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ORIGINAL ARTICLE
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β-blocker and 1-year outcomes among patients hospitalized for heart failure with mid-range ejection fraction

Bin Wang , Lihua Zhang , Shuang Hu , Xueke Bai, Haibo Zhang, Xi Li , Jing Li *†, and Xin Zheng *†

National Clinical Research Center for Cardiovascular Diseases, NHC Key Laboratory of Clinical Research for Cardiovascular Medications, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center for Cardiovascular Diseases, Building C, Fengcunxili 15, Mentougou District, Beijing 102308, China

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Aims The beneficial effect of β-blocker on heart failure with reduced ejection fraction is well established. However, its effect on the 1-year outcome of heart failure with mid-range ejection fraction (HFmrEF) remains unclear.

Methods and results We analysed the data of the patients with left ventricular ejection fraction (LVEF) between 40% and 49% in China Patient-centred Evaluative Assessment of Cardiac Events Prospective Heart Failure Study (China PEACE 5p-HF Study), in which patients hospitalized for heart failure from 52 Chinese hospitals were recruited from 2016 to 2018. Two primary outcomes were all-cause death and all-cause hospitalization. The associations between β-blocker use at discharge and outcomes were assessed by inverse probability of treatment weighting (IPTW)-weighted Cox regression analyses. To assess consistency, IPTW adjusting medications analyses, multivariable analyses and dose-effect analyses were performed. A total of 1035 HFmrEF patients were included in the analysis. The mean age was 65.5 ± 12.7 years and 377 (36.4%) were female. The median (interquartile range) of LVEF was 44% (42–47%). Six hundred and sixty-one (63.8%) were treated with β-blocker. Patients using β-blocker were younger with better cardiac function, and more likely to use renin–angiotensin system inhibitor and mineralocorticoid receptor antagonist. During the 1-year follow-up, death occurred in 84 (12.7%) treated and 85 (22.7%) untreated patients ($P < 0.0001$); all-cause hospitalization occurred in 298 (45.1%) treated and 188 (50.3%) untreated patients ($P = 0.04$). After IPTW-weighted adjustment, β-blocker use was significantly associated with lower risk of all-cause death [hazard ratio (HR): 0.70; 95% confidence interval (CI): 0.51–0.96, $P = 0.03$], but not with lower all-cause hospitalization (HR, 0.92, 95% CI, 0.76–1.10, $P = 0.36$). Consistency analyses showed consistent favourable effect of β-blocker on all-cause death, but not on all-cause hospitalization.

Conclusions Among patients with HFmrEF, β-blocker use was associated with lower risk of all-cause death, but not with lower risk of all-cause hospitalization.

Keywords Heart failure with mid-range ejection fraction • β-blocker • Mortality • Hospitalization

* Corresponding authors. Tel: 0086-60866800, Email: jing.li@fwoxford.org (J.L.); Tel: 0086-60866719, Email: xin.zheng@fwoxford.org (X.Z.)
† These authors are Joint corresponding authors.

Introduction

Heart failure with mid-range ejection fraction [HFmrEF, left ventricular ejection fraction (LVEF): 40–49%] accounts for approximately 20% of the overall heart failure (HF) population,[1] and portends similar long-term prognosis and equally impaired quality of life with heart failure with reduced ejection fraction (HFrEF, LVEF < 40%) and heart failure with preserved ejection fraction (HFpEF, LVEF ≥ 50%).[2–5] In 2016, the European Society of Cardiology officially recognized this novel HF phenotype to promote research into a population which has been left out of clinical trials.[6] The acknowledgement of HFmrEF as a separate phenotype indicates differences in underlying pathophysiologic mechanisms and responses to medications.[7,8] However, in contrast to HFrEF and HFpEF, treatment evidence for HFmrEF is still lacking, which remains as a barrier to the clinical management of HFmrEF.

Although the benefit of β-blocker on HFrEF is well established, its effect on the outcome of HFmrEF remains unclear. Currently, limited evidence of β-blocker on HFmrEF was largely derived from *post hoc* analyses of clinical trials for HFpEF. A *post hoc* analysis of TOPCAT trial including 194 HF patients with LVEF in 45–50% did not found a significant association between β-blocker use and cardiovascular (CV) death or HF hospitalization due to limited sample size.[9] A meta-analysis of 11 randomized controlled trials including 575 HFmrEF patients revealed that the beneficial effect of β-blocker on all-cause death and CV death of HFmrEF patients with sinus rhythm was similar to HFrEF.[10] However, the skewed distribution of LVEF (interquartile range: 40–43%) in the study population indicated that HFmrEF patients with LVEF in 45–50% was relatively underrepresented. More evidence on effect of β-blocker in HFmrEF is warranted to provide insights for clinical management and future guideline recommendations for HFmrEF.

Therefore, this study aims to explore the association of β-blocker use and 1-year outcomes of HFmrEF patients via inverse probability of treatment weighting (IPTW), using data from a multi-centre prospective cohort of patients hospitalized for HF in China.

Methods

Study design and population

In China Patient-centred Evaluative Assessment of Cardiac Events Prospective Heart Failure Study (China PEACE 5p-HF Study), we enrolled patients hospitalized primarily for HF from 52 Chinese hospitals located in 20 provinces between August 2016 and May 2018. The protocol of China PEACE 5p-HF Study has been published.[11] Patients aged 18 years or older, and hospitalized with a primary diagnosis of new-onset HF or decompensation of chronic HF assessed by local physicians, were enrolled in the study. LVEF was uniformly measured within 7–10 days from admission during the index hospitalization by trained physicians according to standardized protocol. LVEF was obtained from apical two- and four-chamber views and calculated with the Simpson method. In this study, HFmrEF was defined as LVEF in 40–49% ($n = 1058$). We excluded patients who died during the index hospitalization ($n = 5$) or withdrew from treatment because of terminal status ($n = 4$). We also excluded patients with potential contraindications to β-blocker therapy, including asthma ($n = 6$), systolic blood pressure <90 mmHg ($n = 5$), and heart rate <50 b.p.m. ($n = 3$). No patient had second- or third-degree atrioventricular block in the absence of a permanent pacemaker or allergy to β-blocker. A total of 1035 eligible patients were included in the final analysis (*Figure 1*). Enrolled patients completed a baseline interview during the index hospitalization and were followed up at 1-, 6-, and 12-month post-discharge. All the enrolled patients signed an informed consent within 48 h of admission and their blood and urine samples were taken for central laboratory analysis.

The central ethics committee at Fuwai Hospital and local ethics committees at participating hospitals approved the China PEACE 5p-HF Study. The study was registered at www.clinicaltrials.gov (NCT0287 8811). The investigation conformed with the principles outlined in the Declaration of Helsinki.

Data collection

For all enrolled patients, we obtained demographic (age and sex), socioeconomic (marital status and education level), and clinical characteristics through abstraction of medical charts of the index hospitalization and in-person interviews during the index hospitalization. Clinical characteristics included medical history, symptom and sign, laboratory test, prior medication use, and medication prescribed at discharge. The abstraction was performed centrally according to standardized procedures and data dictionaries, and accuracy of abstraction exceeded 98%. The use of β-blocker was determined by the prescriptions recorded at discharge.

Outcomes

The primary outcomes of the study were 1-year all-cause death and all-cause hospitalization. We also included CV death and HF hospitalization as secondary outcomes. CV death included sudden cardiac death, death due to HF, cerebrovascular events, acute coronary syndrome, aortic vascular disease, peripheral arterial disease, pulmonary heart disease, or presumed/unknown CV death.[12] Death was considered non-CV if an unequivocal and documented non-CV cause could be established as the primary cause of death. We collected information on patient survival status and hospitalization events during the 12-month follow-up period from interview, medical documents and death registry. All the data were centrally adjudicated at the national coordinating centre by trained clinicians.

Statistical analysis

We used percentage to describe categorical variables, and mean with standard deviation (SD) or median with interquartile to describe continuous variables where appropriate. In this study, we applied IPTW method to assess the effect of β-blocker. We developed a logistic regression model with β-blocker use as an outcome to obtain the propensity score with the following variables which were clinically relevant to the choice of β-blocker treatment: age, sex, smoking status, education level, marital status, New York Heart Association (NYHA) function class, hypertension, diabetes mellitus, atrial fibrillation, stroke, ischaemic heart disease, previous myocardial infarction, dilated cardiomyopathy, chronic obstructive pulmonary disease, peripheral artery disease, anaemia, history of percutaneous coronary intervention or coronary artery bypass grafting, history of pacemaker implantation, estimated glomerular filtration rate (eGFR), blood urea nitrogen, systolic blood pressure, heart rate, use of β-blocker before admission, use of renin–angiotensin system inhibitor, and use of mineralocorticoid receptor antagonist at discharge. eGFR was calculated with an equation developed by adaptation of the Modification of Diet in Renal Disease equation on the basis of data from Chinese chronic kidney disease patients.[13] Serum creatinine, blood urea nitrogen, systolic blood pressure, and heart rate were determined by the last record before discharge. Detailed definitions of medical history were listed in Supplementary material online, *Table S1*. To assess the performance of

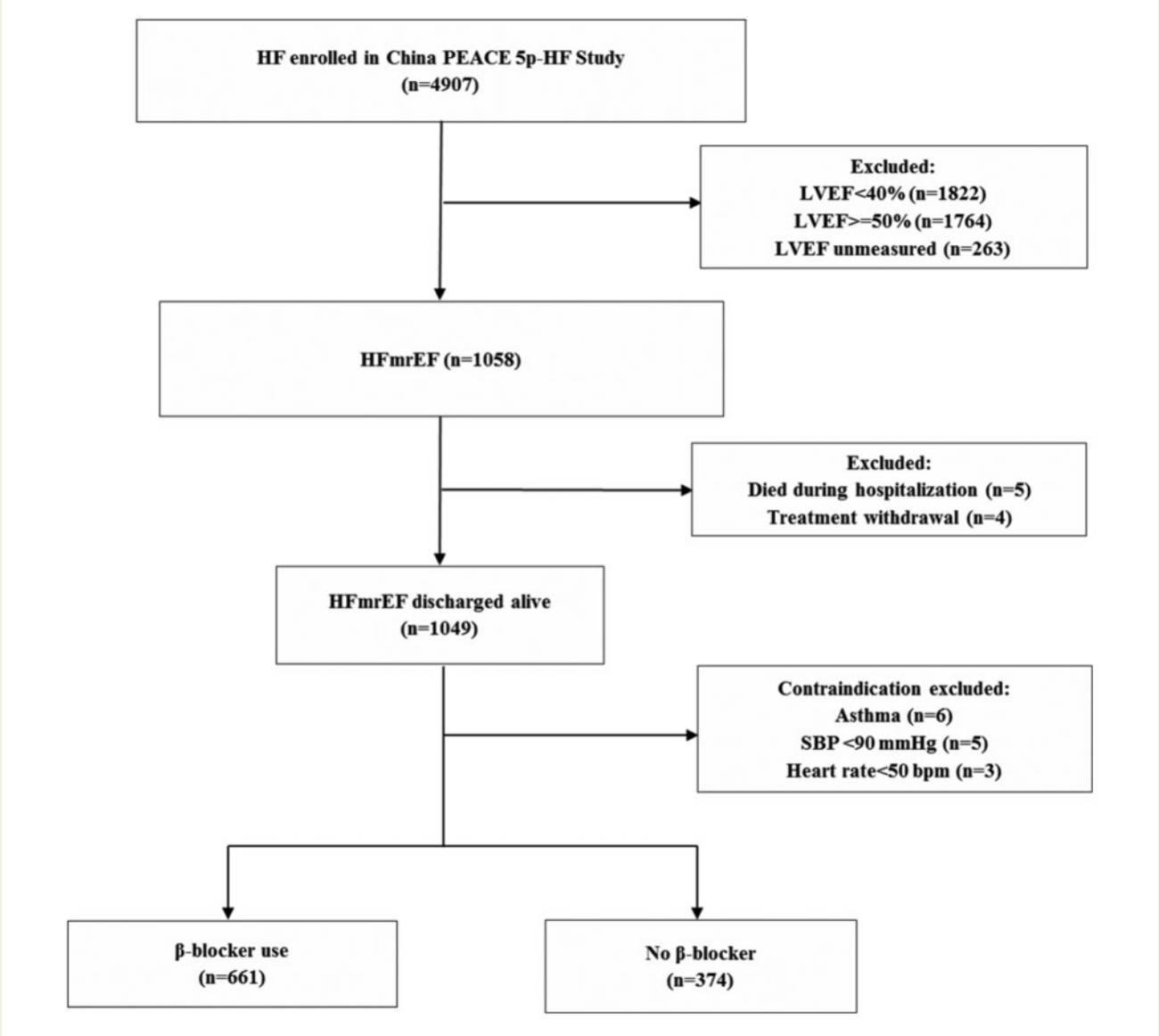

Figure 1 Overall enrolment of the study population. HFmrEF, heart failure with mid-range ejection fraction; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

the logistic regression model, we calculated Harrell C statistic to assess predictive accuracy,[14] and Hosmer–Lemeshow goodness-of-fit test to assess calibration.[15] We calculated IPTW based on the propensity score.[16] We used standardized difference to evaluate and re-evaluate difference between treated and untreated patients of all the baseline characteristics in the original population and IPTW-weighted population, with difference less than 10% accepted. We used a histogram to describe the distribution of propensity score in the unweighted and weighted population. We compared the cumulative incidence of outcomes with Kaplan–Meier method between the treated and untreated patients. We estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) with IPTW-weighted Cox regression model.[17] For outcomes of all-cause hospitalization or HF hospitalization, we performed Fine–Gray analyses with death as competing risk.[18,19] Non-CV death was considered as competing risk when assessing the outcome of CV death. The scaled Schoenfeld residuals and Martingale residuals from the Cox regression model were investigated to assess the proportional hazards assumption, and none were detected. To assess whether differential effect of β-blocker existed between HFmrEF with atrial fibrillation and sinus rhythm, we performed subgroup analysis by adding interaction term of β-blocker use and medical history of atrial fibrillation in the IPTW model.

We performed several consistency analyses to examine the robustness of the results. First, given that patients treated with β-blocker were more likely to use renin–angiotensin system inhibitor and mineralocorticoid receptor antagonist in the IPTW-weighted population, we further adjusted them in the IPTW-weighted Cox regression model. Second, we refitted a multivariable Cox regression model by accounting for baseline characteristics. Third, we explored the dose-effect of β-blocker on the outcomes of HFmrEF. We excluded patient without documentation of β-blocker's dose ($n = 15$). Based on the guideline-recommended target dose for each type of β-blocker (Supplementary material online, *Table S4*), half of the treated patients received 25% target dose. The median

Table 1 Baseline clinical characteristics of heart failure with mid-range ejection fraction by use of β-blocker

Patient characteristics	Unweighted population			Standardized difference (%)	Weighted population			Standardized difference (%)
	Overall (*n* = 1035)	β-blocker use (*n* = 661)	No β-blocker use (*n* = 374)		Overall	β-blocker use	No β-blocker use	
Age (years), mean (SD)	65.5 (12.7)	64.6 (12.6)	67.0 (12.8)	-19.0	66.0 (12.4)	65.8 (12.6)	66.3 (12.0)	-3.8
Female, *n* (%)	377 (36.4)	237 (35.9)	140 (37.4)	-3.3	377 (37.0)	237 (36.4)	140 (38.1)	-3.6
Current smoker, *n* (%)	297 (28.7)	195 (29.5)	102 (27.3)	4.9	297 (26.6)	195 (28.0)	102 (24.1)	8.8
Marital status: single, *n* (%)	192 (18.6)	116 (17.5)	76 (20.3)	-7.1	192 (18.3)	116 (18.0)	76 (19.0)	-2.8
Education level below high school, *n* (%)	731 (70.6)	465 (70.3)	266 (71.1)	-1.7	731 (72.3)	465 (71.1)	266 (74.5)	-7.6
NYHA Class III/IV, *n* (%)	810 (78.3)	500 (75.6)	310 (82.9)	-17.9	810 (77.4)	500 (76.2)	310 (79.4)	-7.6
Medical history, *n* (%)								
Hypertension	649 (62.7)	420 (63.5)	229 (61.2)	4.8	649 (65.4)	420 (63.8)	229 (68.2)	-9.3
Diabetes mellitus	357 (34.5)	236 (35.7)	121 (32.4)	7.1	357 (33.5)	236 (34.0)	121 (32.7)	2.8
Atrial fibrillation	405 (39.1)	256 (38.7)	149 (39.8)	-2.3	405 (40.2)	256 (40.6)	149 (39.5)	2.1
Stroke	213 (20.6)	143 (21.6)	70 (18.7)	7.3	213 (20.6)	143 (20.1)	70 (21.4)	-3.2
Ischaemic heart disease	668 (64.5)	437 (66.1)	231 (61.8)	9.1	668 (64.6)	437 (64.3)	231 (65.0)	-1.4
Previous MI	268 (25.9)	186 (28.1)	82 (21.9)	14.4	268 (25.8)	186 (25.9)	82 (25.7)	0.5
Valvular heart disease	150 (14.5)	86 (13.0)	64 (17.1)	-11.5	150 (14.1)	86 (14.1)	64 (14.2)	-0.3
Dilated cardiomyopathy	152 (14.7)	116 (17.5)	36 (9.6)	23.3	152 (15.2)	116 (14.4)	36 (16.7)	-6.4
COPD	169 (16.3)	103 (15.6)	66 (17.6)	-5.6	169 (19.0)	103 (18.1)	66 (20.4)	-5.9
Peripheral artery disease	116 (11.2)	76 (11.5)	40 (10.7)	2.6	116 (11.0)	76 (10.9)	40 (11.2)	-1.1
Anaemia	256 (24.7)	140 (21.2)	116 (31.0)	-22.5	256 (27.0)	140 (26.5)	116 (27.9)	-3.3
PCI or CABG	217 (21.0)	150 (22.7)	67 (17.9)	11.9	217 (21.2)	150 (21.7)	67 (20.4)	3.1
Pacemaker implantation	43 (4.2)	27 (4.1)	16 (4.3)	-1.0	43 (4.3)	27 (4.0)	16 (4.7)	-3.4
Laboratory examinations								
eGFR (mL/min/1.73 m^2), mean (SD)	83.4 (35.3)	84.2 (33.8)	82.0 (37.8)	6.2	83.1 (35.6)	83.2 (34.1)	83.0 (38.2)	0.4
Blood urea nitrogen (mg/dL), mean (SD)	7.8 (4.0)	7.7 (3.7)	8.0 (4.5)	-8.3	7.7 (3.7)	7.7 (3.8)	7.6 (3.6)	2.1
NT-proBNP[a] (pg/mL), median (IQR)	1463 (641–3254)	1434 (609–3110)	1649 (768–3526)	-8.5	1550 (702–3422)	1470 (664–3427)	1619 (805–3282)	1.4
Haemodynamic measurements								
Systolic BP (mmHg), mean (SD)	123.0 (14.9)	122.3 (14.7)	124.4 (15.2)	-14.0	123.6 (14.8)	123.0 (14.9)	124.7 (14.6)	-11.8
Heart rate (b.p.m.), mean (SD)	73.9 (10.6)	74.2 (10.4)	73.3 (10.8)	8.5	74.1 (10.4)	74.2 (10.1)	74.0 (10.9)	1.5
LVEF[a] (%), median (IQR)	44 (42–47)	44 (42–47)	44 (42–47)	-0.6	44 (42–47)	44 (42–47)	44 (42–47)	-1.8
Medication, *n* (%)								
β-blocker before admission	428 (41.4)	309 (46.7)	119 (31.8)	30.9	428 (40.9)	309 (41.8)	119 (39.3)	5.1
RASI at discharge	589 (56.9)	481 (72.8)	108 (28.9)	97.7	589 (58.3)	481 (58.7)	108 (57.5)	2.3
MRA at discharge	709 (68.5)	553 (83.7)	156 (41.7)	96.3	709 (69.9)	553 (70.2)	156 (69.4)	1.8

BP, blood pressure; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RASI, renin–angiotensin system inhibitor.
[a]Not included in derivation of the propensity score and presented for descriptive purposes.

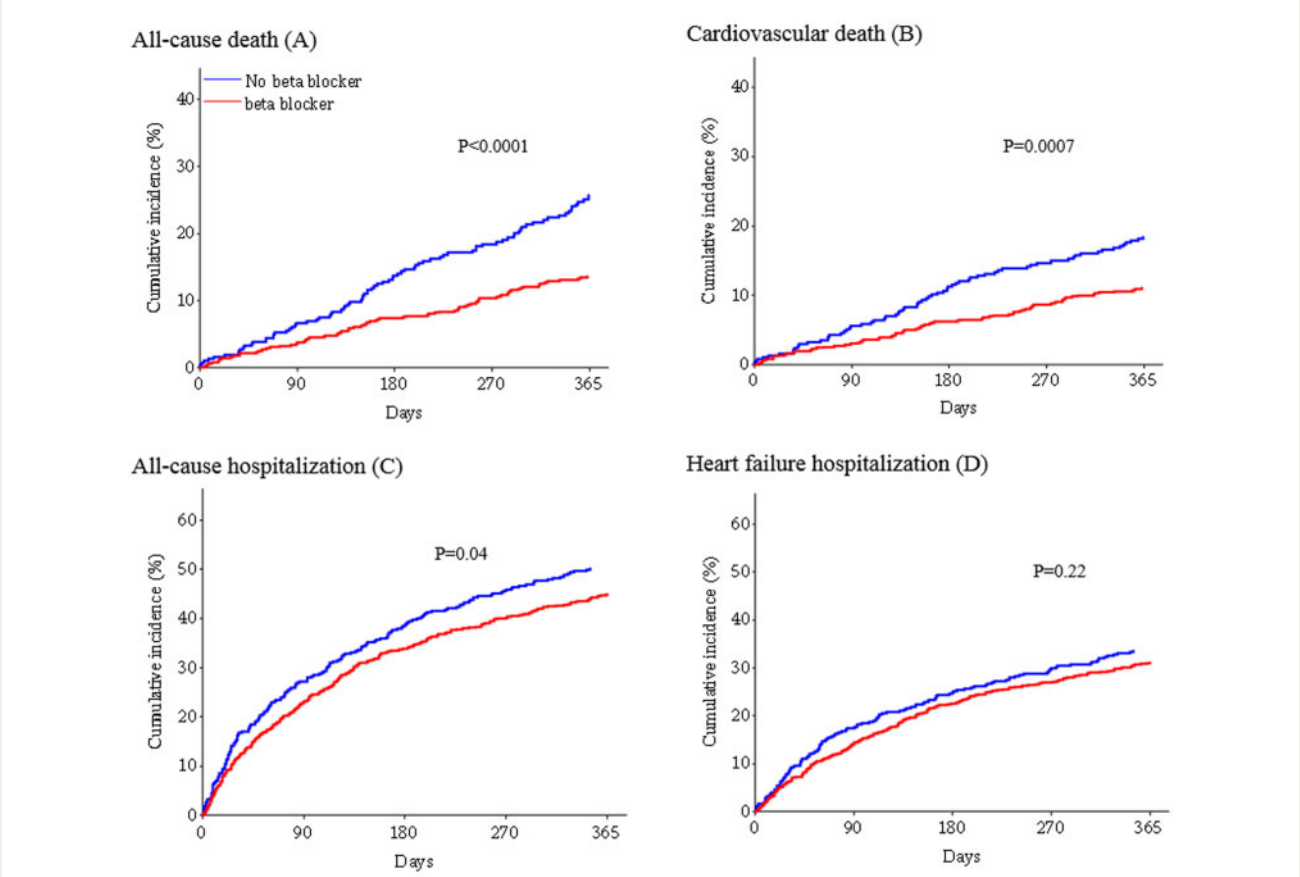

Figure 2 Cumulative incidence of death (*A*), cardiovascular death (*B*), all-cause hospitalization (*C*), and heart failure hospitalization (*D*) for patients with heart failure with mid-range ejection fraction by use of β-blocker with Kaplan–Meier method.

percentage of β-blocker target dose was 25% for overall study population. The median percentages of β-blocker target dose for patients using β-blocker before admission and those with de-novo β-blocker treatment were 25% and 17% (Supplementary material online, *Figure S2*).We stratified patients into three groups to assess the dose-effect of β-blocker: untreated group, <25% of target dose group and ≥25% of target dose group. We compared the outcomes of three groups by Kaplan–Meier method and determined HRs and 95% CIs for effect of two dose groups compared with untreated group by Cox regression analyses adjusting the baseline characteristics.

In total, rates of missing value ranged from 0.1% (systolic blood pressure) to 3.9% (serum urea nitrogen). Missing values were imputed with mean value of the overall population, respectively. The *P*-value <0.05 (two-sided test) was considered statistically significant. All analyses were performed in SAS version 9.4.

Results

Patient characteristics

Our study sample included 1035 HFmrEF patients [mean (SD) age, 65.5 (12.7) years; 36.4% female]. The median (interquartile range) of LVEF was 44% (42–47%). Six hundred and sixty-one (63.9%) patients were prescribed with β-blocker at discharge. Unweighted and weighted baseline characteristics of patients with HFmrEF according to the use of β-blocker were illustrated in *Table 1*. In the unweighted population, exposure to β-blocker differed with regard to age, NYHA class, comorbidities, systolic blood pressure, and concomitant medications. Patients treated with β-blocker were younger with better cardiac function, and more likely to use renin–angiotensin system inhibitor and mineralocorticoid receptor antagonist. After IPTW adjustment, standardized differences were considerably smaller and less than 10% for most baseline characteristics, indicating that they were comparable between the two groups. Propensity score distributions were similar in treated and untreated patients after IPTW adjustment (Supplementary material online, *Figure S1*). Results of multivariable logistic regression analysis determining the use of β-blocker were shown in Supplementary material online, *Table S2*, with C statistics 0.83 and Hosmer–Lemeshow goodness-of-fit 0.67, indicating adequate predictive accuracy and goodness of fit of the model.

Outcomes and treatment effects of β-blocker

In the overall population, a total of 169 (16.3%) patients died and 486 (47.0%) were hospitalized during the 1-year follow-up period. For secondary outcomes, 142 (13.7%) died of CV causes and 332 (32.1%) were hospitalized for HF. Cumulative incidences of

outcomes	Hazard Ratio (95% CI)	P value
All-cause death		
Crude analysis	0.53 (0.39-0.72)	<0.0001
IPTW analysis	0.70 (0.51-0.96)	0.03
IPTW adjusting medications analysis	0.69 (0.50-0.96)	0.03
Multivariable analysis[a]	0.65 (0.45-0.94)	0.02
Cardiovascular death		
Crude analysis	0.57 (0.41-0.80)	0.0009
IPTW analysis	0.73 (0.51-1.03)	0.07
IPTW adjusting medications analysis	0.73 (0.51-1.03)	0.09
Multivariable analysis[a]	0.71 (0.48-1.06)	0.08
All-cause hospitalization		
Crude analysis	0.85 (0.71-1.02)	0.08
IPTW analysis	0.92 (0.76-1.10)	0.36
IPTW adjusting medications analysis	0.92 (0.76-1.10)	0.36
Multivariable analysis[b]	0.89 (0.71-1.11)	0.30
Heart failure hospitalization		
Crude analysis	0.90 (0.72-1.12)	0.35
IPTW analysis	0.93 (0.74-1.16)	0.53
IPTW adjusting medications analysis	0.93 (0.74-1.17)	0.53
Multivariable analysis[b]	0.91 (0.69-1.21)	0.52

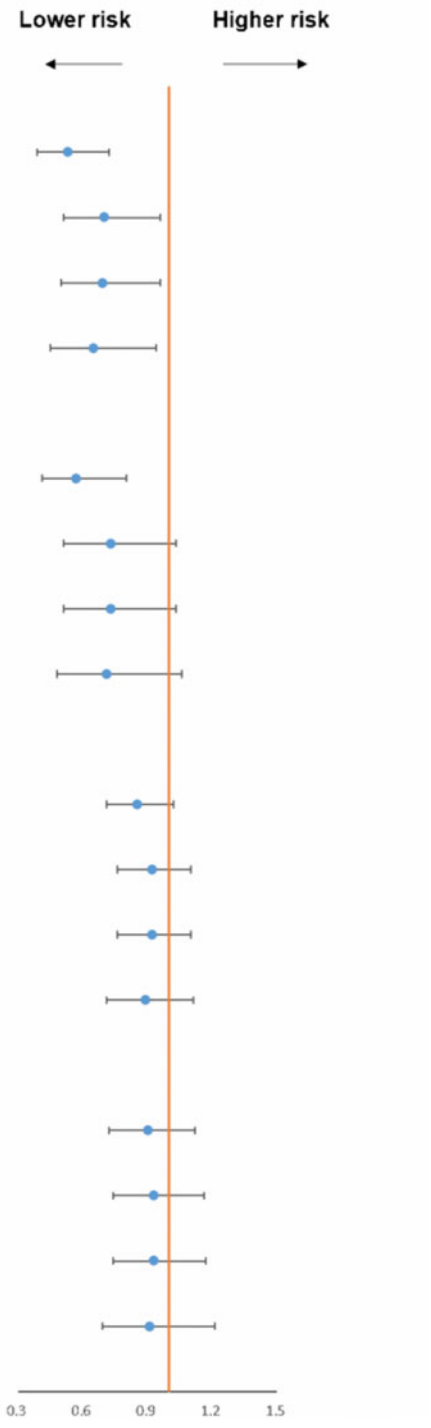

Figure 3 Associations between use of β-blocker and outcomes in the crude analyses, multivariable analyses and propensity-score analyses. [a]Adjusting age, sex, New York Heart Association function class, comorbidities, laboratory tests, systolic blood pressure, heart rate, prior beta-blocker use, and concomitant medications. [b]Adjusting age, sex, smoking status, education level, marital status, New York Heart Association function class, comorbidities, laboratory tests, systolic blood pressure, heart rate, prior beta-blocker use, and concomitant medications.

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outcomes by use of β-blocker were described using Kaplan–Meier method in *Figure 2*. Death occurred in 84 (12.7%) treated and 85 (22.7%) untreated patients ($P < 0.0001$); all-cause hospitalization occurred in 298 (45.1%) treated and 188 (50.3%) untreated patients ($P = 0.04$); CV death occurred in 73 (11.0%) treated and 69 (18.4%) untreated patients ($P = 0.0007$); HF hospitalization occurred in 206 (31.2%) treated and 126 (33.7%) untreated patients ($P = 0.22$).

In IPTW-weighted Cox regression analyses, β-blocker use was significantly associated with lower risk of all-cause death (HR, 0.70; 95% CI, 0.51–0.96, $P = 0.03$), but not with lower all-cause hospitalization (HR, 0.92, 95% CI, 0.76–1.10, $P = 0.36$). For secondary outcomes, β-blocker use was not significantly associated with lower risk of CV death (HR, 0.73, 95% CI, 0.51–1.03, $P = 0.07$) or HF hospitalization (HR, 0.93, 95% CI, 0.74–1.16, $P = 0.53$). For subgroup analyses, we found no significant differential effect of β-blocker between HFmrEF with atrial fibrillation and sinus rhythm on all the outcomes (Supplementary material online, *Table S3*).

In consistency analyses, IPTW-weighted Cox regression model adjusting concomitant medications and multivariable Cox regression analyses showed consistent results on all the outcomes with IPTW analyses (*Figure 3*). For dose-effect analyses, 84.8%, 12.2%, and 3.0% of the treated HFmrEF were treated with metoprolol, bisoprolol, and carvedilol. Cumulative incidences of outcomes for metoprolol, bisoprolol, and carvedilol were illustrated in Supplementary material online, *Table S5*. By stratifying patients into three dose groups, we plotted cumulative incidences of outcomes for untreated group, <25% of target dose group and ≥25% of target dose group by Kaplan–Meier method in Supplementary material online, *Figure S3*. With increasing dose of β-blocker, incidence of all-cause death or CV death showed decreasing trends, but similar trend was not observed on all-cause hospitalization or HF hospitalization. Similar trend patterns were also seen in multivariable analyses stratified by β-blocker doses, which were shown in Supplementary material online, *Table S6*.

Discussion

In this prospective cohort of post-hospitalization patients with HFmrEF, we found that β-blocker use was significantly associated with 30% lower risk of 1-year all-cause death. Similar association was also found between β-blocker use and CV death. However, β-blocker use was not associated with lower risk of all-cause hospitalization or HF hospitalization. Our findings were consistent in the multivariable analyses and were strengthened by a positive dose-effect relationship of β-blocker.

The relatively high proportion of HFmrEF and its poor prognosis in this study highlights the need to bridge knowledge gap of HFmrEF treatment. The proportion of HFmrEF in overall HF population differs in terms of population selection and geographic regions. According to the European Society of Cardiology Heart Failure Long-Term Registry, proportion of HFmrEF in European and Mediterranean countries ranged from 11.8% to 45.6%.[20] Compared with 7.6% of 1-year all-cause mortality reported in the registry, 16.3% of the HFmrEF patients died within 1-year follow-up in our study. The discrepancy was in part due to different clinical setting and patient selection. Worse prognosis was likely attributed to poor baseline cardiac function, high comorbidity burden and inadequate pharmacologic treatment.

Our study extends the literature in two major ways. First, it provides an assessment on the effect of β-blocker in a larger population of HFmrEF with a complete spectrum of LVEF. In the meta-analysis of trials for β-blocker,[10] the majority of HFmrEF patients with sinus rhythm had LVEF of <43% with median value of 40%, which may not represent the whole HFmrEF population. Based on a sample of HFmrEF with normal LVEF distribution, the effectiveness of β-blocker discovered on all-cause death was lower than reported in the meta-analysis (HR, 0.59, 95% CI, 0.34–1.03).[10] Moreover, the magnitude of β-blocker treatment effect on CV death was also lower than a *post hoc* analysis of the TOPCAT trial (HR, 0.62, 95% CI, 0.25–1.58), although it did not reach significance due to small sample size.[9] Second, our study reinforced its findings by applying a propensity score-based approach supported by several consistency analyses. Furthermore, our study observed a proportionally associated reduction in mortality and CV mortality with increasing dose of β-blocker. Since titration of β-blocker to higher dose confers benefit in HFrEF patient,[21,22] our findings suggested that HFmrEF patients were likely to respond similarly to HFrEF patients.

Our study provided treatment evidence for HFmrEF, which has important implications for the clinical management and future guideline recommendations. Currently, the European Society of Cardiology guideline recommends that HFmrEF patients be treated according to the management strategy of HFpEF, which does not recommend β-blocker use. Despite lack of recommendation, accumulating evidence showed that use of β-blocker was a common practice for the clinical management of HFmrEF.[4,23,24] According to the analyses from the European Society of Cardiology Heart Failure Long-Term Registry, approximately 90% of HFmrEF received β-blocker therapy.[20] Our study corroborated the benefit of wide application of β-blocker and justified its use in clinical care. In addition to the previous evidence from trials, our study could provide further evidence for future guideline recommendations of HFmrEF.

Our study indicated that β-blocker therapy could benefit HFmrEF with atrial fibrillation similarly to those with sinus rhythm. The role of β-blocker in HF with atrial fibrillation has been debated, but previous evidence most derived from HFrEF patients.[25–28] One meta-analysis including 146 HFmrEF patients with atrial fibrillation found that β-blocker therapy did not improve patients' survival,[10] but the conclusion was challenged by lack of power in the analysis. Given the scarcity of evidence and high prevalence of atrial fibrillation in HFmrEF, our study provided important insights for clinical practice. Until further evidence from large prospective trial is available, β-blocker is recommended in the management of HFmrEF with atrial fibrillation.

Our study found low prescribed dose of β-blocker therapy at discharge among HFmrEF patients, regardless of whether β-blocker was used before admission. The European Society of Cardiology guideline recommends that in acute HF patients, β-blocker should be cautiously initiated once stabilized, and β-blocker dose should double not less than 2-week intervals.[6] Moreover, physicians may not initiate high dose of β-blocker at discharge with intention to relieve congestion and achieve euvolaemia. However, β-blocker dose for HFmrEF patients with prior β-blocker use was also low, and reason for this phenomenon remains unclear. Given the increased beneficial effect

with up-titration of β-blocker dose, our study highlights that both improved utilization and up-titration of β-blocker are needed to improve the prognosis of HFmrEF.

Despite of the nearly 50% of hospitalization events, our study did not found a significant reduction on all-cause hospitalization or HF hospitalization associated with β-blocker use. In fact, several negative findings were reported in previous studies in HF with LVEF >40%. One analysis from Swedish Heart Failure Registry reported positive effect of β-blocker on all-cause mortality, but negative effect on composite event of death or HF hospitalization in HF with LVEF >40%. A meta-analysis of observational studies showed that β-blocker use was associated with improved all-cause mortality in HF with LVEF >40%, but not for HF hospitalization.[29] Reason for this divergence remains speculative. One possible explanation is that hospitalization was influenced by multi-dimensional factors, including psychosocial and socioeconomic ones, which we were unable to address in this study.

The results of our study should be interpreted with the following limitations. First, our study only included HFmrEF patients who signed informed consent within 48 h of admission and were discharged alive, and the results could not be extrapolated to overall HFmrEF patients. Second, our observational study is prone to confounding. Although we performed IPTW analyses accounting for extensive baseline characteristics and conducted several consistency analyses to examine the robustness of the results, unmeasured and residual confounding could not be eliminated. Third, information on discontinuation or initiation of β-blocker during the follow-up were not collected and therefore not considered in the analysis, which may underestimate the benefit of β-blocker. Fourth, our study did not collect information on previous documentation of LVEF, and thus could not differentiate HFmrEF into HF with recovered mid-range ejection fraction (with prior LVEF < 40%) or HFmrEF with no recovered ejection fraction (without prior LVEF < 40%), two HFmrEF phenotypes reported to portend different prognosis.[30] Fifth, given the low proportion of bisoprolol or carvedilol use, our study was underpowered to compare the agent-specific effect of β-blocker among HFmrEF. Moreover, the beneficial effect of β-blocker was largely due to metoprolol, and whether bisoprolol or carvedilol exert similar effect remains to be validated.

In conclusion, among patients with HFmrEF, use of β-blocker was associated with 30% lower risk of 1-year all-cause death, but not with lower risk of all-cause hospitalization. These findings will provide valuable insights for decision-making for HFmrEF management.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article currently cannot be shared publicly.

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