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## Journal

American Journal of Medicine, 131(12)

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## Publication Date

2018-12-01

## DOI

10.1016/j.amjmed.2018.07.008

Peer reviewed

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*Am J Med*. Author manuscript; available in PMC 2023 August 29.

Published in final edited form as:

*Am J Med*. 2018 December ; 131(12): 1473–1481. doi:10.1016/j.amjmed.2018.07.008.

# Role of High-Dose Beta-Blockers in Patients with Heart Failure with Preserved Ejection Fraction and Elevated Heart Rate

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## Abstract

**Background—**Beta-blockers are not recommended for heart failure with preserved ejection fraction (HFpEF). However, treatment effect may be more pronounced in high-risk subgroups, and patients with HFpEF and heart rate ≥70 beats/minute have emerged as such as a high-risk subset. We examined the association of high-dose beta-blocker use with outcomes in these patients.

**Methods—**Of the 8462 hospitalized patients with HFpEF (ejection fraction ≥50%) in the Medicare-linked OPTIMIZE-HF registry, 5422 had discharge heart rate ≥70 beats/minute. Of the 4537 patients who had no contraindications to beta-blocker use, 2797 received a prescription for a beta-blocker and 1740 did not receive one. Of the 2592 patients who had data on beta-blocker dosage, 730 received high-dose beta-blockers, defined as atenolol ≥100 mg/day, carvedilol ≥50 mg/day, metoprolol tartrate or succinate ≥200 mg/day, or bisoprolol ≥10 mg/day. Using propensity scores for the receipt of high-dose beta-blockers, we assembled a cohort of 1280 matched patients, balanced on 58 characteristics.

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**Results—**All-cause mortality occurred in 63% and 68% of matched patients receiving high-dose beta-blocker versus no beta-blocker during 6 years (median, 2.8) of follow-up, respectively (hazard ratio {HR}, 0.86; 95% confidence interval {CI}, 0.75–0.98; p=0.027). HRs (95% CIs) for all-cause readmission and the combined endpoint of all-cause readmission or all-cause mortality associated with high-dose beta-blocker use were 0.90 (0.81–1.02) and 0.89 (0.80–1.00), respectively.

**Conclusions—**In patients with HFpEF and heart rate ≥70 beats/minute, high-dose beta-blocker use was associated with a significantly lower risk of total mortality. Future randomized controlled trials are needed to examine this association.

### Keywords

Heart Failure with Preserved Ejection Fraction; High-Dose Beta-Blocker; Heart Rate; All-Cause Mortality

Heart failure with preserved ejection fraction (HFpEF) accounts for about half of all patients admitted for HF and has emerged as a prominent cause of significant morbidity and mortality.[1, 2] Evidence-based pharmacotherapy effective in the treatment of patients with heart failure with reduced ejection fraction (HFrEF) so far has not been shown to be effective in HFpEF.[3] High-dose beta-blockers are recommended for patients with heart failure with reduced ejection fraction (HFrEF), but no such evidence exists for HFpEF.[3–8] Considering that the negative chronotropic properties of beta-blockers would be expected to be greater at higher doses and that treatment effects are often greater in subgroups of high-risk patients,[9–11] we hypothesized that high-dose beta-blocker use would be associated with improved outcomes in the high-risk subset of patients with HFpEF and elevated heart rate. We have recently demonstrated that older patients with HFpEF and heart rate of ≥70 beats/minute have a higher risk of all-cause mortality.[1] The objective of our study was to examine the association of high-dose beta-blocker use and outcomes in a propensity score-matched cohort of patients with HFpEF and a discharge heart rate ≥70 beats/minute.

## Methods

### Data Source and Study Population

The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) is a registry based on 48,612 heart failure hospitalizations in 259 hospitals in 48 states between March 1, 2003 and December 31, 2004. Charts were abstracted based on ICD-9 code for a principal discharge diagnosis of heart failure. Extensive data on demographics, patient and hospital characteristics, quality of care, and outcomes were collected using a Web-based registry. Detailed descriptions of the OPTIMIZE-HF have been described elsewhere.[2, 12] For the current analysis, we used the Medicare-linked OPTIMIZE-HF data that included 26,376 unique patients, of which 8873 had HFpEF, defined as ejection fraction ≥50%.[2, 13] We excluded 95 patients with heart rate <40 or >150 beats/minute and 3356 patients with heart rate <70 beats/minute, thus assembling a cohort of 5422 patients with heart rate ≥70 beats/minute.

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### Discharge Use of Beta-Blockers

Of the 5422 patients with HFpEF and heart rate ≥70 beats/minute, information on discharge beta-blocker use and dosages was available in 5366 patients, of whom 4537 had no contraindications to beta-blocker use. Of the 4537, 2797 received a prescription for a beta-blocker and 1740 did not receive one. Of the 2797 patients, 2592 had data on beta-blocker dosage, of whom 549 (21%) received carvedilol, 893 (35%) received metoprolol succinate, 662 (26%) received metoprolol tartrate, 23 (1%) received bisoprolol, and 465 (18%) received atenolol. Overall, 730 patients received prescriptions for high-dose beta-blockers, which were defined as a daily dose of carvedilol ≥50 mg (28%; 155/549), metoprolol succinate ≥200 mg (15%; 133/893), metoprolol tartrate ≥200 mg (49%; 318/652), bisoprolol ≥10 mg (26%; 6/23), and atenolol ≥100 mg (25%; 118/465). Thus, our high-dose beta-blocker cohort consisted of 2470 patients, of whom 730 received high-dose beta-blockers, and 1740 did not receive a beta-blocker (Figure 1).

### Assembly of a Balanced Study Cohort

In randomized controlled trials, patients have a 50% probability of receiving a treatment, which is equal for patients receiving and not receiving treatment. This equal probability between the two treatment groups ensures that patients are balanced on baseline characteristics. Because patients in the real world are not randomly given a prescription for medications, the probability varies between 0 and 100%. This probability is a propensity score and can be estimated using measured baseline characteristics in a multivariable logistic regression model.[14–16] We separately calculated propensity scores for use of a high-dose beta-blocker based on 58 baseline characteristics displayed in Figure 2. We then used a greedy matching algorithm to match patients based on their propensity scores.[17] We matched 88% of the 730 patients receiving high-dose beta-blockers with 730 patients not receiving beta-blockers, thus assembling a matched cohort of 1280 patients (Figure 1).

### Outcomes Data

The primary outcome of the current analysis was all-cause mortality during overall follow-up of 6 (median, 2.8) years up to December 31, 2008. Secondary outcomes included all-cause readmission, heart failure readmission, the combined endpoint of all-cause readmission or all-cause mortality, and the combined endpoint of heart failure readmission or all-cause mortality. Medicare 100% Medicare Provider Analysis and Review (MEDPAR) and 100% Beneficiary Summary files were used to obtain data on events and time to events.[13] These files contain information for 100% of Medicare beneficiaries using hospital inpatient services and dates of death.

### Statistical Analyses

Between-group baseline characteristics were compared using Pearson's Chi-square and Wilcoxon rank-sum tests, as appropriate. All outcome analyses were conducted using matched data. Kaplan-Meier survival analysis was used to generate plots for all-cause mortality by discharge prescription for high-dose beta-blocker versus no beta-blocker, and Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for outcomes associated with high-dose beta-blocker versus no beta-blocker.

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To examine if significant associations observed in our matched data could be explained away by an unmeasured baseline characteristic, we conducted formal sensitivity analyses. We used Rosenbaum's approach which uses a sign-score test to calculate "sensitivity bounds" for how much an unmeasured confounder would need to increase the odds of exposure (here, receiving a discharge prescription for high-dose beta-blockers) in order to explain away any significant associations between the exposure and outcome.[18] In order to apply the method to time-to-event data, survival times within each matched pair are compared to determine whether one member of the pair can be clearly determined to have had a longer survival time (or event-free survival time for non-mortality outcomes) than the other member. Of note, for some pairs, it may not be possible to declare a clear "winner" due to censoring of one or both members. For the subset of pairs where a clear winner can be declared, we then test whether, in the absence of a hidden bias, if subjects in one group are significantly more likely to have longer survival times than their counterparts in the other group. Subgroup analyses were conducted to determine the homogeneity of the association of high-dose beta-blocker use and all-cause mortality in our primary matched cohort. Finally, we used a multivariable-adjusted logistic regression model to identify significant clinical predictors for use of high-dose in 2592 patients receiving beta-blockers. We set our statistical significance level at two-tailed alpha of 0.05. We used IBM SPSS Statistics for Windows software, version 24 (IBM Corp., Armonk, NY, USA) and SAS software, version 8 for Windows (SAS Institute Inc., Cary, NC, USA) for statistical analysis.

## Results

### Baseline Characteristics

The 1280 matched patients had a mean (±SD) age of 76 (±11) years, 66% were women, and 15% were African American, and had a mean (±SD) ejection fraction of 59 (±7) % and discharge heart rate of 82 (±10) beats/minute. Before matching, patients discharged on a high-dose beta-blocker had a lower mean age, and a greater proportion of these patients had hypertension, coronary artery disease, diabetes, and atrial fibrillation (Table 1). These and other measured baseline characteristics were balanced after matching, and absolute standardized difference for all 58 baseline characteristics were <10%, suggesting inconsequential between-group differences (Table 1 and Figure 2).

### High-Dose Beta-Blocker Use and Outcomes

Among the 1280 matched patients, all-cause mortality occurred in 63% and 68% of those receiving a discharge prescription for high-dose beta-blocker versus no beta-blocker, respectively, during 6 (median 2.8) years of follow-up (HR, 0.86; 95% CI, 0.75–0.98; p=0.027; Table 2 and Figure 3). Of the 640 matched pairs, for 551 pairs we were able to determine a clear "winner", of which in 311 (56.4%) pairs, patients who received a discharge prescription for high-dose beta-blockers had longer survival time than their matched counterparts who did not receive those drugs. In the absence of a hidden bias, a sign-score test for matched data with censoring demonstrates that this difference was statistically significant (p=0.003). There was no evidence that the beneficial association of high-dose beta-blocker with all-cause mortality varied by heart rate (Figure 4). The association of high-dose beta-blocker with mortality was also homogenous across various

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clinically relevant subgroups, except by race (Figure 4). The use of high-dose beta-blocker had no significant association with hospital readmission, but there was trend toward a lower risk for the combined endpoint of all-cause readmission and all-cause mortality (Table 2).

### Predictors of High-Dose Beta-Blocker Use

Among the 2592 pre-match patients with HFpEF who were eligible for beta-blockers, older age and chronic obstructive pulmonary disease were associated with lower odds of high-dose beta-blocker use, while atrial fibrillation and anti-hypertensive drug use were associated with higher odds of high-dose beta-blocker use (Table 3).

## Discussion

Findings from our study demonstrate that among hospitalized patients with HFpEF and a discharge heart rate ≥70 beats/minute, high-dose beta-blocker use was associated with a significantly lower risk of all-cause mortality. To the best of our knowledge, this is the first study to demonstrate a beneficial association between high-dose beta-blocker use and long-term outcomes in a propensity score-matched cohort of a high-risk subset of patients with HFpEF and heart rate ≥70 beats/minute.

Beta-blockers in high target doses have been shown to improve clinical outcomes in HFrEF.[19–21] However, there is no randomized controlled trial evidence of efficacy of beta-blocker in HFpEF (ejection fraction ≥50%) and findings from observational studies have been variable.[22–25] Treatment effects are known to be more pronounced in high-risk subsets of patients[9–11] and patients with HFpEF and elevated heart rate have emerged as such a high-risk subset.[1] An elevated heart rate is a marker of increased sympathetic activity, arrhythmogenicity and premature atherogenesis.[26–29] If high-dose beta-blockers exert a greater negative chronotropic effect in these high-risk HFpEF patients with elevated heart rate, then that would at least in part explain the lower mortality observed in our study. In the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) trial, in older patients with both HFpEF and HFrEF, beta-blockers (~ 30% received high dose) reduced heart rate by 5–8 bpm at 3 months.[30] The effect of beta-blockers on heart rate would be expected to be greater at higher doses during longer follow-up.[4–6]

Several studies have examined the association of beta-blocker use with outcomes in patients with HFpEF in general.[23–25] However, to the best of our knowledge, this is the first study to report a significant beneficial association between the use of high-dose beta-blockers and improved clinical outcomes in a high-risk subset of patients with HFpEF. Our study is also distinguished by the use of ejection fraction cutoff of 50% to define HFpEF, the use of propensity score matching to assemble a balanced cohort, the use of subgroup analyses to demonstrate homogeneity, and the use of formal sensitivity analyses to assess bias by a potential unmeasured confounder.

Currently there is no evidence-based therapy for HFpEF that can improve survival.[22] If the hypothesis-generating findings from our study are confirmed in a prospective randomized controlled trial, then high-dose beta-blockers may emerge as a potential therapy to improve outcomes in a large subset of high-risk of patients with HFpEF. About two-thirds of patients

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with HFpEF have heart rate >70 beats/minute.[1] However, the impact of such therapy may be limited by patients' ability to tolerate a high dose of beta-blocker. In our study, about a third of the patients who were taking beta-blockers were on a high dose, which is similar to that observed in the CIBIS-ELD trial.[30] One of the main reasons for intolerance of high-dose beta-blocker is hypotension. Systolic blood pressure <120 or 130 mm Hg has been shown to be associated with poor outcomes in HFpEF.[31] Future studies may examine high-dose beta-1 selective blockers may be better tolerated in HFpEF.[32]

There are several limitations to our study. Despite propensity score matching, confounding due to residual or hidden bias is possible. A hidden covariate that would increase the odds of receiving a discharge prescription for high-dose beta-blockers by 9.5% could potentially explain away this association. For such an imaginary unmeasured binary covariate to become a confounder, it would also need to be a near perfect predictor of all-cause readmission and could not be strongly correlated to any of the variables used in our propensity score model. We had no data on adherence, titration of beta-blockers, and heart rate during follow-up. Finally, our analysis was restricted to older hospitalized fee-for-service Medicare beneficiaries, which may limit generalizability.

In conclusion, in hospitalized older patients with HFpEF and a discharge heart rate ≥70 beats/minute, high-dose beta-blocker use is associated with a lower risk of all-cause mortality and the combined endpoint of all-cause readmission or all-cause mortality. If these findings can be confirmed in prospective randomized controlled trials, the beneficial role of high-dose beta-blockers, well known in HFrEF, may be extended to HFpEF, albeit to a large high-risk subset who can tolerate these drugs in high doses.

## Acknowledgments

**Funding**: Dr. Ali Ahmed was in part supported by the National Institutes of Health through grants (R01-HL085561, R01-HL085561-S and R01-HL097047) from the National Heart, Lung, and Blood Institute. Dr. Gregg Fonarow was the Principle Investigator of OPTIMIZE-HF, which was sponsored by GlaxoSmithKline.

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda.Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring

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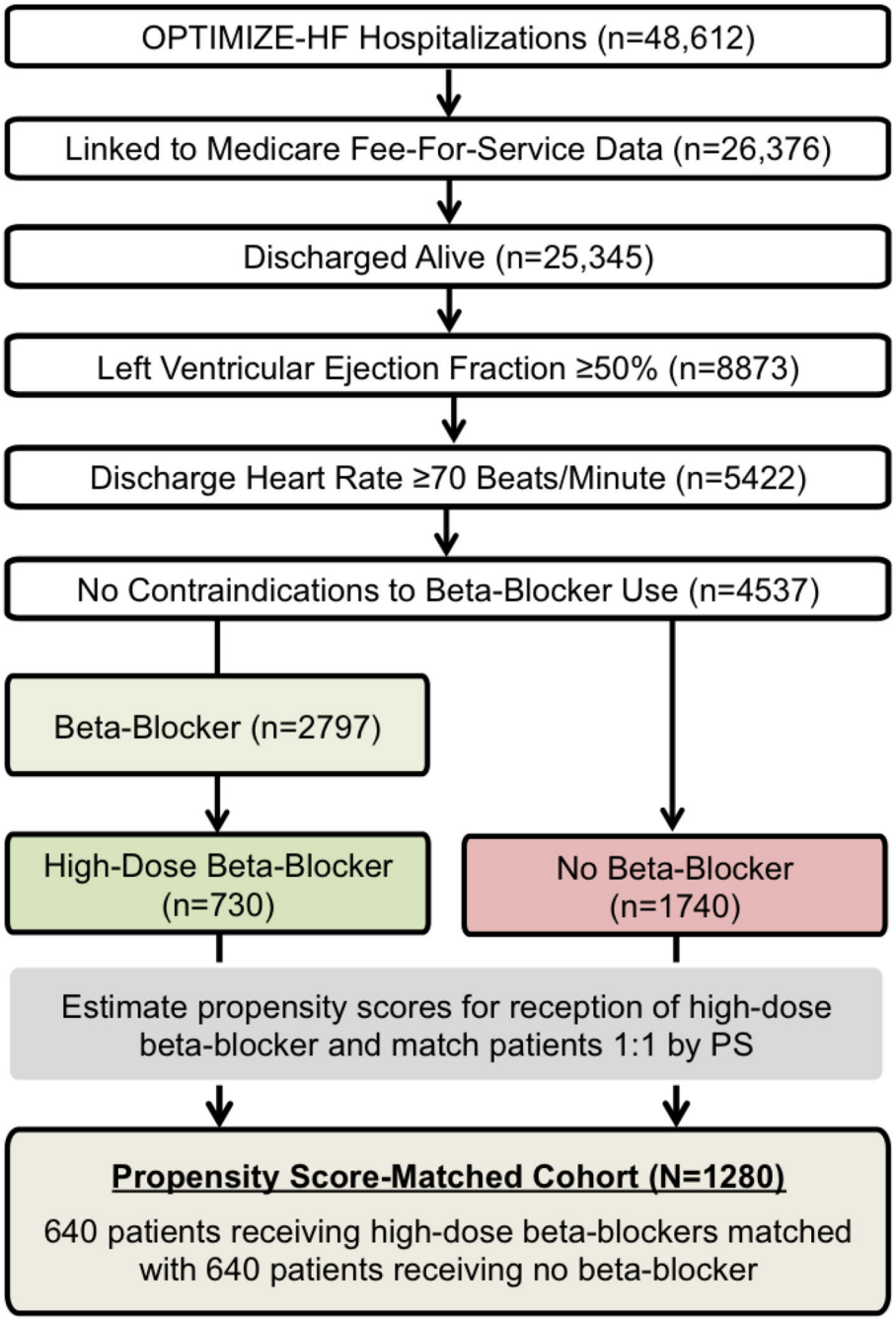


**Figure 1.**
Flow chart displaying assembly of propensity score (PS) matched cohort of patients with heart failure with preserved ejection fraction and discharge heart rate ≥70 beats/minute, by discharge prescriptions for high-dose beta-blocker versus no beta-blocker

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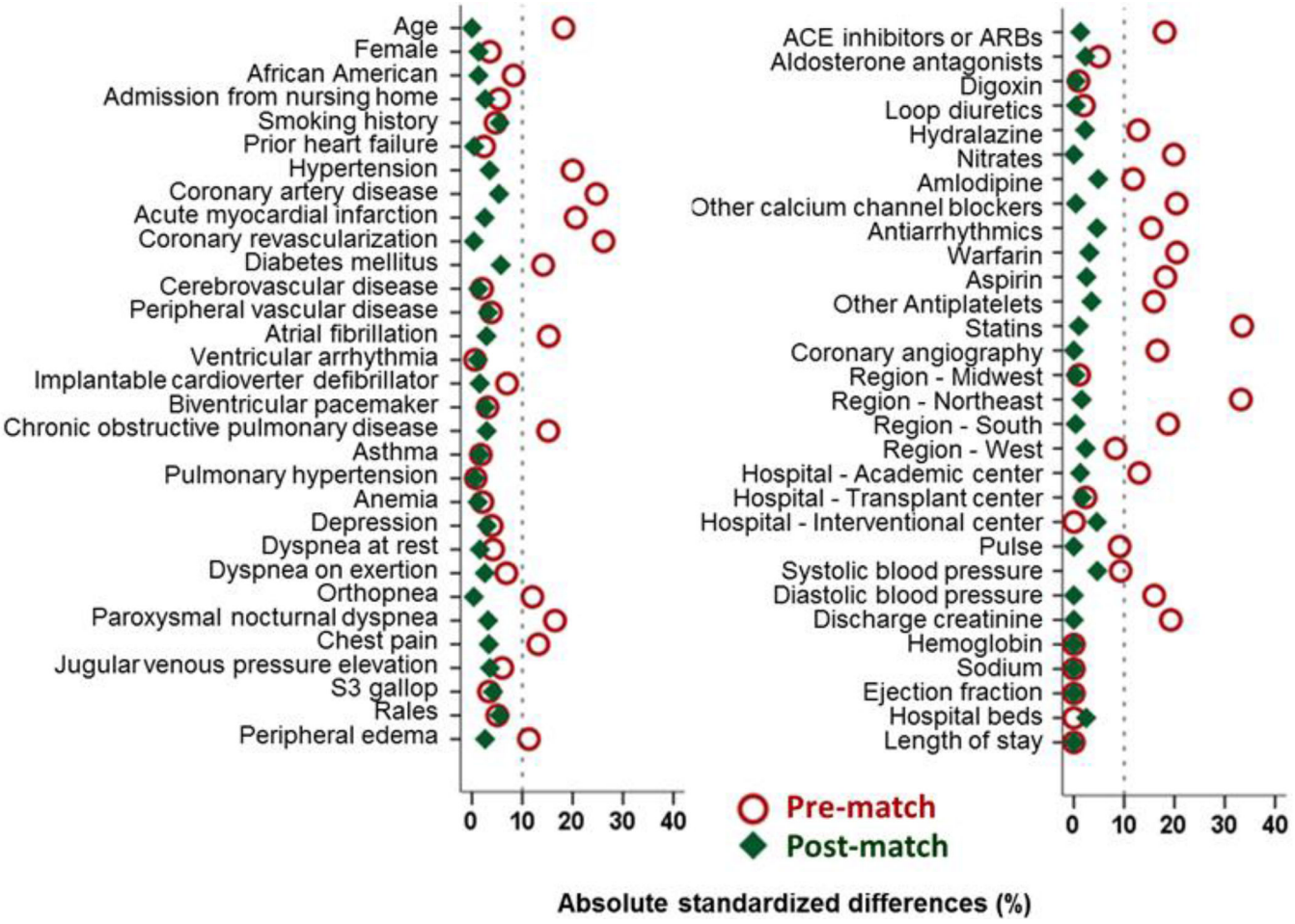


**Figure 2.**

Love plot displaying absolute standardized differences comparing 58 baseline characteristics (the 4 hospital regions are used as a single variable) between 640 pairs of patients with heart failure with preserved ejection fraction (≥50%) and discharge heart rate ≥70 beats/minute, by discharge prescriptions for high-dose beta-blocker versus no beta-blocker, before and after propensity score matching (ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blockers; S3=third heart sound

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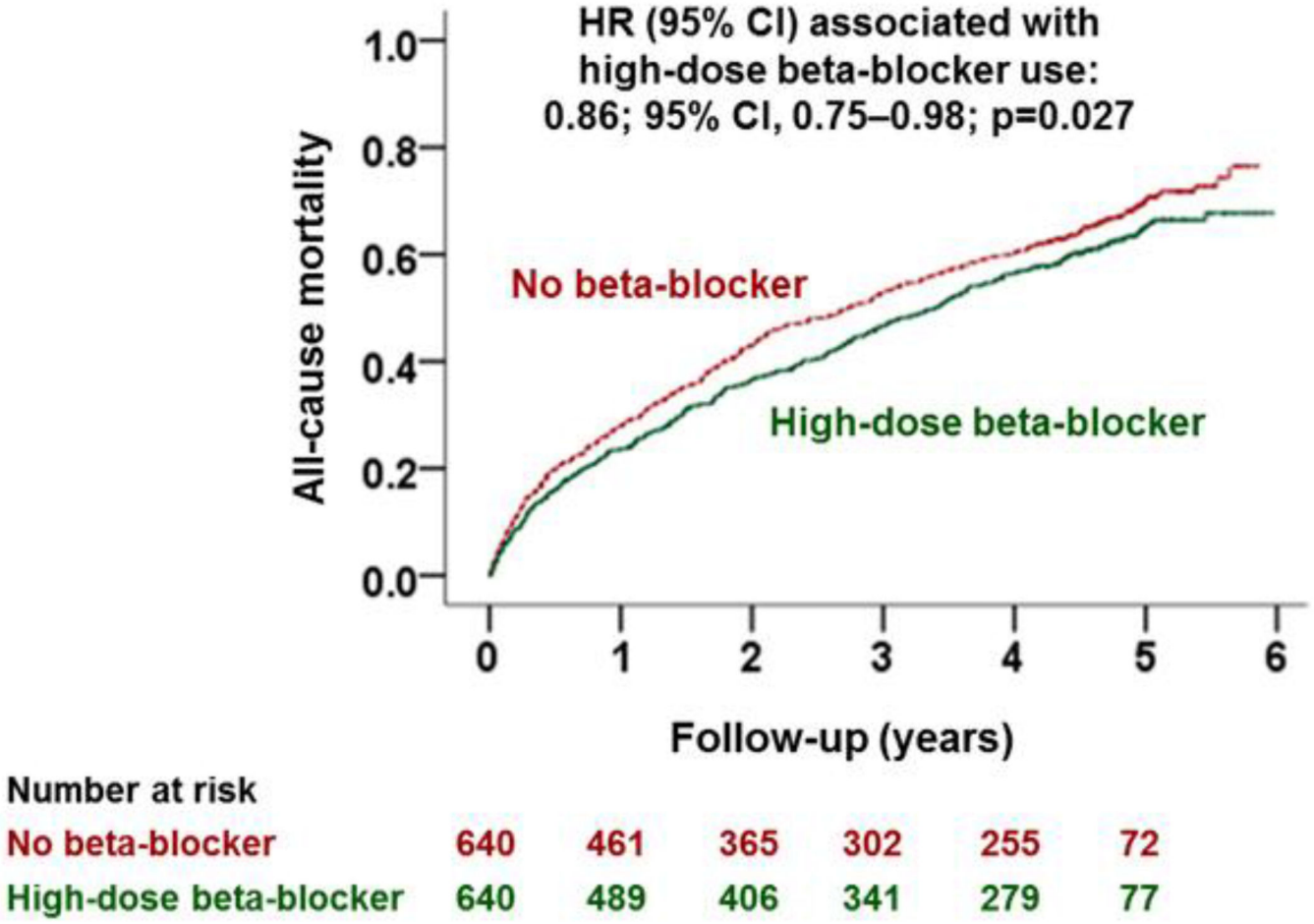


**Figure 3.**

Kaplan Meier plots for all-cause mortality in propensity score-matched patients with heart failure and preserved ejection fraction (≥50%) and discharge heart rate ≥70 beats/minute, by discharge prescriptions for high-dose beta-blocker versus no beta-blocker

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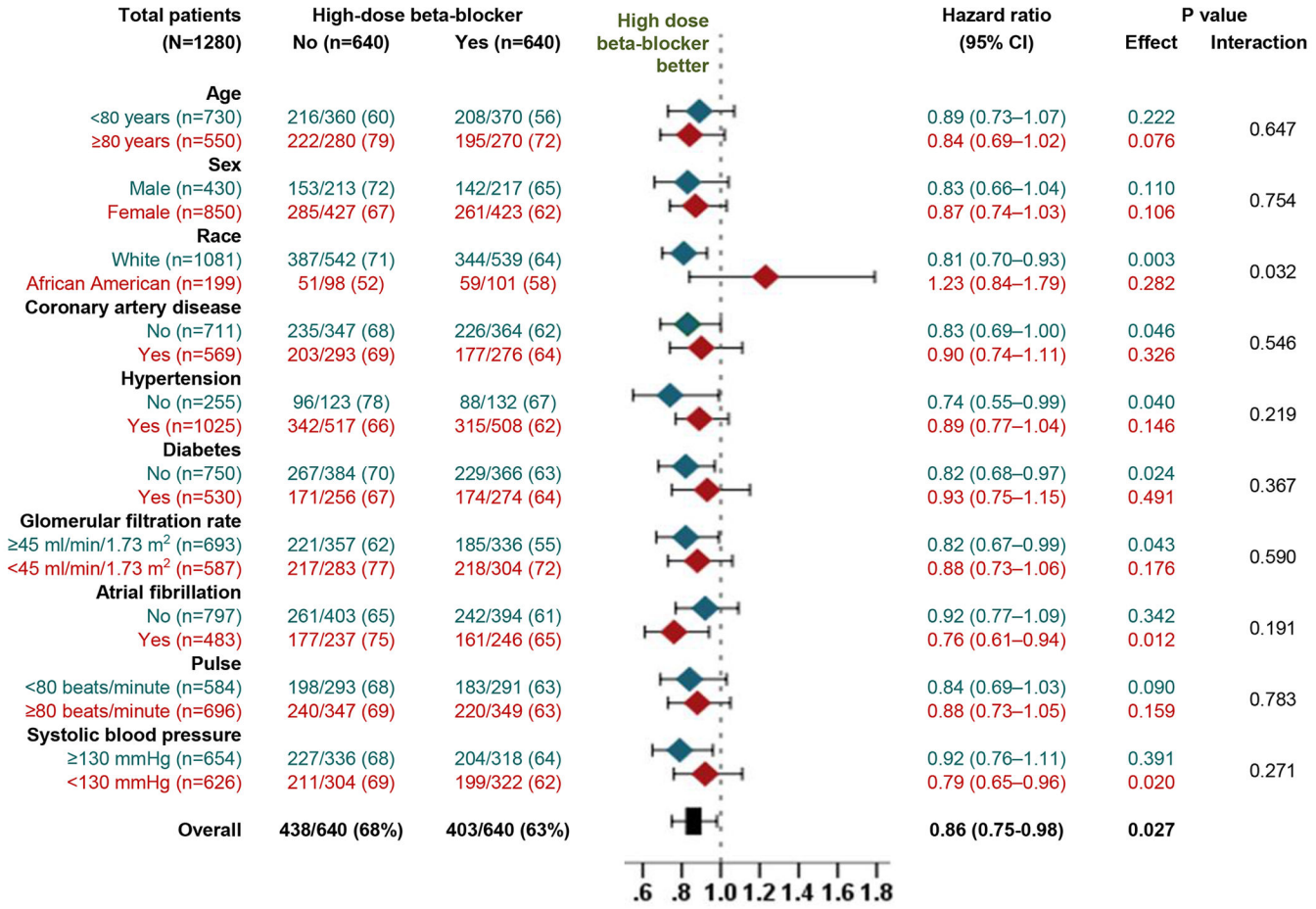


**Figure 4.**

Forest plots displaying hazard ratios and 95% confidence intervals (CI) for all-cause mortality in subgroups of propensity score-matched patients with heart failure with preserved ejection fraction (≥50%) and discharge heart rate ≥70 beats/minute, by discharge prescriptions for high-dose beta-blocker versus no beta-blocker

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**Table 1.**

Baseline Characteristics in Patients with Heart Failure with Preserved Ejection Fraction ≥50% and Heart Rate ≥70 Beats/Minute, by High-Dose Beta-Blocker Versus No Beta-Blocker Use

| n (%) or mean (±SD) | Before propensity score matching (n=2470) | | | After propensity score matching (n=1280) | | |
|---|---|---|---|---|---|---|
| | No beta-blocker (n=1740) | High-dose beta-blocker (n=730) | P value | No beta-blocker (n=640) | High-dose beta-blocker (n=640) | P value |
| Age (years) | 78 (11) | 76 (11) | <0.001 | 76 (12) | 76 (11) | 0.993 |
| Female | 1171 (66%) | 479 (67%) | 0.418 | 427 (67%) | 423 (66%) | 0.813 |
| African American | 226 (13%) | 116 (16%) | 0.057 | 98 (15%) | 101 (16%) | 0.817 |
| Admission from nursing home | 39 (2%) | 11 (2%) | 0.237 | 8 (1%) | 10 (2%) | 0.635 |
| Smoking history | 189 (11%) | 69 (10%) | 0.296 | 75 (12%) | 64 (10%) | 0.323 |
| Past medical history | | | | | | |
| Prior heart failure | 1495 (86%) | 621 (85%) | 0.582 | 546 (85%) | 547 (86%) | 0.937 |
| Hypertension | 1260 (72%) | 590 (81%) | <0.001 | 517 (81%) | 508 (79%) | 0.529 |
| Coronary artery disease | 592 (34%) | 336 (46%) | <0.001 | 293 (46%) | 276 (43%) | 0.339 |
| Acute myocardial infarction | 193 (11%) | 134 (18%) | <0.001 | 107 (17%) | 101 (16%) | 0.649 |
| Coronary revascularization | 268 (15%) | 189 (26%) | <0.001 | 147 (23%) | 146 (23%) | 0.947 |
| Diabetes mellitus | 661 (38%) | 328 (45%) | 0.001 | 256 (40%) | 274 (43%) | 0.307 |
| Cerebrovascular disease | 299 (17%) | 120 (16%) | 0.652 | 101 (16%) | 104 (16%) | 0.819 |
| Peripheral vascular disease | 216 (12%) | 100 (14%) | 0.383 | 83 (13%) | 90 (14%) | 0.567 |
| Atrial fibrillation | 562 (32%) | 289 (40%) | 0.001 | 237 (37%) | 246 (38%) | 0.604 |
| Ventricular arrhythmia | 32 (2%) | 14 (2%) | 0.895 | 12 (2%) | 13 (2%) | 0.840 |
| Implantable cardioverter defibrillator | 10 (1%) | 9 (1%) | 0.088 | 6 (1%) | 7 (1%) | 0.780 |
| Biventricular pacemaker | 20 (1%) | 11 (2%) | 0.467 | 8 (1%) | 10 (2%) | 0.635 |
| Chronic obstructive pulmonary disease | 529 (30%) | 173 (24%) | 0.001 | 151 (24%) | 159 (25%) | 0.602 |
| Asthma | 77 (4%) | 35 (5%) | 0.687 | 28 (4%) | 26 (4%) | 0.781 |
| Pulmonary hypertension | 130 (8%) | 56 (8%) | 0.864 | 51 (8%) | 50 (8%) | 0.917 |
| Anemia | 343 (20%) | 150 (21%) | 0.636 | 132 (21%) | 135 (21%) | 0.836 |
| Depression | 200 (12%) | 75 (10%) | 0.379 | 75 (12%) | 69 (11%) | 0.596 |
| Signs and Symptoms on Admission | | | | | | |
| Dyspnea at rest | 768 (44%) | 307 (42%) | 0.341 | 276 (43%) | 271 (42%) | 0.778 |
| Dyspnea on exertion | 1041 (60%) | 461 (63%) | 0.123 | 403 (63%) | 395 (62%) | 0.644 |
| Orthopnea | 369 (21%) | 192 (26%) | 0.006 | 159 (25%) | 160 (25%) | 0.948 |
| Paroxysmal nocturnal dyspnea | 178 (10%) | 115 (16%) | <0.001 | 84 (13%) | 91 (14%) | 0.569 |
| Chest pain | 317 (18%) | 172 (24%) | 0.002 | 151 (24%) | 142 (22%) | 0.549 |
| JVP elevation | 410 (24%) | 191 (26%) | 0.169 | 168 (26%) | 158 (25%) | 0.521 |
| Third heart sound | 99 (6%) | 36 (5%) | 0.449 | 37 (6%) | 31 (5%) | 0.455 |
| Pulmonary rales | 1054 (61%) | 460 (63%) | 0.256 | 413 (65%) | 396 (62%) | 0.324 |
| Peripheral edema | 1192 (69%) | 461 (63%) | 0.010 | 414 (65%) | 406 (63%) | 0.641 |
| Discharge medications | | | | | | |

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| n (%) or mean (±SD) | Before propensity score matching (n=2470) | | | After propensity score matching (n=1280) | | |
|---|---|---|---|---|---|---|
| | No beta-blocker (n=1740) | High-dose beta-blocker (n=730) | P value | No beta-blocker (n=640) | High-dose beta-blocker (n=640) | P value |
| ACE inhibitors or ARBs | 913 (53%) | 448 (61%) | <0.001 | 391 (61%) | 387 (61%) | 0.819 |
| Aldosterone antagonists | 109 (6%) | 55 (8%) | 0.247 | 52 (8%) | 48 (8%) | 0.677 |
| Digoxin | 358 (21%) | 153 (21%) | 0.830 | 132 (21%) | 133 (21%) | 0.945 |
| Loop diuretics | 1373 (79%) | 582 (80%) | 0.648 | 506 (79%) | 507 (79%) | 0.945 |
| Hydralazine | 49 (3%) | 39 (5%) | 0.002 | 28 (4%) | 31 (5%) | 0.689 |
| Nitrates | 342 (20%) | 205 (28%) | <0.001 | 168 (26%) | 168 (26%) | 1.000 |
| Amlodipine | 164 (9%) | 96 (13%) | 0.006 | 71 (11%) | 81 (13%) | 0.388 |
| Other calcium channel blockers | 426 (25%) | 119 (16%) | <0.001 | 112 (18%) | 113 (18%) | 0.941 |
| Antiarrhythmics | 184 (11%) | 46 (6%) | 0.001 | 35 (6%) | 42 (7%) | 0.411 |
| Warfarin | 406 (23%) | 237 (33%) | <0.001 | 185 (29%) | 194 (30%) | 0.582 |
| Aspirin | 657 (38%) | 341 (47%) | <0.001 | 292 (46%) | 284 (44%) | 0.653 |
| Other antiplatelet drugs | 191 (11%) | 120 (16%) | <0.001 | 99 (16%) | 91 (14%) | 0.529 |
| Statins | 390 (22%) | 274 (38%) | <0.001 | 216 (34%) | 219 (34%) | 0.859 |
| In-hospital events | | | | | | |
| Coronary angiography | 77 (4%) | 62 (9%) | <0.001 | 45 (7%) | 45 (7%) | 1.000 |
| Clinical findings | | | | | | |
| Discharge heart rate (bpm) | 83 (11) | 82 (11) | 0.018 | 82 (10) | 82 (11) | 0.892 |
| Discharge systolic BP (mm Hg) | 129 (21) | 131 (22) | 0.040 | 132 (21) | 131 (22) | 0.666 |
| Discharge diastolic BP (mm Hg) | 67 (12) | 69 (13) | <0.001 | 69 (12) | 69 (13) | 0.687 |
| Discharge creatinine (mg/dL) | 1.6 (1.4) | 1.9 (1.7) | <0.001 | 1.8 (1.8) | 1.8 (1.6) | 0.913 |
| Admission hemoglobin (g/dL) | 12.0 (4) | 11.6 (2) | 0.046 | 11.7 (2) | 11.7 (2) | 0.642 |
| Admission sodium (mEq/L) | 137 (11) | 137 (10) | 0.509 | 137 (10) | 137 (10) | 0.934 |
| Ejection fraction (%) | 59.2 (8) | 58.6 (7) | 0.028 | 59.0 (7) | 58.7 (7) | 0.481 |
| Length of stay (days) | 6 (5) | 6 (5) | 0.305 | 6 (5) | 6 (5) | 0.103 |
| Hospital capacity (beds) | 395 (251) | 395 (231) | 0.967 | 408 (261) | 402 (231) | 0.640 |
| Hospital characteristics | | | | | | |
| Region | | | | | | |
| Midwest | 552 (32%) | 228 (31%) | <0.001 | 208 (33%) | 207 (32%) | 0.976 |
| Northeast | 196 (11%) | 173 (24%) | | 129 (20%) | 125 (20%) | |
| South | 615 (35%) | 195 (27%) | | 181 (28%) | 180 (28%) | |
| West | 377 (22%) | 134 (18%) | | 122 (19%) | 128 (20%) | |
| Academic center | 734 (42%) | 355 (49%) | 0.003 | 303 (47%) | 307 (48%) | 0.823 |
| Transplant center | 294 (17%) | 117 (16%) | 0.597 | 112 (18%) | 108 (17%) | 0.589 |
| Interventional center | 1328 (76%) | 557 (76%) | 0.991 | 508 (79%) | 496 (78%) | 0.415 |

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; bpm=beats per minute; BP=blood pressure

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**Table 2.**

Outcomes Patients with Heart Failure with Preserved Ejection Fraction ≥50% and Heart Rate ≥70 Beats/Minute, by High-Dose Beta-Blocker Versus No Beta-Blocker Use

| | Events (%) | | |
|---|---|---|---|
| | **No beta-blocker (n=640)** | **High-dose beta-blocker (n=640)** | **Hazard ratio* (95% confidence interval)** |
| All-cause mortality | 438 (68%) | 403 (63%) | 0.86 (0.75–0.98); p=0.027 |
| All-cause readmission | 566 (88%) | 565 (88%) | 0.90 (0.81–1.02); p=0.100 |
| Heart failure readmission | 294 (46%) | 287 (45%) | 0.93 (0.79–1.09); p=0.362 |
| All-cause readmission or all-cause mortality | 619 (97%) | 607 (95%) | 0.89 (0.80–1.00); p=0.044 |
| Heart failure readmission or all-cause mortality | 522 (82%) | 496 (78%) | 0.90 (0.80–1.02); p=0.091 |

*Associated with high-dose beta-blocker use

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**Table 3.**

Predictors of High-Dose Beta-Blocker Use Among 2592 Pre-Match Patients with Heart Failure with Ejection Fraction ≥50% and Heart Rate ≥70 Beats/Minute Receiving Beta-Blockers with Dosage Data

| | **Multivariable-adjusted odds ratio* (95% confidence interval)** |
|---|---|
| Age ≥80 years | 0.67 (0.56–0.81); p<0.001 |
| Female | 0.99 (0.82–1.19); p=0.893 |
| African American | 1.31 (1.00–1.72); p=0.048 |
| Atrial fibrillation | 1.26 (1.04–1.52); p=0.016 |
| Chronic obstructive pulmonary disease | 0.75 (0.61–0.91); p=0.005 |
| Discharge prescription for ACE inhibitor or ARBs** | 1.23 (1.02–1.48); p=0.029 |
| Discharge prescription for hydralazine | 1.93 (1.22–3.05); p=0.005 |
| Discharge prescription for calcium channel blockers | 1.32 (1.08–1.61); p=0.008 |
| Serum creatinine (increments of 0.1 mg/dL) | 1.10 (1.03–1.17); p=0.008 |
| Hospital, Northeast region | 1.33 (1.07–1.65); p=0.009 |
| Hospital, Academic | 1.18 (0.98–1.41); p=0.079 |

*Also adjusted for hypertension, coronary artery disease, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, discharge systolic blood pressure ≥120 mm Hg, discharge heart rate ≥80 beats per minute, left ventricular ejection fraction, and discharge prescription for diuretics

**ACE=Angiotensin-converting enzyme; ARB=angiotensin receptor blocker