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## Beta-blockers in older patients with heart failure and preserved ejection fraction: class, dosage, and outcomes

Kanan Patel, MBBS, MPH<sup>a</sup>, Gregg C. Fonarow, MD<sup>b</sup>, O. James Ekundayo, MD, DrPH<sup>c</sup>, Inmaculada B. Aban, PhD<sup>d</sup>, Meredith L. Kilgore, PhD<sup>d</sup>, Thomas E. Love, PhD<sup>e</sup>, Dalane W. Kitzman, MD<sup>f</sup>, Mihai Gheorghiade, MD<sup>g</sup>, Richard M. Allman, MD<sup>h</sup>, and Ali Ahmed, MD, MPH<sup>d,i</sup>

<sup>a</sup>University of California, San Francisco, CA

<sup>b</sup>University of California, Los Angeles, CA

<sup>c</sup>Meharry Medical College, Nashville, TN

<sup>d</sup>University of Alabama at Birmingham, Birmingham, AL

<sup>e</sup>Case Western Reserve University, Cleveland, OH

<sup>f</sup>Wake Forest School of Medicine, Winston-Salem, NC

<sup>g</sup>Northwestern University, Chicago, IL

<sup>h</sup>Department of Veterans Affairs, Geriatrics and Extended Care Services, Washington, DC

<sup>i</sup>Veterans Affairs Medical Center, Birmingham, AL

### Abstract

**Background**—We examined the clinical effectiveness of beta-blockers considered evidenced-based to heart failure and reduced ejection fraction (HFrEF) and recommended target dosing in older adults with HF and preserved ejection fraction (HFpEF).

**Methods**—In OPTIMIZE-HF (2003–2004) linked to Medicare (2003–2008), of the 10,570 older (age 65, mean, 81 years) adults with HFpEF (EF 40%, mean 55%), 8373 had no contraindications to beta-blocker therapy. After excluding 4614 patients receiving pre-admission beta-blockers, the remaining 3759 patients were potentially eligible for new discharge prescriptions for beta-blockers and 1454 received them. We assembled a propensity-matched

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**Corresponding author:** Ali Ahmed, MD, MPH, University of Alabama at Birmingham, 1720 2<sup>nd</sup> Ave South, CH-19, Ste-219, Birmingham, AL 35294-2041; **Telephone:** 1-205-934-9632; **Fax:** 1-205-975-7099; aahmed@uab.edu.

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**Conflict of Interest:** None

All other authors have no conflict of interest to declare.

#### Contributors

AA, GCF, IBA, TEL conceived the study hypothesis and design, and KP, OJE, GCF, and AA wrote the first draft. AA and KP conducted statistical analyses in collaboration with TEL and IBA. All authors interpreted the data, participated in critical revision of the paper for important intellectual content, and approved the final version of the article. AA, KP and IBA had full access to the data.

cohort of 1099 pairs of patients receiving beta-blockers and no beta-blockers, balanced on 115 baseline characteristics. Evidence-based beta-blockers for HF<sub>r</sub>EF, namely, carvedilol, metoprolol succinate, and bisoprolol and their respective guideline-recommended target doses were 50, 200, and 10 mg/day.

**Results**—During 6 years of follow-up, new discharge prescriptions for beta-blockers had no association with the primary composite endpoint of all-cause mortality or HF rehospitalization (hazard ratio, 1.03; 95% confidence interval {CI}, 0.94–1.13;  $p=0.569$ ). This association did not vary by beta-blocker evidence class or daily dose. Hazard ratios for all-cause mortality and HF rehospitalization were 0.99 (95% CI, 0.90–1.10;  $p=0.897$ ) and 1.17 (95% CI, 1.03–1.34;  $p=0.014$ ). The latter association lost significance when higher EF cutoffs of 45%, 50% and 55% were used.

**Conclusions**—Initiation of therapy with beta-blockers considered evidence-based for HF<sub>r</sub>EF and in target doses recommended for HF<sub>r</sub>EF had no association with the composite or individual endpoints of all-cause mortality or HF rehospitalization in HF<sub>p</sub>EF.

## Keywords

Beta-blockers; heart failure; preserved ejection fraction

## 1. Introduction

Beta-blockers constitute one of the mainstays of evidence-based therapy for patients with heart failure and reduced ejection fraction (HF<sub>r</sub>EF) [1]. Nearly half of the estimated 6 million HF patients have HF with preserved ejection fraction (HF<sub>p</sub>EF) [2]. Findings from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry suggest that despite some differences in baseline characteristics, patients with HF<sub>p</sub>EF are prognostically similar to those with HF<sub>r</sub>EF [3, 4]. The vast majority of HF patients are  $\geq 65$  years, and most of the older HF patients have HF<sub>p</sub>EF [5]. Yet, they were often excluded from major randomized controlled trials (RCTs) [6]. In the OPTIMIZE-HF, the initiation of beta-blocker therapy had no association with all-cause mortality or all-cause hospital readmission during the first year of follow-up in older HF<sub>p</sub>EF patients [6]. However, their associations with hospital readmission due to HF, long-term mortality beyond one year, and whether these outcomes varied between beta-blockers considered evidence-based for HF<sub>r</sub>EF (versus other beta-blockers) and between target doses recommended for HF<sub>r</sub>EF (versus below-target doses) remain unknown and these important questions are unlikely to be answered by new RCTs. When RCTs are unavailable, impractical, or unethical, propensity score-matched non-RCT studies, which allow outcome-blinded retrospective assembly of balanced cohorts, may provide timely and cost-effective [7–10]. Therefore, in the current study, we examined the association of beta-blocker therapy with long-term outcomes in propensity-matched cohorts of real-world older HF<sub>p</sub>EF patients, overall, and by their HF<sub>r</sub>EF evidence class and target doses.

## 2. Materials and methods

### 2.1. Source of data and study patients

The OPTIMIZE-HF is a United States national registry of hospitalized HF patients and has been well described in the literature [11–13]. Briefly, patients with a primary discharge diagnosis of HF based on International Classification of Diseases, 9<sup>th</sup> Revision codes were eligible for inclusion in OPTIMIZE-HF [14]. Extensive data on baseline demographics, medical history including admission and discharge medications, hospital course, and discharge disposition were abstracted and collected by trained staff from 48,612 charts from 259 hospitals from 48 states between March 2003 and December 2004 [11]. To prevent out-of-range entry or duplicate patients, electronic data checks were done automatically. A random 5% sample of the first 10,000 patients was verified against source documents [13]. Considering that HF patients with EF 40% to 50% are characteristically and prognostically similar to those with EF >50% [4], we used EF  $\geq$  40% to define HFpEF. Of the 48,612 hospitalizations, 20,839 were due to HFpEF (EF  $\geq$  40%). Because of unavailability of long-term outcomes data in OPTIMIZE-HF, we linked OPTIMIZE-HF to Medicare outcomes data up to December 31, 2008, obtained from the Centers for Medicare and Medicaid Services [15]. Of the 20,839 HF hospitalizations due to HFpEF, we were able to link 13,270 to the Medicare data that occurred in 11,997 unique patients, of whom 10,889 were 65 years or older and 10,570 of them were discharged alive (Figure 1) [15].

### 2.2. Data on beta-blocker use

Names, doses and frequency of beta-blockers and for those not receiving these drugs, data on reason for non-use or contraindications were collected. From the 10,570 patients, we excluded 101 patients with missing data on discharge beta-blocker use, 1740 patients with contraindications, and 356 patients whose pre-admission beta-blocker therapy was discontinued prior to hospital discharge. Contraindications included prior allergy, second or third-degree heart block without a pacemaker, symptomatic bradycardia, symptomatic hypotension, cardiogenic shock, or reactive airway disease [16]. The final working sample consisted of 8373 patients who were considered potentially eligible for beta-blocker therapy, of which 2305 (28%) were not prescribed one (Figure 1). Of the 6068 who received a discharge prescription for beta-blockers, 3234 (58%) received beta-blockers considered evidence-based for HFrEF: carvedilol (n=1401), metoprolol succinate (n=1799), and bisoprolol (n=34). Of the non-evidence-based beta-blockers, 1105 received atenolol, 1330 received metoprolol tartrate, and 399 received other beta-blockers. Based on guideline recommended target doses for HFrEF, target doses for evidence-based beta-blockers were defined as follows: 50 mg/day for carvedilol, 200 mg/day for metoprolol succinate, and 10 mg/day for bisoprolol [1, 17]. The dose threshold for 2 non-evidence-based beta-blockers was 200 mg/day for atenolol and 200 mg/day for metoprolol tartrate as previously described [17].

### 2.3. Assembly of an eligible cohort for initiation of beta-blocker therapy

To minimize selection bias or left truncation associated with prevalent drug use [18–20], we assembled an inception cohort in which those receiving a new prescription of beta-blockers could be compared with those not receiving a discharge prescription. Of the 6068 patients

who received beta-blockers during hospital discharge, 4614 were receiving beta-blockers before hospital admission. Thus, 1454 patients received a new discharge prescription for beta-blockers. Taken together with the 2305 who did not receive a beta-blockers, the assembled inception cohort consisted of 3759 patients, of whom 39% (n=1454) received beta-blockers (Figure 1).

#### 2.4. Assembly of balanced study cohorts

To minimize bias associated with imbalances in the distribution of baseline characteristics between patients receiving and not receiving beta-blockers, we used propensity scores to assemble cohorts that would be balanced on all measured baseline characteristics [7–9, 21]. We estimated propensity scores for the receipt of beta-blockers using non-parsimonious multivariable logistic regression models, in which the receipt of beta-blockers was the dependent variable and 115 baseline characteristics displayed in Figure 2 were used as covariates [22, 23]. Using a greedy matching protocol, we were able to match 1099 patients receiving initial beta-blocker therapy with another 1099 patients not receiving these drugs who had similar propensity for their receipt [24, 25]. The effectiveness of propensity score model was assessed by estimating absolute standardized differences, and presented as a Love plot [26]. Absolute standardized difference values <10% are considered inconsequential and 0% indicates no residual bias. We repeated the above process to assemble 2 other matched cohorts: (1) a prevalent-user cohort of 1870 pairs of patients receiving and not receiving a prescription to continue beta-blockers therapy (Figure 1) and (2) an all-user cohort of 2104 pairs of patients receiving or not receiving a prescription for initiation or continuation of beta-blockers during discharge,.

#### 2.5. Outcomes

The primary outcome for this study was the composite endpoint of all-cause mortality or HF rehospitalization during a median 2.2 years of follow-up (minimum, 0 and maximum, 6 years). Secondary outcomes were all-cause mortality, HF rehospitalization, and all-cause rehospitalization. All outcomes data were obtained from the 100% MedPAR File and 100% Beneficiary Summary File from March 01, 2003 to December 31, 2008 [15]. Medicare-linked OPTIMIZE-HF patients have been shown to be characteristically and prognostically similar to HF patients in the general Medicare population [27].

#### 2.6. Statistical analysis

For descriptive analyses, Pearson's Chi-square, Wilcoxon rank-sum, McNemar's, and paired sample t tests were used for pre- and post-match between-group comparisons, as appropriate. To estimate the association of discharge prescriptions for beta-blockers with outcomes, we used Kaplan-Meier and Cox regression analyses. Proportional hazards assumptions were checked using log-minus-log scale survival plots. Formal sensitivity analyses may estimate the degree of hidden bias that could potentially eliminate a significant association among matched patients [28], but was not conducted for reasons explained under the results section. Subgroup analyses were conducted to determine the homogeneity of association between the use of beta-blockers and the composite primary endpoint in the inception cohort. We then compared evidence-based and non-evidence-based beta-blockers to those not receiving beta-blockers, and those receiving at or above target and below-target

doses of beta-blockers to those not receiving beta-blockers. In addition, we conducted sensitivity analyses by replicating the above process and assembling 3 propensity-matched cohorts of HFpEF, using alternative EF cutoffs of 45%, 50% and 55%. All statistical tests were 2-tailed with a p-value <0.05 considered significant. SPSS for Windows version 20 (2011, IBM Corp., Armonk, NY) was used for data analysis.

### 3. Results

Overall, matched patients in the inception cohort (n=2198) had a mean ( $\pm$ SD) age of 81 ( $\pm$ 8) years, mean ( $\pm$ SD) EF of 55 ( $\pm$ 10) percent, 65% were women, and 11% were African American. Before matching, those receiving beta-blockers were more likely to be older, have lower EF and have higher prevalence of myocardial infarction, and more likely to receive angiotensin-converting enzyme (ACE) inhibitors, which along with the remaining 115 baseline characteristics were balanced after matching, with absolute standardized differences values <10% (Tables 1 and 2, and Figure 2).

Discharge prescriptions for beta-blockers to older HFpEF patients who were not receiving these drugs prior to admission had no association with the primary composite endpoint of all-cause mortality or HF rehospitalization during a median of 2.2 years of follow-up, (hazard ratio {HR}, 1.03; 95% confidence interval {CI}, 0.94–1.13; p=0.569; Figure 3 and Table 3). Because this association was not statistically significant, we were not able to perform a formal sensitivity test [28]. This association was homogeneous across various clinically relevant subgroups of HFpEF patients (Figure 4). HRs for all-cause mortality and HF rehospitalization associated with a prescription for initiation of beta-blocker therapy were 0.99 (95% CI, 0.90–1.10; p=0.897) and 1.17 (95% CI, 1.03–1.34; p=0.014), respectively (Figure 3 and Table 3). Similar associations were observed in matched cohorts of HFpEF patients, defined by EF cutoffs 45%, 50% and 55%, except that the association with HF rehospitalization lost significance. HRs for HF rehospitalization for HFpEF patients with EF 45%, 50% and 55% were 1.10 (95% CI, 0.96–1.27; p=0.184), 1.08 (95% CI, 0.92–1.25; p=0.357), and 1.09 (95% CI, 0.92–1.30; p=0.330), respectively.

HRs (95% CIs) for composite endpoint of all-cause mortality or HF rehospitalization associated with initiation of evidence-based and non-evidence-based beta-blockers were 1.00 (0.90–1.12; p=0.939) and 1.07 (0.94–1.20; p=0.312), and use of target and below-target doses were 0.98 (0.82–1.18; p=0.864) and 1.04 (0.95–1.15; p=0.397), respectively (Table 3). Corresponding HRs (95% CIs) for other outcomes by class and target dose are displayed in Table 3.

Among matched patients, HR (95% CI) for the composite endpoint associated with prevalent use (continuation only, n=3740) of beta-blocker therapy during hospital discharge was 0.94 (0.87–1.00; p=0.059; Table 4). Similar association was observed when any use (prevalent or new) was considered (HR, 0.94; 95% CI, 0.88–1.00; p=0.048; Table 4). These associations also did not vary by evidence class or target doses. HRs (95% CIs) for other outcomes are displayed in Table 4.

## 4. Discussion

Findings from the current study demonstrate that in a propensity-matched balanced cohort of older HFpEF patients not previously receiving beta-blockers, a new discharge prescription of these drugs had no association with the primary composite endpoint of all-cause mortality or HF rehospitalization or with the secondary individual endpoints of all-cause mortality, HF rehospitalization, and all-cause rehospitalization. Further, these associations were similar regardless of whether beta-blockers considered evidence-based for HFrEF and in target doses recommended for HFrEF were used. These findings based on nationally representative real-world HFpEF patients and rigorously-conducted propensity-matched studies provide further insights into the role of betablockers in older HFpEF patients.

Despite differences in ventricular remodeling, both HFrEF and HFpEF are associated with similar hemodynamic and neurohormonal changes [29, 30]. Thus, it would seem plausible that beta-blockers, which are beneficial in HFrEF [1], would also improve outcomes in HFpEF. However, angiotensin receptor blockers and to some extent, ACE inhibitors, both beneficial in HFrEF, have failed to improve outcomes in HFpEF [31–33]. Preliminary evidence also points to a similar lack of evidence for aldosterone antagonists in HFpEF [34, 35]. Thus, the lack of evidence of benefits of neurohormonal antagonists in HFpEF most likely points to different pathophysiologic mechanisms from that of HFrEF and that it may not be amenable neurohormonal blockade. In future, mechanistic studies are needed to better understand the pathophysiology of HFpEF and there is an urgent need to develop and test novel interventions that may prevent disease progression and improve outcomes in patients with HFpEF. In addition, most patients with HFpEF are older adults who suffer from multiple comorbid conditions, many non-cardiovascular in nature, which explain the higher rates of non-cardiovascular events in these patients [36–38]. These suggest that improving outcomes in HFpEF may also require interventions that would need to address noncardiovascular comorbidities in real-world older patients with HFpEF [38].

Although the associations between prevalent drug use and outcomes may be biased by confounding due to the left truncation and adjustment of baseline mediators affected by prevalent drug use [18–20], these biases may be inconsequential in regards to the association of prevalent beta-blocker use and lower mortality observed in our study. If beta-blockers reduced mortality in HFpEF, the surviving prevalent users would progressively become more susceptible relative to nonusers and the benefit of the drug would be underestimated [18]. Similarly, if beta-blockers increased mortality, it would lead to a more resilient surviving prevalent users and treatment effect would be overestimated [18]. However, findings from our inception cohort suggest that beta blockers had no intrinsic association with mortality in older HFpEF patients, suggesting lack of evidence for left truncation. Prevalent beta-blocker use may have affected some baseline characteristics such as heart rate and blood pressure and their adjustment could have underestimated a true association, should one exist. The duration of beta-blocker therapy is unlikely to explain the lower mortality observed among prevalent users as no such association was observed during long follow-up of our inception cohort.



The higher HF rehospitalization associated with initiation of beta-blocker therapy while plausible given negative inotropic properties of beta-blockers, is also somewhat counterintuitive given that beta-blockers reduced the risk of HF hospitalization in patients with HFrEF in the RCT setting [1]. Prior studies of neurohormonal antagonists including ACE inhibitors and angiotensin receptor blockers have not consistently demonstrated reduction in HF hospitalizations in patients with HFpEF [31–33, 39]. Findings from our Kaplan-Meier plots suggest that there was no association between initiation of beta-blocker and HF rehospitalization during the first year of follow-up when nearly half of the events occurred. Finally, our sensitivity analysis using different EF cutoffs to define HFpEF suggest a lack of evidence of higher risk of HF rehospitalization associated with initiation of therapy with beta-blockers.

Most RCTs of beta-blockers in HF excluded older HFpEF patients [1]. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIOR) trial, nebivolol reduced composite endpoint of total mortality or cardiovascular rehospitalization in older HF patients, but not the individual endpoint components [40]. However, these patients had a mean EF was 36%. A subgroup analysis of SENIOR patients with EF >35% (mean, 47%) suggested similar associations [40, 41]. In a small randomized outcome-blinded trial in 245 patients with HFpEF (EF>40%), carvedilol did not improve outcomes during 3.2 years of median follow-up [42]. Several observational studies have also examined the effect of beta-blockers in HFpEF [43, 44]. However, findings from the current study, taken together with those from the prior report based on OPTIMIZE-HF [6], provide the most comprehensive evidence regarding the association of both incident and prevalent use of beta-blockers with short- and long-term outcomes in older HFpEF patients, overall, and by evidence class and target dose.

Our study has several limitations. We had no data on post-discharge adherence. Substantial crossover during follow-up may result in potential regression dilution and underestimation of true associations [45]. However, findings from ACE inhibitors in HF suggest that the degree of crossover would likely be modest [46], and unlikely to completely nullify true associations. The analyses were restricted to fee-for-service older Medicare patients. However, Medicare-linked OPTIMIZE-HF patients have been shown to be characteristically and prognostically similar to HF patients in the general Medicare population [27]. We did not assess health-related quality of life, functional capacity, or other outcomes that may be of interest. Finally, data for the current analysis were collected from medical records and thus dependent on the accuracy and completeness of clinical documentation.

In conclusion, in real-world hospitalized older patients with HFpEF, we found no evidence that beta-blocker therapy has independent associations with long-term outcomes, regardless of evidence class or daily dosages used.

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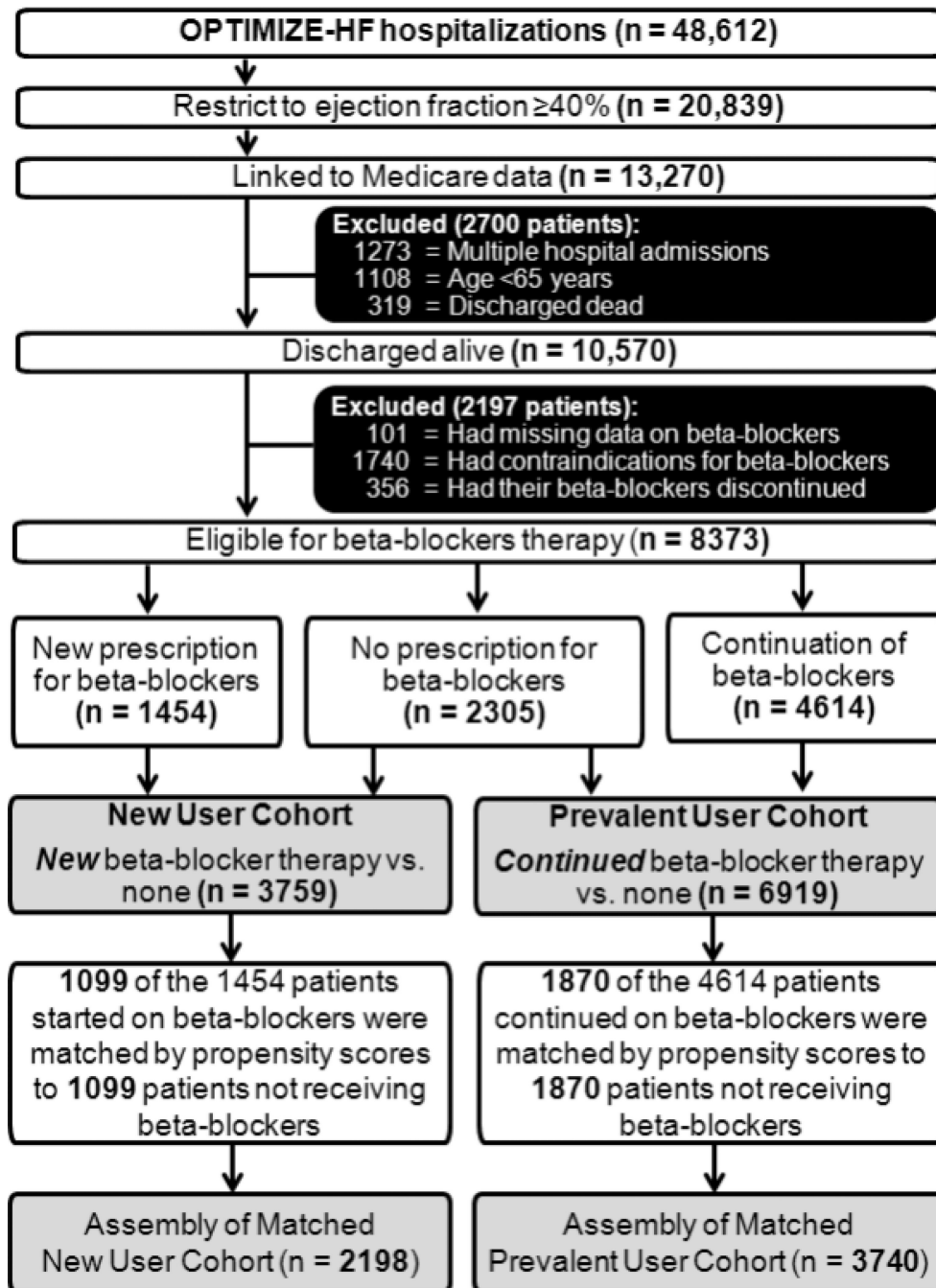
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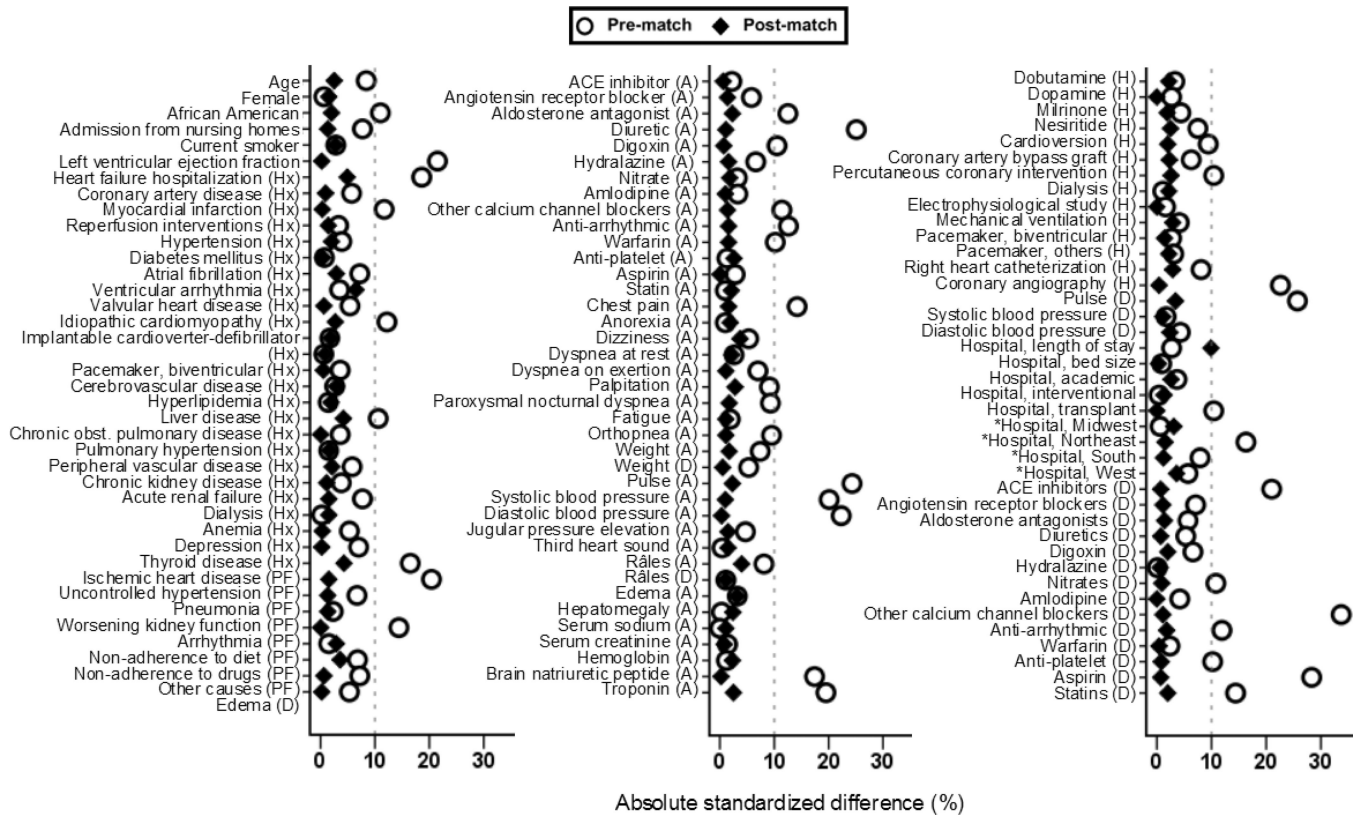


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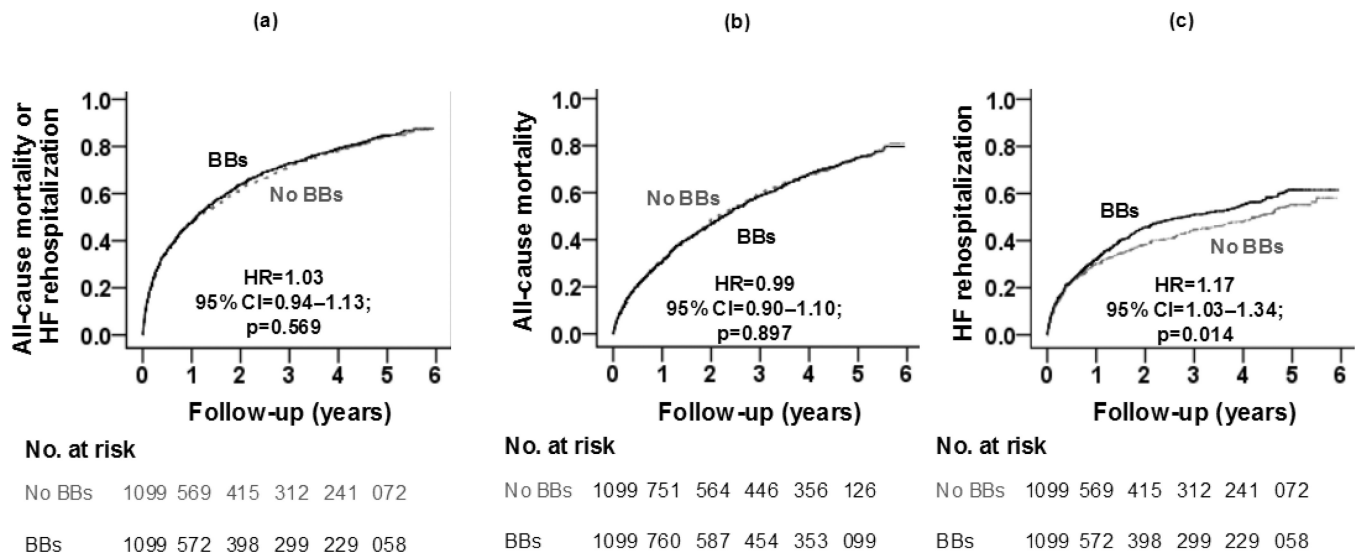
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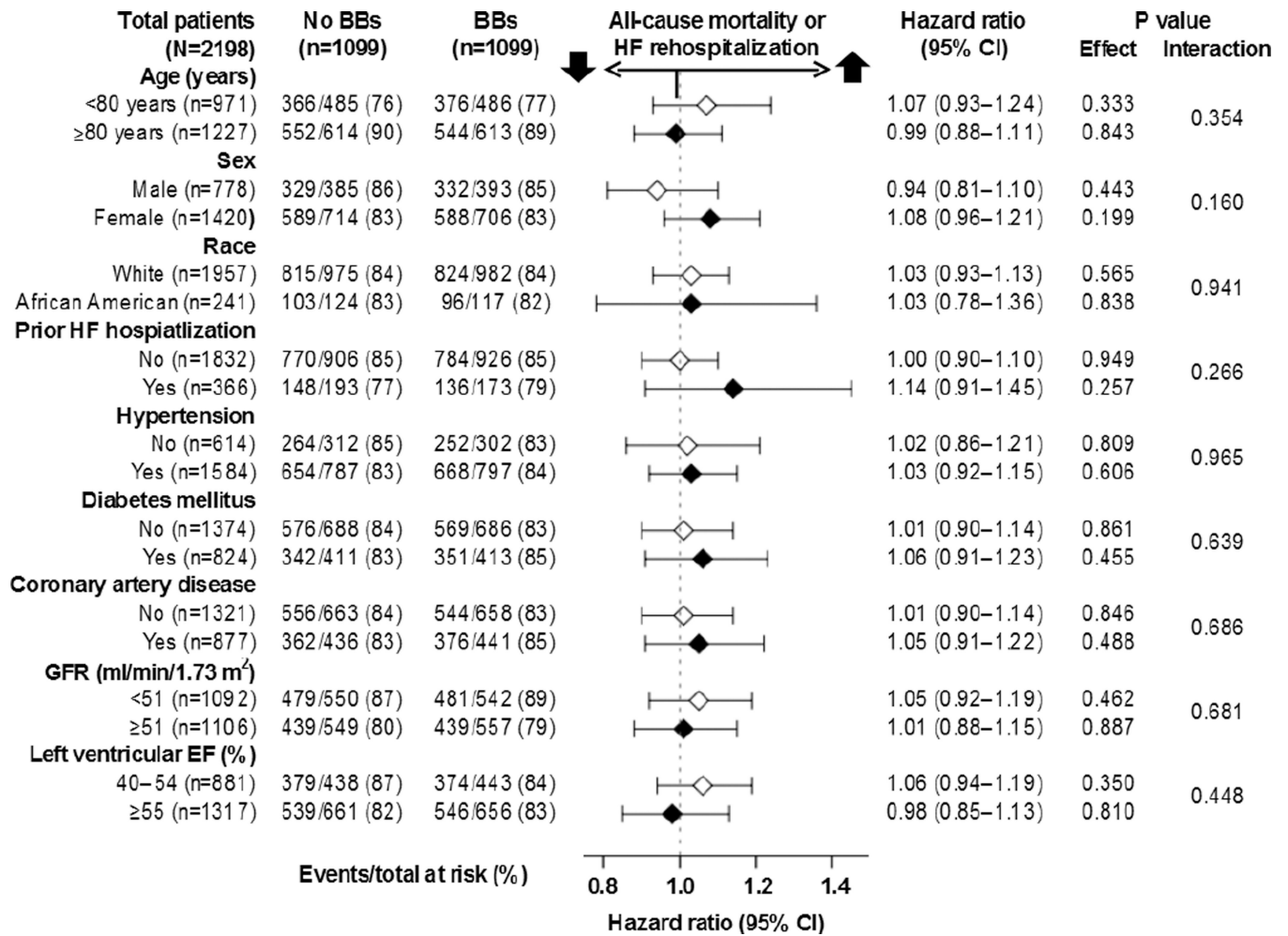
**Figure 1.** Flow chart displaying assembly of matched new user and prevalent user cohorts of patients with heart failure and preserved ejection fraction



**Figure 2.** Love plots displaying absolute standardized differences comparing 115 baseline characteristics between older adults with heart failure and preserved ejection fraction, receiving new discharge prescriptions for beta-blockers (versus none), before and after propensity score matching (Hx=before admission; A=admission; D=discharge; H=during hospitalization; PF=precipitating factor for hospital admission; ACE=angiotensin-converting enzyme; \*In the propensity score model, the 4 hospital regions were used as a single categorical variable with 4 values)



**Figure 3.** Kaplan-Meier plot for (a) primary composite endpoint (b) all-cause mortality (c) HF rehospitalization by initiation of beta-blocker (BBs) therapy versus no BBs in a propensity-matched cohort of older patients with heart failure and preserved ejection fraction (HF=heart failure; HR=hazard ratio; CI=confidence interval)



**Figure 4.** Association of new discharge prescriptions of beta-blockers (BBs) with primary composite endpoint of all-cause mortality or HF rehospitalization in subgroups of propensity-matched inception cohort of older patients with heart failure and preserved ejection fraction (CI=confidence interval; EF=ejection fraction; GFR=glomerular filtration rate; HF=heart failure)



Table 1

Baseline patient and care characteristics of older patients with heart failure and preserved ejection fraction (HFpEF), by new discharge prescription of beta-blockers, before and after propensity score matching

Variables Mean ( $\pm$ SD) or n (%)	Before propensity score matching		After propensity score matching		P value
	Beta-blockers		Beta-blockers		
	No (n=2305)	Yes (n=1454)	No (n=1099)	Yes (n=1099)	
Age (years)	80.7 ( $\pm$ 8)	81.3 ( $\pm$ 8)	81.3 ( $\pm$ 8)	81.1 ( $\pm$ 8)	0.558
Female	1484 (64)	940 (65)	714 (65)	706 (64)	0.757
African American	213 (9)	184 (13)	124 (11)	117 (11)	0.685
Left ventricular ejection fraction (%)	56 ( $\pm$ 9)	54 ( $\pm$ 10)	55 ( $\pm$ 9)	55 ( $\pm$ 10)	0.971
Past medical history					
Coronary artery disease	868 (38)	588 (40)	436 (40)	441 (40)	0.858
Myocardial infarction	280 (12)	236 (16)	153 (14)	154 (14)	1.000
Hypertension	1637 (71)	1058 (73)	787 (72)	797 (73)	0.675
Diabetes mellitus	850 (37)	531 (37)	411 (37)	413 (38)	0.964
Atrial fibrillation	833 (36)	476 (33)	394 (36)	379 (35)	0.522
Hyperlipidemia	604 (26)	398 (27)	310 (28)	296 (27)	0.528
Chronic obstructive pulmonary disease	686 (30)	364 (25)	289 (26)	269 (25)	0.352
Peripheral vascular disease	300 (13)	182 (13)	135 (12)	141 (13)	0.745
Chronic kidney disease	1480 (64)	893 (61)	696 (63)	685 (62)	0.666
Admission symptoms and signs					
Dyspnea on exertion	1404 (61)	935 (64)	685 (62)	691 (63)	0.826
Orthopnea	495 (22)	371 (26)	265 (24)	270 (25)	0.842
Paroxysmal nocturnal dyspnea	250 (11)	202 (14)	137 (13)	131 (12)	0.748
Dyspnea at rest	1006 (44)	616 (42)	472 (43)	460 (42)	0.638
Chest pain	393 (17)	330 (23)	234 (21)	227 (21)	0.752
Pulse (beats per minute)	85 ( $\pm$ 20)	90 ( $\pm$ 23)	88 ( $\pm$ 22)	87 ( $\pm$ 21)	0.996
Systolic blood pressure (mm Hg)	145 ( $\pm$ 29)	151 ( $\pm$ 33)	149 ( $\pm$ 29)	148 ( $\pm$ 32)	0.816
Diastolic blood pressure (mm Hg)	73 ( $\pm$ 17)	77 ( $\pm$ 20)	75 ( $\pm$ 18)	75 ( $\pm$ 19)	0.945
Jugular venous pressure elevation	568 (25)	388 (27)	280 (26)	287 (26)	0.765

Variables Mean (±SD) or n (%)	Before propensity score matching		After propensity score matching		P value
	Beta-blockers		Beta-blockers		
	No (n=2305)	Yes (n=1454)	No (n=1099)	Yes (n=1099)	
Pulmonary rales	1442 (63)	966 (66)	733 (67)	712 (65)	0.369
Lower extremity edema	1532 (67)	944 (65)	704 (64)	721 (66)	0.477
Laboratory values					
Serum sodium (mEq/L)	136 (±12)	136 (±11)	136 (±12)	136 (±11)	0.792
Serum creatinine (mg/dL)	1.52 (±1.09)	1.50 (±1.22)	1.50 (±1.10)	1.51 (±1.26)	0.855
Serum hemoglobin (g/dL)	12 (±4)	12 (±3)	12 (±2)	12 (±3)	0.594
Serum brain natriuretic peptide	819 (±758)	960 (±860)	894 (±857)	896 (±807)	0.955
Serum troponin elevation*	298 (13)	293 (20)	186 (17)	176 (16)	0.605
Discharge symptoms & signs					
Pulse (beats per minute)	77 (±13)	74 (±13)	74 (±13)	75 (±13)	0.422
Systolic blood pressure (mm Hg)	129 (±21)	129 (±22)	129 (±21)	129 (±21)	0.980
Diastolic blood pressure (mm Hg)	66 (±12)	66 (±12)	65 (±12)	66 (±12)	0.573
Pulmonary rales	316 (14)	194 (13)	151 (14)	147 (13)	0.851
Lower extremity edema	500 (22)	284 (20)	218 (20)	219 (20)	1.000
Length of hospital stay	12 (±304)	6 (±5)	6 (±4)	6 (±5)	<0.001
Hospital characteristics					
Bed size	392 (±250)	390 (±240)	388 (±245)	389 (±241)	0.939
Academic	933 (41)	615 (42)	451 (41)	465 (42)	0.576
Interventional	1751 (76)	1102 (76)	834 (76)	840 (76)	0.802
Transplant	367 (16)	179 (12)	144 (13)	144 (13)	1.000
Hospital location by region					
Midwest	731 (32)	465 (32)	352 (32)	368 (34)	
Northeast	273 (12)	256 (18)	161 (15)	167 (15)	0.825
South	796 (35)	448 (31)	355 (32)	349 (32)	
West	505 (22)	285 (20)	231 (21)	215 (20)	

\* Determined by local laboratories.

**Table 2**  
Treatment and procedure characteristics of older patients with heart failure and preserved ejection fraction (HFpEF), by new discharge prescription of beta-blockers, before and after propensity score matching

Variables Mean (±SD) or n (%)	Before propensity score matching		After propensity score matching		P value
	Beta-blockers		Beta-blockers		
	No (n=2305)	Yes (n=1454)	No (n=1099)	Yes (n=1099)	
<b>Admission medication</b>					
Angiotensin-converting enzyme inhibitors	707 (31)	431 (30)	341 (31)	344 (31)	0.927
Angiotensin receptors blockers	285 (12)	153 (11)	126 (12)	121 (11)	0.791
Diuretics	1477 (64)	753 (52)	625 (57)	631 (57)	0.825
Aldosterone antagonists	102 (4)	32 (2)	27 (3)	31 (3)	0.694
Digoxin	459 (20)	231 (16)	196 (18)	199 (18)	0.908
Hydralazine	50 (2)	19 (1)	16 (2)	14 (1)	0.856
Nitrates	376 (16)	220 (15)	169 (15)	176 (16)	0.732
Amlodipine	215 (9)	122 (8)	97 (9)	100 (9)	0.883
Non-amlodipine calcium channel blockers	514 (22)	258 (18)	201 (18)	207 (19)	0.781
Anti-arrhythmic drugs	244 (11)	102 (7)	98 (9)	93 (9)	0.764
Warfarin	497 (22)	255 (18)	217 (20)	224 (20)	0.750
Anti-platelet drugs	218 (10)	132 (9)	91 (8)	99 (9)	0.598
Aspirin	775 (34)	508 (35)	391 (36)	391 (36)	1.000
Statins	560 (24)	347 (24)	281 (26)	271 (25)	0.658
<b>In-hospital treatment/procedure</b>					
Dobutamine	29 (1)	24 (2)	15 (1)	18 (2)	0.728
Dopamine	42 (4)	32 (2)	19 (2)	19 (2)	1.000
Milrinone	4 (0.2)	6 (0.4)	3 (0.3)	2 (0.2)	1.000
Nesiritide	130 (6)	109 (8)	71 (7)	78 (7)	0.614
Right heart catheterization	45 (2)	47 (3)	25 (2)	30 (3)	0.583
Coronary angiography	95 (4)	143 (10)	74 (7)	73 (7)	1.000
Coronary artery bypass grafting	9 (0.4)	13 (0.9)	6 (0.5)	8 (0.7)	0.774
Percutaneous coronary intervention	14 (1)	25 (2)	11 (1)	14 (1)	0.690

Variables Mean (±SD) or n (%)	Before propensity score matching			After propensity score matching		
	Beta-blockers		P value	Beta-blockers		P value
	No (n=2305)	Yes (n=1454)		No (n=1099)	Yes (n=1099)	
Electro physiological study	12 (0.5)	6 (0.4)	0.641	4 (0.4)	4 (0.4)	1.000
Cardioversion	12 (1)	21 (1)	0.003	8 (1)	10 (1)	0.815
Mechanical ventilation	42 (2)	35 (2)	0.217	20 (2)	16 (2)	0.618
Pacemaker-biventricular	12 (0.5)	5 (0.3)	0.432	4 (0.4)	5 (0.5)	1.000
Pacemaker-other	28 (1)	23 (2)	0.343	18 (2)	15 (1)	0.728
Dialysis	76 (3)	45 (3)	0.732	29 (3)	33 (3)	0.704
Discharge medication						
Angiotensin-converting enzyme inhibitors	969 (42)	763 (53)	<0.001	532 (48)	536 (49)	0.898
Angiotensin receptors blockers	328 (14)	172 (12)	0.035	139 (13)	135 (12)	0.846
Diuretics	1884 (82)	1158 (80)	0.112	896 (82)	893 (81)	0.912
Aldosterone antagonists	166 (7)	127 (9)	0.088	83 (8)	79 (7)	0.800
Digoxin	527 (23)	293 (20)	0.050	273 (22)	228 (21)	0.666
Hydralazine	60 (3)	38 (3)	0.984	24 (2)	25 (2)	1.000
Nitrates	457 (20)	353 (24)	0.001	241 (22)	245 (22)	0.882
Amlodipine	216 (9)	119 (8)	0.214	99 (9)	99 (9)	1.000
Non-amlodipine calcium channel blockers	526 (23)	152 (11)	<0.001	148 (14)	144 (13)	0.843
Anti-arrhythmic drugs	287 (13)	128 (9)	0.001	113 (10)	107 (10)	0.725
Warfarin	555 (24)	365 (25)	0.477	274 (25)	276 (25)	0.960
Anti-platelet drugs	260 (11)	214 (15)	0.002	137 (13)	140 (13)	0.897
Aspirin	888 (39)	763 (53)	<0.001	511 (47)	515 (47)	0.895
Statins	547 (24)	438 (30)	<0.001	307 (28)	297 (27)	0.665

**Table 3**

Initiation of beta-blocker therapy and post-discharge outcomes in a propensity-matched inception cohort of hospitalized older patients with heart failure and preserved ejection fraction (HFpEF), by evidence class and target doses recommended for heart failure and reduced ejection fraction

Outcomes	Events (%)		Absolute risk difference*	Hazard ratio† (95% CI)	P value
	Beta-blockers				
	No	Yes			
<b>Initiation of beta-blockers, overall (n=1099)</b>					
All-cause mortality or HF rehospitalization	918 (84%)	920 (84%)	0%	1.03 (0.94–1.13)	0.569
All-cause mortality	818 (74%)	811 (74%)	0%	0.99 (0.90–1.10)	0.897
HF rehospitalization	435 (40%)	501 (46%)	+6%	1.17 (1.03–1.34)	0.014
All-cause rehospitalization	946 (86%)	944 (86%)	0%	1.00 (0.91–1.09)	0.967
<b>Initiation of beta-blockers, by evidence class</b>					
<b>Evidence-based‡ (n=1099)</b>					
All-cause mortality or HF rehospitalization	918 (84%)	559 (84%)	0%	1.00 (0.90–1.12)	0.939
All-cause mortality	818 (74%)	497 (74%)	0%	1.00 (0.89–1.12)	0.986
HF rehospitalization	435 (40%)	303 (45%)	+5%	1.14 (0.99–1.32)	0.078
All-cause rehospitalization	946 (86%)	578 (86%)	0%	0.99 (0.89–1.09)	0.770
<b>Non-evidence-based‡ (n=430)</b>					
All-cause mortality or HF rehospitalization	918 (84%)	361 (84%)	0%	1.07 (0.94–1.20)	0.312
All-cause mortality	818 (74%)	314 (73%)	-1%	0.99 (0.87–1.12)	0.827
HF rehospitalization	435 (40%)	198 (46%)	+6%	1.23 (1.04–1.45)	0.016
All-cause rehospitalization	946 (86%)	366 (85%)	-1%	1.02 (0.90–1.15)	0.768
<b>Initiation of beta-blockers, by recommended target dosages</b>					
<b>Target dose§ (n=1099)</b>					
All-cause mortality or HF rehospitalization	918 (84%)	128 (79%)	-5%	0.98 (0.82–1.18)	0.864
All-cause mortality	818 (74%)	107 (66%)	-8%	0.87 (0.71–1.07)	0.177
HF rehospitalization	435 (40%)	81 (50%)	+10%	1.32 (1.04–1.67)	0.022

Outcomes	Events (%)		Absolute risk difference*	Hazard ratio <sup>†</sup> (95% CI)	P value
	Beta-blockers				
	No	Yes			
All-cause rehospitalization	946 (86%)	139 (86%)	0%	1.07 (0.89–1.28)	0.475
<b>Below-target dose<sup>§</sup></b>	<b>(n=1099)</b>	<b>(n=871)<sup>§</sup></b>			
All-cause mortality or HF rehospitalization	918 (84%)	738 (85%)	+1%	1.04 (0.95–1.15)	0.397
All-cause mortality	818 (74%)	657 (75%)	+1%	1.02 (0.92–1.14)	0.645
HF rehospitalization	435 (40%)	389 (45%)	+5%	1.15 (1.00–1.32)	0.046
All-cause rehospitalization	946 (86%)	753 (87%)	+1%	1.00 (0.91–1.10)	0.965

\* Absolute risk differences were calculated by subtracting percent events in patients not receiving beta-blockers from those receiving those drugs

<sup>†</sup> Hazard ratios comparing patients receiving beta-blockers versus those not receiving those drugs

<sup>‡</sup> Evidence-based beta-blockers included bisoprolol, carvedilol or metoprolol succinate; and non-evidence-based BBs included atenolol, metoprolol tartrate and others

<sup>§</sup> Target doses for HFpEF based on recommendations for HFpEF and were defined as follows: atenolol (200 mg/day), bisoprolol (10 mg/day), carvedilol (50 mg/day), metoprolol succinate (200 mg/day), and metoprolol tartrate (200 mg/day)

<sup>§</sup> Based on patients with non-missing data on daily dose



Continuation or any use (continuation or initiation) of beta-blockers and post-discharge outcomes in propensity-matched cohorts of hospitalized older patients with heart failure and preserved ejection fraction (HFpEF)

**Table 4**

Outcomes	Events (%)		Absolute risk difference*	Hazard ratio <sup>†</sup> (95% CI)	P value
	Beta-blockers				
	No	Yes			
<b>Continuation of beta-blockers (n=1870)</b>					
All-cause mortality or HF rehospitalization	1585 (85%)	1542 (83%)	-2%	0.94 (0.87-1.00)	0.059
All-cause mortality	1379 (74%)	1321 (71%)	-3%	0.91 (0.84-0.98)	0.010
HF rehospitalization	832 (45%)	817 (44%)	-1%	0.95 (0.86-1.04)	0.247
All-cause rehospitalization	1629 (87%)	1625 (87%)	0%	0.92 (0.86-0.99)	0.020
<b>Continuation or initiation of beta-blockers (n=2104)</b>					
All-cause mortality or HF rehospitalization	1775 (84%)	1723 (82%)	-2%	0.94 (0.88-1.00)	0.048
All-cause mortality	1546 (74%)	1482 (70%)	-4%	0.91 (0.85-0.98)	0.011
HF rehospitalization	897 (43%)	935 (44%)	+1%	1.01 (0.92-1.10)	0.906
All-cause rehospitalization	1820 (87%)	1834 (87%)	0%	0.94 (0.88-1.01)	0.077

\* Absolute risk differences were calculated by subtracting percent events in patients not receiving beta-blockers from those receiving those drugs

<sup>†</sup> Hazard ratios comparing patients receiving beta-blockers versus those not receiving those drugs