (76.6)	0.068	141 (59.5)	146 (74.9)	130 (65.3)	0.003	393 (67.4)	244 (70.9)	127 (68.3)	0.533
Thiazide	60 (8.6)	69 (7.3)	58 (5.6)	0.053	20 (8.4)	22 (11.3)	10 (5.0)	0.077	69 (11.8)	33 (9.6)	15 (8.1)	0.275

BMI body mass index, *BNP* B-type natriuretic peptide, *BUN* blood urea nitrogen, *COPD* chronic obstructive pulmonary disease, *DBP* diastolic blood pressure, *HF* heart failure, *HFmrEF* heart failure with midrange ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduce ejection fraction, *HR* heart rate, *LAD* left atrial diameter, *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonist, *NP* natriuretic peptide, *NT-proBNP* N terminal proB-type natriuretic peptide, *NYHA* New York Heart Association, *RAS* renin–angiotensin system, *SBP* systolic blood pressure


(A)
5-Year all cause mortality
(crude population)
HFrEF
HFmrEF
HFpEF
All HFrEF
Log-rank P<0.001
NP 1st tertile
Log-rank P=0.002
NP 2nd tertile
Log-rank P<0.001
NP 3rd tertile
Log-rank P<0.001
All HFmrEF
Log-rank P=0.118
NP 1st tertile
Log-rank P=0.167
NP 2nd tertile
Log-rank P=0.974
NP 3rd tertile
Log-rank P=0.118
All HFpEF
Log-rank P=0.079
NP 1st tertile
Log-rank P=0.150
NP 2nd tertile
Log-rank P=0.974
NP 3rd tertile
Log-rank P=0.041
Cumulative survival
BB (+)
BB (-)
Number at risk
Years
(B)
5-Year all cause mortality
(IPTW population)
HFrEF
HFmrEF
HFpEF
All HFrEF
P<0.001
NP 1st tertile
P=0.030
NP 2nd tertile
P=0.006
NP 3rd tertile
P=0.003
All HFmrEF
P=0.177
NP 1st tertile
P=0.231
NP 2nd tertile
P=0.880
NP 3rd tertile
P=0.173
All HFpEF
P=0.072
NP 1st tertile
P=0.099
NP 2nd tertile
P=0.736
NP 3rd tertile
P=0.033
Cumulative survival
BB (+)
BB (-)
Number at risk
Years

◂**Fig. 2** Clinical outcomes according to beta-blocker medication. The Kaplan–Meier survival curves for 5-year mortality according to beta-blocker use is presented in both (**a**) crude population and (**b**) IPTW cohort. Patients were classified according to HF phenotypes and NP tertiles. *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *HFmrEF* heart failure with midrange ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *IPTW* inverse-probability treatment-weighted, *NP* natriuretic peptide

Discussion

In this study, we confirmed an inverse relationship between LVEF and NP level and that the use of beta-blockers was associated with improved survival in HFrEF, but not in HFmrEF and HFpEF, in a large cohort of AHF patients. Regarding NP levels, taking beta-blockers improved clinical prognosis in patients with HFrEF compared to those not taking beta-blockers with similar NP levels [21]. Interestingly, although HFpEF patients had the lowest circulating NPs, when stratifying the patients according to NP tertiles, the use of beta-blockers was associated with reduced mortality in HFpEF patients with high NP levels. This study suggests that NP level may be used to identify beta-blocker responders among HFpEF patients.

HFrEF and HFpEF are characterised by different anatomy and degree of neurohumoral activation, but they demonstrate a similar prognosis [3, 16]. RAS-inhibitors, beta-blockers, MRA, ivabradine, and sacubitril/valsartan improved the prognosis of patients with HFrEF [22–25], but not of those with HFpEF [26–28]. The reason for the differential effect of these drugs according to HF types is not clear. Some possible explanations include the fact that HFpEF is a systemic inflammatory disease with multiple comorbidities and may not be amenable to pharmaceutical intervention [29, 30]. Nonetheless, there have been attempts to identify a sub-population in HFpEF patients who may benefit from medical treatment using NP levels. Regarding the interaction of drug effect and NP levels in HFpEF, in the post-hoc analysis of the TOPCAT study [31], there was a significant interaction between the effect of spironolactone and baseline NP terciles for the primary outcome ($P=0.017$), with the greater benefit of the drug in the lower compared with higher NP terciles. In the post-hoc analysis of the I-PRESERVE trial [32], irbesartan had a beneficial effect on the primary outcome (HR, 0.74; 95% CI, 0.60–90; $P=0.003$), all-cause mortality (HR, 0.75; 95% CI, 0.56–0.99; $P=0.046$), and HF composite outcome (HR, 0.57; 95% CI, 0.41–0.80; $P=0.001$) in patients with NT-proBNP below the median. The beneficial effect of the spironolactone and irbesartan in lower-risk patients with HFpEF suggests that drug intervention may be successful early but not later in the natural history of HFpEF. In the post-hoc analysis of the PARAGON-HF study [33], NT-proBNP level at screening did not modify the effect of sacubitril/valsartan compared with valsartan on the primary endpoint (P for interaction = 0.96). Since the differential effect of beta-blockers according to NP levels was unknown, our study finding contributes significantly to a better understanding of the patients with HFpEF.

In this study, we showed that HFpEF patients with increased NP levels had a lower mortality when they received beta-blockers and revealed the possibility that NP may be used to indicate beta-blocker responders in HFpEF. NP is a cardiac hormone that is mainly secreted by the ventricles in response to increased myocardial wall tension. NP has been also reported as a discerning biomarker for assessing the degree of neurohumoral activation [12, 34]. According to the law of Laplace, wall tension correlates with the LV diameter and the wall pressure, but inversely with the wall thickness. Therefore, HFrEF patients, who have an enlarged LV cavity and a relatively preserved wall thickness, have higher wall tension and, accordingly, higher NP levels than do HFpEF patients, who have a preserved LV diameter and an increased wall thickness. Indeed, a previous study showed that the release of NP from myocardium was determined mainly by left ventricular end-systolic wall stress, while diastolic stress was not a major contributor [35]. We speculate that high NP levels reflect increased myocardial wall stress and neurohumoral activation, and those patients may benefit more from beta-blockers. The fact that the proportion of patients with high NP level was small among HFpEF, might explain the overall neutral effect of beta-blockers in HFpEF.

Clinical implication

Our study provides an important hypothetical rationale for the development of a treatment strategy for patients with HFpEF. We showed that HFpEF patients with increased NP levels may benefit from beta-blocker therapy with a similar degree of impact as HFrEF patients. The beneficial effect of beta-blockers was consistent in the univariate, multivariable, and IPTW analyses, suggesting the robustness of the findings.

It would be of clinical interest to evaluate whether HFpEF patients with high NP levels may benefit from the use of other oral heart failure therapies such as RAS inhibitors or sacubitril-valsartan or MRAs. Further randomized controlled studies are demanded to verify the beneficial effects of beta-blockers demonstrated in this study.

Strengths and limitations

There are several limitations to this study. First, we analysed the data from a prospective cohort study, and unexpected confounders may have influenced the results. Second, as we enrolled and analysed patients whose LVEF and NP data were available, there might be selection bias. Third, because

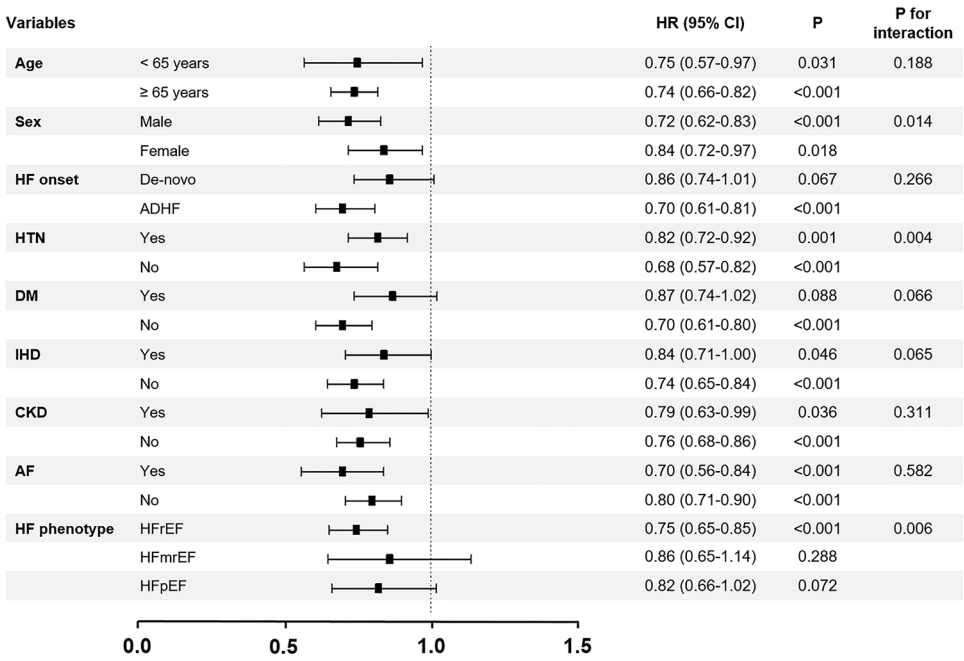


Fig. 3 Association between 5-year all-cause mortality and beta-blocker use. The effect of beta-blockers in subgroups is presented. The squares with horizontal lines indicate the HRs and corresponding 95% CIs. *AF* atrial fibrillation, *CKD* chronic kidney disease, *DM* diabetes mellitus, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF*, heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HTN* hypertension, *IHD* ischemic heart disease

we only enrolled East Asians, the study findings cannot be directly extrapolated to other populations of different ethnicities with HF. In addition, the use of beta-blockers may have been changed during follow-up. Therefore, a randomized controlled study is demanded to verify the efficacy of beta-blockers in patients with HFpEF and high NP levels. The study also has some strengths. The KorAHF registry is a well-designed, prospective cohort with all events adjudicated, and all patients were planned to be prospectively followed up at least 5 years after index hospitalisation due to AHF. To minimise the bias, we performed several statistical analyses and the interaction between beta-blocker use and clinical outcomes in HFpEF patients in the 3rd NP tertile were consistent in the univariate, multivariable, and IPTW analyses. Despite the strengths of this study, a randomised clinical trial is warranted to rigorously evaluate the effect of beta-blockers in HFpEF patients with a high NP level.

Conclusions

The use of beta-blockers at discharge is beneficial in AHF patients with HFrEF. This study is the first to show an extension of the benefit of beta-blocker therapy to AHF patients with HFpEF and high NP levels. Further randomised controlled studies are necessary to confirm the effect of beta-blockers in the latter patients.

Acknowledgements The authors appreciate John McMurrary (University of Glasgow) for his insightful advice regarding study design and the interpretation of study results.

Sources of funding None.

Compliance with ethical interest

Conflict of interest None declared.

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