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Prescription of beta-blockers in patients with advanced heart failure and preserved left ventricular ejection fraction. Clinical implications and survival[☆]

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Abstract

Background: The effects of β -blockers in patients with heart failure (HF) and preserved left ventricular ejection fraction (LVEF) are not well established.

Aims: To assess the association between β -blocker prescription at discharge and mortality in a cohort of patients with advanced HF and preserved LVEF.

Methods and results: We prospectively studied a cohort of 443 patients with advanced HF and preserved LVEF (LVEF $\geq 40\%$). Mean age was 78 years, 56% female, 33% NYHA class IV. Overall, 227 patients (51%) had a β -blocker prescribed at discharge. Mean duration of follow-up was 25 (± 18) months. Death (all cause) occurred in 40 patients (17.6%) who were receiving a β -blocker at discharge and 73 patients (33.8%) who were not on a β -blocker. In multivariate Cox analysis, including adjustment for propensity score, prescription of a β -blocker remained associated with a 43% relative mortality risk reduction (HR 0.57, 95% CI 0.37 to 0.88, $p=0.01$).

Conclusions: In this cohort of patients with advanced HF and preserved LVEF, prescription of a β -blocker was associated with a significant mortality reduction. This beneficial effect of β -blocker use needs to be further confirmed in prospective, randomised clinical trials.

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Keywords: Heart failure; Preserved ejection fraction; β -blockers; Mortality

1. Introduction

The syndrome of heart failure (HF) may arise in the presence of either a depressed or a normal left ventricular ejection fraction (LVEF) [1,2]. Prior studies have shown that

up to 50% of patients with HF have a preserved LVEF; and that advancing age, hypertension and female sex are all correlates of this syndrome [3,4]. HF with preserved LVEF confers a considerable burden on patients, with the risk of disability, hospital admission and mortality comparable to that of HF with depressed LVEF [5–7].

There is clear evidence that β -blockers increase survival in HF patients with depressed LVEF [8–10]. Treatment with β -blockers may be also beneficial in HF patients with preserved LVEF [11]. However, no large randomised trial or cohort study addressing the role of β -blocker therapy in HF with preserved LVEF has been yet completed. Such information is

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particularly important given the high percentage of patients with HF and preserved LVEF, and the lack of evidence-based recommendations for its management [12].

The EuroHeart Failure Survey showed that patients with HF and preserved LVEF were less likely to receive β -blockers compared to patients with depressed LVEF, while no significant difference in β -blocker effect on mortality between the two groups was observed [13]. However, it should be noted that in the EuroHeart Failure Survey patients were only followed-up for three months. Previous randomised trials or cohort studies that assessed the effect of β -blocker therapy on mortality, have either had a small sample size [14,15], or have presented an overall effect of β -blockers in elderly patients with HF, regardless of LVEF [16–18].

In this study, we therefore aimed to assess the association between β -blocker prescription at discharge and mortality in a cohort of patients with advanced HF and preserved LVEF.

2. Methods

2.1. Patients

Patients were selected at the Cardiology Department of Rijnland General Hospital, Leiderdorp, The Netherlands, between January 2000 and June 2005. Patients admitted to hospital with New York Heart Association (NYHA) class III or IV heart failure, and aged ≥ 30 years were eligible for the study. Referral of patients for admission was made by general practitioners, other units of the hospital, or the outpatient clinic. HF with *depressed LVEF* was diagnosed on the basis of clinical presentation (signs and symptoms of HF), and the presence of systolic functional impairment by echocardiography ($EF < 40\%$). HF with *preserved LVEF* was diagnosed based on clinical symptoms, radiographic evidence of HF and/or evidence of underlying heart disease, and $EF \geq 40\%$ [6,13]. The latter group forms the present study population.

2.2. Medication and clinical variables

Demographic characteristics, clinical data, and medication prescribed at discharge were collected prospectively from the patients' files. Since β -blockers are usually prescribed in multiple drug combinations, the following classes of medication were considered: angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone antagonists, loop diuretics, digitalis, calcium-channel blockers, antiarrhythmics, nitrates and oral anticoagulants. In addition, to explore the effect of low and high dose therapy, β -blockers were classified into one of three mutually exclusive groups: not dispensed, low dose or high dose. Low-dose β -blockers was defined as $< 50\%$ of the target dose achieved in randomized clinical trials (RCTs); high dose was defined as $\geq 50\%$ of the dose used in RCTs [12,18]. We selected this classification because only a small percentage of patients were prescribed target doses of β -blockers. Target doses were 50 mg for carvedilol, 200 mg for metoprolol, 10 mg for bisoprolol,

and 10 mg for nebivolol. After discharge, we considered medication constant during follow-up.

Clinical characteristics considered as candidate variables for adjustment included: age, sex, history of hypertension or myocardial infarction (MI), severity of CHF assessed by NYHA class, heart rate, mean arterial pressure, renal function assessed by glomerular filtration rate, haemoglobin levels, and comorbidities such as diabetes, chronic obstructive pulmonary disease (COPD), stroke, and atrial fibrillation (AF). Glomerular filtration rate (GFR) was calculated using the Cockcroft–Gault equation: $[(140 - \text{age in years}) \times (\text{body weight in kg})] / \text{serum creatinine in } \mu\text{mol/L}$. In men, the value is multiplied by 1.25. Mean arterial pressure was calculated as the sum of $2/3$ diastolic blood pressure and $1/3$ systolic blood pressure. Anaemia was defined as haemoglobin < 8.5 mmol/L for men, and < 7.5 mmol/L for women. Sixty one patients (7.7%) who did not have an EF measurement at discharge, and 20 patients (3%) transferred to other departments were excluded from the analysis. Patients without an EF measurement at discharge did not differ significantly in sex, or mortality rate, but were on average six years older than patients in the study group. Haemoglobin levels were missing in 41 patients (5.2%), and the values were obtained by estimated mean imputation, a statistical method used to replace missing values.

2.3. Outcomes

Clinical outcome included all-cause mortality. Follow-up was calculated from the date of discharge until July 2005. Deaths during follow-up were obtained from hospital records, next-of-kin review or by telephone.

2.4. Statistical analysis

Differences between the patient subgroups were evaluated using t test, ANOVA or Chi-square test, as appropriate.

To assess the association between β -blocker prescription and mortality during follow-up we used multivariate Cox proportional hazard models. We controlled for baseline characteristics that had an independent association with survival up to $p \leq 0.1$. Other variables considered as important confounders (sex, and heart rate) were also kept in the model. To investigate whether the relationship between survival and continuous variables was linear, hazard ratios of the quintiles were calculated. If linearity was not demonstrated, the variable was recoded categorically. To minimize selection bias, we also adjusted for propensity score of β -blocker use [19]. For each patient, a propensity score indicating the likelihood of being prescribed a β -blocker was calculated by logistic regression. Baseline characteristics that had an independent association with prescription of a β -blocker ($p < 0.5$) and those known as important predictors were included in the multivariate logistic model. Goodness of fit of the propensity score was evaluated by the Hosmer–Lemeshow test and discrimination by the c statistic. Propensity score was included as a covariate in the model.

Table 1
Baseline characteristics of the whole study population

Variables	EF < 40% (range 10–39%) (n = 289)	EF ≥ 40% range (40–70%) (n = 443)	P value ^a
Age, mean (SD)	74.1 (11.3)	77.6 (10.1)	<0.001
Sex (% female)	33.2	55.5	<0.001
History of myocardial infarction (%)	52.6	36.1	<0.001
History of hypertension (%)	37.4	49.4	0.001
NYHA (% class IV)	33.9	33.4	0.8
Heart rate, beats/min, mean (SD)	99.9 (24.8)	97.6 (29.1)	0.3
Mean arterial pressure, mm Hg (SD)	97.6 (20.2)	104.4 (22.6)	<0.001
Diabetes (%)	29.8	28.7	0.7
Atrial fibrillation (%)	32.5	44.5	0.001
COPD (%)	28.7	28.4	0.9
Stroke (%)	11.4	12.6	0.6
Sodium serum < 137 mmol/L (%)	33.6	28.2	0.1
Haemoglobin < 8.5/7.5 mmol/L (%)	53.3	54.4	0.7
GFR ≤ 40 mL/min (%)	49.1	55.8	0.08
Medication at discharge (%)			
β-blocker	50.1	51.2	0.7
β-blocker			0.07
Low dose	30.4	21.0	
High dose	19.7	30.2	
ACE inhibitor	76.5	65.5	0.002
Angiotensin-receptor blocker	9.7	12.0	0.3
Loop diuretic	90.0	88.0	0.4
Spironolactone	42.2	40.6	0.7
Digoxin	22.5	22.1	0.9
Antiarrhythmic	26.6	20.1	0.04
Nitrates	50.9	46.5	0.2
Calcium-channel blockers	8.0	15.3	0.003
Oral anticoagulant	84.8	81.9	0.3

NYHA = New York Heart Association; LVEF = Left ventricular ejection fraction; GFR = glomerular filtration rate, COPD = chronic obstructive pulmonary disease.

Low-dose β-blocker is defined as <50% of the target dose attained in RCT; High dose is defined as ≥ 50% of the target dose attained in RCT.

^a For group differences on continuous measures, we used *t* test. Categorical variables were compared with Chi-square test.

A secondary analysis that assessed the association between β-blocker dose and mortality was performed. The risk of death was presented by hazard ratios (HR) with 95% confidence intervals (CI). All reported probabilities were two-tailed, and a *p* value < 0.05 was considered statistically significant. Data were analyzed with SPSS version 12.0.

We acknowledge the fact that the discussion on how to define HF with preserved LVEF is still on-going, and the threshold of 40% for the distinction of preserved LVEF may be challenged [12,20,21]. Therefore, subsidiary analysis including patients with preserved LVEF defined as EF ≥ 45%, and EF ≥ 50% were performed.

3. Results

3.1. Patient characteristics

3.1.1. Total cohort

The total cohort at discharge included 732 patients, of whom 443 (60%) had preserved LVEF (EF ≥ 40%), and 289 (40%) depressed LVEF (EF < 40%) (Table 1). Patients with preserved LVEF were older, more often female, had a higher mean arterial pressure at discharge and more often a history of AF and hypertension. Patients with depressed LVEF were more likely to have a history of MI. Furthermore, patients with preserved LVEF were more often prescribed calcium-channel blockers, but less often ACEI or antiarrhythmic agents compared to patients with depressed LVEF. There

Table 2
Characteristics of patients with advanced HF and preserved EF according to β-blocker use

Variables	No β-blocker (n = 216)	β-blocker (n = 227)	P value ^a
Age, mean (SD)	78.4 (9.2)	76.8 (10.8)	0.09
Sex (% female)	53.2	57.7	0.3
History of myocardial infarction (%)	36.1	36.1	0.9
History of hypertension (%)	44.0	54.6	0.03
NYHA (% class IV)	36.1	30.8	0.2
LVEF, mean (SD)	53.9 (10.2)	53.0 (10.2)	0.4
Mean arterial pressure, mmHg (SD)	100.5 (20.5)	104.1 (22.5)	<0.001
Heart rate, beats/min, mean (SD)	95.4 (28.6)	99.9 (28.9)	0.3
Angina (%)	19.2	25.2	0.1
Diabetes (%)	29.6	27.8	0.6
COPD (%)	36.6	20.7	<0.001
Atrial fibrillation (%)	45.4	43.6	0.7
Stroke (%)	13.0	12.3	0.8
Sodium serum < 137 mmol/L (%)	29.6	26.9	0.5
Haemoglobin < 8.5/7.5 mmol/L (%)	52.8	55.9	0.5
GFR ≤ 40 mL/min (%)	52.3	59.0	0.1
CABG	16.2	12.3	0.2
PTCA	8.3	11.0	0.3
Medication at discharge (%)			
ACE inhibitors	66.2	64.8	0.7
Angiotensin-receptor blocker	10.6	13.2	0.5
Loop diuretic	87.5	88.5	0.7
Spironolactone	41.7	39.6	0.7
Digoxin	28.2	16.3	0.002
Antiarrhythmic	27.8	12.8	<0.001
Nitrates	40.7	52.0	0.02
Calcium-channel blockers	16.7	14.1	0.5
Oral anticoagulant	77.3	86.3	0.01

NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; GFR = glomerular filtration rate; CABG = coronary artery by-pass graft; PTCA = percutaneous transluminal coronary angioplasty, COPD = chronic obstructive pulmonary disease.

^a For group differences on continuous measures, we used *t* test. Categorical variables were compared with Chi-square test.

was no significant difference in β -blocker use between the two groups, but more patients with preserved LVEF received higher doses of β -blockers.

3.2. Patients with preserved LVEF ($EF \geq 40$)

The mean age of patients was 78 years (median 80 years, 90% reference range 56 to 90 years), 56% were female, and 33% were in NYHA IV (Table 1). Approximately 50% of patients had a history of hypertension, and 36% had a history of MI. The prevalence of diabetes, AF and COPD was 29%, 45% and 28%, respectively. Fifty-six percent of patients had a $GFR \leq 40$ ml/min. Overall, 227 patients (51%) had a β -blocker prescribed at discharge. The most frequently prescribed β -blockers were metoprolol (55%), carvedilol (29%), and bisoprolol (12%).

Patients receiving β -blockers more often had a history of hypertension, a higher mean arterial pressure at discharge, and a lower prevalence of COPD (Table 2). In addition, patients on β -blockers tended to be younger, with more symptoms of angina, and a lower GFR. Users of β -blockers were less likely to receive digoxin and antiarrhythmics. Conversely, they were more often prescribed nitrates and oral anticoagulants. There was no significant difference in prescribing levels for ACEIs, loop diuretics or spironolactone between those patients receiving β -blockers and those who were not.

3.3. Mortality outcome

Mean duration of follow-up was 25 (± 18) months. Death (all cause) occurred in 40 patients (17.6%) receiving a β -blocker and 73 patients (33.8%) who were not receiving a β -blocker.

In univariate analysis, the following variables were associated with a higher risk of death: lower mean arterial pressure ($p=0.005$), COPD ($p=0.008$), low GFR ($p=0.006$), ischaemic aetiology (versus history of hypertension) ($p=0.02$), non-prescription of a β -blocker ($p=0.001$), and prescription of digoxin ($p=0.09$), and older age ($p=0.1$).

Table 3
Odds ratios for propensity scores associated with β -blocker prescription

Variable ^a	β -blocker Odds ratio (95% CI)
Age	0.96 (0.93–0.98)
MAP	1.02 (1.002–1.03)
COPD	0.51 (0.32–0.82)
$GFR \leq 40$ mL/min	1.91 (1.14–3.21)
Digoxin	0.39 (0.22–0.67)
Antiarrhythmic	0.27 (0.16–0.49)
Nitrates	2.03 (1.28–3.21)
Oral anticoagulant	2.99 (1.64–5.47)

^a Variables that had an independent relationship with the decision to prescribe a β -blocker at $p < 0.5$ and those known as important predictors were included in the multivariate logistic regression model to form the propensity score.

Table 4

Multivariate relation between β -blocker use and mortality in patients with advanced HF and $EF \geq 40\%$

Variable	N (%)	Adjusted HR	95% CI	P value
β -blockers	227 (51)	0.57	0.37–0.88	0.01
$GFR \leq 40$ mL/min	247 (56)	2.14	1.37–3.34	0.001
COPD	126 (28)	1.60	1.04–2.45	0.03
Sex (male)	197 (44)	1.48	1.00–2.19	0.05
Digoxin	98 (22)	1.58	1.006–2.47	0.05

Adjusted for age, sex, mean arterial pressure, history of hypertension, heart rate, GFR, COPD, digoxin, and propensity scores for β -blocker use.

3.4. Determinants of β -blocker use (propensity score analysis)

Propensity score for β -blocker use included 23 clinical variables: age, sex, history of MI, history of hypertension, pulmonary hypertension, LVEF, NYHA class, MAP, heart rate, diabetes, COPD, AF, GFR, CABG, PTCA, ACEI, loop diuretics, spironolactone, digoxin, antiarrhythmics, nitrates, calcium-channel blockers and oral anticoagulants. Multivariate logistic analysis revealed that patients were more likely to be prescribed β -blockers if they were younger, had a higher mean arterial pressure, a low GFR, or had a nitrate or an oral anticoagulant prescribed. In contrast, β -blockers were less likely to be prescribed if patients had COPD, or had an antiarrhythmic or digoxin prescribed (Table 3). The model had a good discriminatory power and good fit (c -statistics, 0.75; overall goodness of fit Hosmer–Lemeshow test; $\chi^2=13$, $p=0.1$). Inclusion of different variables in the model, including angina (with 4% missing values), showed similar results.

Fig. 1. Cox adjusted survival curves in HF patients with preserved LVEF who received or who did not receive a β -blocker at discharge. Adjusted for age, sex, mean arterial pressure, history of hypertension, heart rate, GFR, COPD, digoxin, and propensity scores for β -blocker use.

Table 5

Multivariate relation between β -blocker dose and mortality in patients with advanced HF and EF $\geq 40\%$

Variable	N (%)	Adjusted HR	95% CI	P value
β -blockers				
Low dose	93 (41)	0.74	0.45–1.21	0.2
High dose	134 (59)	0.51	0.30–0.86	0.01

Adjusted for age, sex, mean arterial pressure, history of hypertension, heart rate, GFR, COPD, and digoxin use.

Low-dose β -blocker is defined as $<50\%$ of the target dose attained in RCT; High dose is defined as $\geq 50\%$ of the target dose attained in RCT.

3.5. Multivariate analysis

Prescription of a β -blocker remained associated with a significant decrease in mortality risk after adjustment for relevant clinical variables ([HR] 0.60, 95% CI 0.40 to 0.90), as well as after additional adjustment for propensity score ([HR] 0.57, 95% CI 0.37 to 0.87) (Table 4). Survival benefit appeared early after discharge and was constant during follow-up (Fig. 1). The other variables independently associated with an increased risk of death were low GFR, COPD, male sex, and prescription of digoxin (Table 4). Sensitivity analysis including patients with preserved LVEF defined as either EF $\geq 45\%$ or EF $\geq 50\%$ showed similar results.

3.6. β -blocker dose and mortality

Of the 227 patients (51%) who had a β -blocker prescribed at discharge, 93 (41%) received low-dose therapy ($<50\%$ target dose), and 134 (59%) received high-dose therapy ($\geq 50\%$ target dose). Of the 134 patients prescribed high-dose therapy, 93 (69%) received half of the target dose and 41 (31%) received target doses of β -blockers. Patients receiving high doses of β -blockers were more often younger (mean age 75 versus 79 years) ($p=0.008$), had a higher mean arterial pressure at discharge ($p<0.001$), a higher prevalence of hypertension (0.005), and a lower prevalence of COPD ($p<0.001$). Users of high dose β -blockers were significantly less likely to receive antiarrhythmics and digoxin, but more likely to receive nitrates and oral anticoagulants (results not shown).

After adjustment for relevant clinical variables, there was a difference in the relative mortality reduction between high and low dose β -blocker therapy; high dose β -blocker therapy was associated with a 49% relative risk reduction ([HR] 0.51, 95% CI 0.30 to 0.86), whereas low-dose therapy was associated with a 26% risk reduction (not significant) (Table 5).

4. Discussion

This prospective observational study is the first to indicate that treatment with β -blockers reduces mortality in patients with advanced HF and preserved LVEF (EF ≥ 40). Although β -blocker users have a different clinical risk profile than non-users, the positive effects of β -blockers remain consistent after adjustment for these differences. Further-

more, our data suggest that β -blocker benefit may be dose-related, with high-dose therapy being associated with a lower risk of death than low-dose therapy.

Similar to previous reports, we identified older age, female sex, and a history of hypertension and AF as correlates of preserved LVEF in our HF population [5,6]. The rate of prescription for β -blockers ($\sim 50\%$) was similar to that reported in CHARM-Preserved [20], and was mainly correlated with a high mean arterial pressure at discharge. Interestingly, patients with renal impairment had a higher chance of receiving a β -blocker, possibly due to the risk of prescribing an ACEI in this group (Table 3). The higher prescription of oral anticoagulants among β -blocker users may be related to the increased risk of stroke in this population, in the clinical context of hypertension and AF [22].

Heart failure with preserved LVEF represents nearly half of all HF patients, and is associated with high morbidity and mortality [5–7]. However, despite the high medical and economic impact, treatment of this syndrome remains highly speculative due to the lack of large RCTs [24]. To date, only CHARM-Preserved (candesartan) and the DIG trial (digoxin) have reported on patients with preserved LVEF [20,23]. Results showed that the ARB candesartan reduced cardiovascular hospitalisations, and digoxin reduced HF hospitalisations, but neither drug significantly affected the primary end point (cardiovascular death or heart failure hospitalisation) or cardiovascular death. In a small RCT propranolol was shown to reduce the combined end point of death or non-fatal MI in elderly patients (age ≥ 65 years) with prior MI, HF and EF $\geq 40\%$ [14]. SENIORS was the first trial to assess the effects of the β -blocker nebivolol in elderly patients with HF, 35% of whom had preserved LVEF [16]. Nebivolol reduced the combined end point of death or hospital admission, but the effect on all-cause mortality was lower compared to that reported in younger patients with systolic dysfunction. As the trial was not designed to assess the separate effects of nebivolol in patients with preserved LVEF, it remains unclear whether the lower effect was due to inclusion of this specific group [25]. Cohort studies in HF with preserved EF are also limited. The EuroHeart Failure Survey was the first observational study that suggested a similar effect of β -blockers in patients with preserved and depressed LVEF [13]. Compared to the EuroHeart Survey, we described the clinical setting of β -blocker use, and we performed a more robust analysis, using propensity score to assess the effect of medication in an observational design. In contrast to our findings, Kezner et al. did not report prescription of a β -blocker to be among significant predictors of mortality in patients with HF and EF $\geq 40\%$ [15]. However, the study included only a small sample size. Other cohort studies that assessed the effects of β -blockers on mortality in patients with HF and both depressed and preserved LVEF have reported a relative risk reduction of $\sim 40\%$ [17,18]. However, these studies did not assess the separate effects of β -blockers in patients with preserved LVEF.

The mechanism by which β -blockers may provide benefit in HF with preserved LVEF has not been clearly established. It

might be, that by reducing heart rate and increasing relaxation, β -blockers increase diastolic filling, thereby improving myocardial perfusion and leading to less ischaemia [11,24,26]. The anti-hypertensive actions of β -blockers may also be important. In chronic hypertension, active therapy reduces the incidence of HF by as much as 50%. Increased blood pressure might also impact on mortality in HF patients with preserved LVEF [27]. Animal research has shown that β -blocker treatment prevented LV hypertrophy, myocardial fibrosis and further progression of LV diastolic dysfunction while improving survival in a hypertensive diastolic HF model [28]. Other benefits of β -blockers may include prevention and reduction of arrhythmias [29,30], and reduction in acute coronary events, especially since about 40% of patients in our study had a prior MI. Whether or not β -blockers provide benefit through sympathetic modulation is uncertain, as previous reports present contradictory findings on sympathetic activation in HF with preserved LVEF [2,31]. Thus, one may speculate that β -blockers act through a different primary mechanism in patients with depressed and those with preserved LVEF.

Our finding of a dose-related effect of β -blockers on mortality is of clinical interest. In this, as well as in other studies of older patients with HF, only a small percentage of subjects received target doses of β -blockers [18]. Thus, the high-dose β -blocker group mainly comprised patients on moderate β -blocker doses. The dose prescribed was related to the risk profile, as patients receiving low doses were older, and had lower blood pressure. Given the risk status, it is possible that the target dose was often not achieved due to patient intolerance. However, it is also possible that physicians feared that higher doses of β -blockers would be associated with side effects, and therefore prescribed doses cautiously. In older patients, an altered response to β -blocker therapy may occur [32,33], thus accounting for a lower effect of low-dose medication. On the other hand, the increased risk of dying from multiple causes in the elderly may also underscore a potential benefit of β -blockers.

At present, it is widely acknowledged that patients enrolled in RCTs are a highly selected group [34,35]. In particular, exclusion of patients with severe comorbidities, especially renal dysfunction may limit the generalizability of the results of RCTs. A strength of our study is therefore the inclusion of “real-life” patients, so that our results may be extrapolated to daily practice in patients with advanced HF and preserved LVEF.

Our study has a number of limitations. First, because it is not a randomised trial, other risk factors may have played a role. To address this issue, we adjusted for many variables, and we used statistical techniques to minimize selection bias. However, propensity score technique cannot adjust for unmeasured or unknown covariates that could have influenced both prescription of beta-blockers and survival, and thus residual confounding is still possible. Second, we assumed that patients with signs and symptoms of HF, underlying heart disease and preserved LVEF have diastolic dysfunction, but no additional investigation was attempted to diagnose diastolic

dysfunction as a cause of symptoms [36,37]. Finally, we assumed that medication prescribed at discharge was constant during follow-up. Previous studies have shown that patients discharged without a β -blocker prescription are unlikely to be started on this therapy as outpatients [38]. However, in patients who are discharged on β -blockers, there is a slight decline in use after discharge. If this is the case, the effect of β -blockers in our study might be overestimated, though we assume not to a great extent. To account for a potential change in medication during follow-up readmissions, we performed the analysis with readmitted patients excluded, and the results were similar. Nevertheless, given the potential limitations of the observational design, the results have to be interpreted with caution, and further randomised studies are needed to confirm these findings.

In conclusion, this study suggests that prescription of a β -blocker is associated with a significant mortality reduction in patients with advanced HF and preserved LVEF. These beneficial effects of β -blocker use need to be further confirmed in prospective, randomised clinical trials.

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