Association of Beta Blocker Exposure with Outcomes in Heart Failure

Differs Between African American and White Patients

Lanfear et al: Beta Blocker Benefit in Heart Failure by Race

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Abstract

Background—Beta blockers (BB) are a mainstay of heart failure (HF) treatment, yet there is inconclusive data regarding their efficacy in African American individuals.

Methods and Results—We performed a retrospective study of insured patients who received care from a large health system who were hospitalized for HF between January, 2000 and June, 2008, and had a documented ejection fraction <50%. BB exposure was estimated over six-month rolling windows using pharmacy claims data. Proportional hazards regression was used to test the association between BB exposure and all-cause hospitalization or death with adjustment for baseline covariates and other HF medication exposure. We performed analyses stratified by race, and overall with a BB exposure*Race interaction term. A total of 1,094 patients met inclusion criteria (476 white and 618 African American individuals). Median follow up was 2.1 years. In adjusted models BB exposure was associated with lower risk of death or hospitalization in both groups, but more so in white individuals (HR 0.40, 95%CI 0.27, 0.60, p<0.001) compared with African American individuals (HR 0.67, 95%CI 0.48, 0.94, p=0.024). A formal test for interaction indicated that the protection association for BB exposure differed by race (p=0.098, β=0.40). Reanalysis restricted to BBs approved for HF, or HF-specific hospitalizations did not substantively alter the findings.

Conclusions—BB appears to be 40-50% less effective in preventing death or hospitalization among African American patients with HF as compared with white individuals. Further study is needed to better understand BB effectiveness in African Americans with HF.

Key Words: heart failure, beta adrenergic receptor blocker, race, hospitalization, systolic dysfunction, adherence
Heart failure (HF) continues to be an enormous public health problem, despite the many advances in its pharmacotherapy over the past 25 years, with a prevalence of 5.7 million individuals affected and an incidence of over 500,000 new cases annually. Beta-adrenergic antagonists (BB) are a cornerstone of therapy for systolic HF with morbidity and mortality benefits demonstrated in multiple randomized clinical trials. However, the consistency of this benefit across racial-ethnic subgroups is not clear and warrants further investigation. While the point-estimates generated from post-hoc subgroup analyses of clinical trials suggest a benefit, the number of African American individuals included in these trials was very small, resulting in wide confidence intervals, even in a pooled analysis, and therefore some ongoing uncertainties regarding the influence of race. Even more concerning were the results of another BB trial using bucindolol which showed little overall benefit in a diverse study population but a clear difference in efficacy by race-ethnicity. While it is possible that this difference in efficacy by race is specific to bucindolol, (which has unique pharmacologic properties distinct from other members of the class), it is also plausible that treatment response differs by race in most BBs and that there is simply not enough data regarding other agents to illuminate this association. It is thus important to re-assess the effectiveness of commonly used BB in African Americans with HF, as there is limited data in this group.

Existing observational studies which have attempted to examine the relationship between BB use and HF outcomes among African American individuals have been limited by number of factors such as the use of historical controls, minimal adjustment for potential confounders, and most importantly limited accounting of actual BB use (i.e.,
medication adherence and dose) over time. Accounting for the continuous variation in medication exposure, rather than treating it as a single dichotomous measure, should allow improved analyses of medication effects in observational studies by more closely capturing the true range of medication exposure. The use of pharmacy claims data for adherence quantification is well established and additionally incorporating dose information provides a valid estimate of medication exposure over time. To better examine the benefits of BB therapy in African Americans, we performed a retrospective study using administrative and pharmacy claims data to assess the relationship between BB exposure with outcomes in a diverse patient population consisting of self-identified white and African American individuals with HF and reduced ejection fraction (EF). Estimates of BB exposure accounted for variation in use by assessing rolling six-month window periods over the duration of follow-up.

Methods

Study Population

Subjects were identified from patients receiving care through Henry Ford Health System, a vertically integrated, health system serving the primary and specialty health care needs of individuals in southeastern Michigan, and which includes several hospitals, a multispecialty physician group of approximately 1200 physicians, as well as an affiliated health maintenance organization (HMO). The system maintains a central repository of administrative data which was queried for this study. For the subset of patients enrolled in the HMO this data includes insurance claims information as well as enrollment and disenrollment dates. The study population was limited to individuals who
were continuously enrolled in the HMO for at least 1 year prior to the index hospitalization and received care through system physicians. Therefore the study team had electronic information available for all health care visits and prescription fills, both within and outside of the health system. Using automated data sources, we identified all patients ≥18 years of age with a primary hospital discharge diagnosis of HF between January 1, 2000 and June 30, 2008. The index hospitalization was the first inpatient admission during the period of observation. A primary hospital discharge diagnosis of HF has been shown by our group\textsuperscript{16} and others\textsuperscript{17} to be a highly specific claim signature for HF (specificity 95 -100%). Patients were followed until they reached a study endpoint (i.e., death or re-hospitalization) or were censored at the earlier of either disenrollment from the health plan or final follow up on December 31, 2008. The study was approved by the Institutional Review Board at Henry Ford Hospital.

Data Sources

Data for this study came from the following sources: electronic administrative databases maintained by the health system, vital records from the Michigan Department of Community Health, and the Social Security Administration Death Master File (DMF). The administrative data captured claims (i.e., coded diagnoses, procedures, and prescription fills; see appendix for codes utilized) occurring both within and outside the health system. A master patient index contained demographic data (i.e., date of birth, sex and race). Information on race-ethnicity in the database is usually self-reported, but may occasionally be assigned by the system/healthcare staff who registered the patient. We have previously found excellent agreement between self-reported race-ethnicity and that
which is recorded in the electronic database. Laboratory results were available for all tests performed within the health system. The DMF, available through the National Technical Information Service, was supplemented with the Michigan State Division of Vital Records and Health Statistics, and both or which were queried with patients’ social security number to identify deaths. Left ventricular EF was abstracted from the medical record using the clinical test which reported it (i.e. echocardiography, nuclear stress tests, angiography or radionuclide blood pool imaging) closest in proximity to the time of patients’ admission with decompensated HF. Patients had to have a documented EF <50% to be included in the current analysis.

Pharmacy Claims and Estimation of Beta Blocker Exposure

To be able to examine medication exposure across the BB class of agents (i.e. include all BB in the exposure estimate) equivalent doses across agents were established. This was based on what proportion of a target dose for each specific agent was used. These target doses were adopted from the target dose for systolic HF used in clinical trials, or the maximum daily dose for BB agents that are not approved for use in treating systolic HF (e.g., atenolol). Specifically these target/maximal daily doses were 50mg for carvedilol, 200mg for metoprolol (for both long-acting and short-acting formulations), 10mg for bisoprolol, 100mg for atenolol, and 600 mg for labetalol. For example, 25 mg of carvedilol per day (i.e. 12.5 mg bid) was considered a 0.5 BB dose equivalent.

Chronic exposure to BB was then calculated as the drug-equivalent strength (described above) multiplied by the quantity of medication dispensed in a 6-month time block, divided by the total number of days in the 6-month time block. A specific BB
exposure estimate was calculated for each patient for every day of observation, starting 6-months after hospital discharge date. Thus each patient had a quantitative estimate of their last 6 months of BB exposure for each day of follow-up (i.e., exposure over the preceding 6 months). Individual exposure measures could thus vary daily, and could include periods of no exposure. Therefore this method accounts for both dose and adherence over a rolling period of time (in this case 6 months), which we have demonstrated is superior to single time-point, dichotomous classification of BB exposure in terms of correlation to heart rate and death or hospitalization (e.g. discharge medication status). As an example, if a patient was prescribed 12.5 mg of carvedilol twice daily and had picked up pills such that there appeared to be continuous availability over the previous 6 months, the BB exposure estimate would be 0.5. Similar to the above, a dose equivalence calculation was established for both angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACE/ARB), and ACE/ARB exposure was estimated in the same manner using pharmacy claims data.

Covariates

The covariates examined included age, race, gender, and baseline co-morbidities (atrial fibrillation, diabetes, hypertension, vascular disease, stroke, pre-existing HF, renal dysfunction, and coronary disease). These covariates were included in all multivariate models. We also included an estimate of ACE/ARB exposure to adjust for the effect of this therapy (as it is also known to improve outcomes in HF patients) as well as to adjust for non-BB adherence behaviors. The latter is important since adherence is known to affect outcomes regardless of treatment modality including placebo.
diabetes and hypertension, baseline comorbidities were defined as having a primary or secondary ICD-9 diagnosis code or certain procedure codes in any setting in the year prior to the index hospitalization date. Hypertension required two claims with the relevant ICD-9 diagnostic codes from any clinical setting OR at least one primary diagnosis from a hospitalization in the baseline year. A diagnosis of diabetes mellitus required two claims from any clinical setting OR one primary diagnosis from a hospitalization in the baseline year OR at least one prescription filled for a diabetic medication in the baseline year (see appendix for the list of medications). In addition to diagnostic codes, procedure codes related to treatment were used to identify peripheral vascular disease, stroke/transient ischemic attack, end stage renal disease, and coronary artery disease.

Endpoint Assessment

The primary endpoint was the time to death or re-hospitalization for any cause. Hospital re-admissions were identified from claims data, all of which were available for health plan members enrolled in this study. We also performed secondary analyses limited to HF hospitalizations. Deaths were identified using data obtained from health system administrative data, vital records from the State of Michigan, and the DMF, as described above. The endpoints were analyzed as a time-to-event using proportional hazards regression (see statistical analysis below for details) so associations with repeated hospitalizations (beyond the first readmission) or the total number of hospitalizations were not tested. As stated above, since the exposure metric required a 6 month observation window, the first day of observation for outcomes was 6 months after
discharge from the index hospitalization (Figure 1). Thus, patients who died in the first 6 months after index hospitalization were not included in the study cohort and hospitalizations in this period were not considered.

Statistical Analysis

Baseline variables were compared using either chi-squared tests for categorical variables or two-sample Student’s t-tests for continuous variables. Those variables which were not distributed normally were compared using a two-sample Mann-Whitney test. Proportional hazards regression models were used to assess the relationship of BB exposure with the composite endpoint of mortality or re-hospitalization following discharge, with adjustment for all baseline covariates. The BB exposure estimates, generated as described above, were then tested for association the combined event of death or hospitalization. A proportional hazards regression analysis with time dependent covariates was used to evaluate this relationship. Models using all the data, as well as stratified by race, were developed. Multivariable models were adjusted for age, sex, comorbidities (i.e., atrial fibrillation, diabetes, hypertension, pulmonary vascular disease, stroke, HF, and chronic kidney disease), EF, sodium level, and ACE/ARB exposure (calculated similarly to the BB exposure variable). Figure 2 depicts the estimated survival curve (calculated from the Cox model) evaluated at the average covariate value (except race which was stratified) and a set value of BB exposure. BB exposure was set at either the median value or the 75th percentile to demonstrate the independent effect of differing levels of exposure to the outcome probability estimation within each racial group. Additional analyses were also performed to examine the effect of BB exposure on
HF hospitalizations, the effect of approved BB agents only (i.e. carvedilol, metoprolol succinate, and bisoprolol) on the primary endpoint (composite of death and all-cause hospitalization), and excluding patients who had no fills of any cardiac medicine. For primary effects, p values <0.05 were considered statistically significant. For interactions, p values <0.1 were considered significant. All analyses were performed in SAS version 9.1.3 (SAS Institute, Cary, North Carolina).

Results

The total study population consisted of 1,094 subjects, of which 56% were African American. Baseline characteristics are summarized in Table 1. African American patients tended to be younger, were more often female, had lower rates of coronary disease and atrial fibrillation, and had lower EF’s and serum sodium when compared to white patients. The average exposure to BB and ACE/ARB did not differ significantly between African American and white patients. There were a total of 478 deaths and 890 first re-hospitalizations during the follow-up period, and the median length of follow-up was 33 months.

BB exposure was associated with a lower risk for the combined endpoint of death or hospitalization in both race groups, however, a larger protective association was seen in white patients as compared with African American patients. BB exposure was associated with a 60% reduced hazard among white patients (HR 0.40, 95%CI 0.27, 0.60, p<0.001) but only a 33% reduction in hazard among African American patients (HR 0.67, 95%CI 0.48, 0.94, p<0.02). As further support of this apparent treatment difference by race, we tested the interaction between race and BB exposure on the primary outcome.
among all subjects and observed a significant interaction ($\beta=0.40$, $p=0.098$). Figure 2 shows estimated survival curves using the Cox regression model, comparing median BB exposure and 75th percentile BB exposure for African American individuals and white individuals separately. This illustrates the magnitude of the beneficial effect of greater BB exposure within the two groups as estimated from these data. The greater separation of the curves among white patients is indicative of enhanced outcome improvement associated with BB exposure relative to that seen in African American patients.

To better understand this effect, we also examined the individual endpoints of death and hospitalization separately (Table 2). BB exposure appeared less protective in African Americans for hospitalization, mirroring the composite outcome. In contrast the survival impact appeared more uniform across the two race groups (HR 0.30 for white patients vs. 0.24 for African American patients; $p=NS$). In order to evaluate whether differences in hospitalizations may have been confounded by other disease states, we also examined hospitalizations specifically for HF. When restricted to hospitalizations in which HF was a discharge diagnosis there was a total of 841 events, and if limited to hospitalization with a primary discharge diagnosis of HF there were 546 events. The reanalyzed results using HF hospitalization as the outcome were very similar to that seen for all-cause hospitalization. BB exposure was associated with reduced event rates of HF hospitalization in both white patients (HR=0.37, 95%CI 0.24, 0.57) and African American patients (HR=0.65, 95%CI 0.45, 0.93), but again the BB-associated reduction in HF hospitalization was significantly greater for white patients as compared with African American patients ($\beta=0.47$, $p=0.067$ for the interaction). Restricting the analysis further to hospitalizations with HF as the primary discharge diagnosis as the outcome, BB
protectiveness appeared enhanced among white patients (HR=0.33, 95%CI 0.19, 0.58) when compared with African American patients (HR=0.52, 95%CI 0.33 - 0.82), though the interaction term for this last outcome was not statistically significant (p=0.267).

Additional analyses were performed based on the oral beta blocker used, specifically those agents recommended versus not indicated for treatment of systolic HF. Among the 460 patients receiving unapproved BB agents, metoprolol tartrate was used most frequently (n=384, 83%), followed by atenolol (n=62, 13%), with all others accounting for only 14 patients (3%). Use of recommended BB agents (carvedilol, metoprolol succinate, bisoprolol) was slightly but not significantly higher in African American patients compared with white patients (42.1% vs. 38.1%, respectively; p=0.285). Furthermore, there was not a significant interaction between type of BB (recommended in systolic HF vs. not), BB exposure and outcomes (p interaction >0.9).

Finally, we excluded patients who predominantly received the non-recommended agents, which did not substantively alter our findings. For white patients with HF, BB exposure was associated with 62% reduction in risk of death or hospitalization (HR=0.38, 95%CI 0.21, 0.69) while for African Americans there was a 34% reduction (HR=0.66, 95%CI 0.83,1.05). The interaction term did not meet statistical significance (p=0.224) possibly to due smaller sample size, though the effect size in terms of the beta coefficient was similar (β=0.41).

We also performed an analysis excluding patients who had no fills of any heart failure medicine (i.e. BB, ACE, ARB, vasodilators, and diuretics). This excluded 100 patients (9.1%) resulting in a reduced cohort size of 994. Among these subjects, effect estimates for BB exposure in terms of death or rehospitalization were very similar to
those in the primary analysis above for both African American individuals (HR 0.63, 95%CI 0.45 - 0.89, p=0.009) and white patients (HR 0.39; 95%CI 0.26 - 0.59, p=0.001), again suggesting differences by race despite a non-significant interaction term (β=0.32; p=0.19) in this smaller analytic subset.

Discussion

Defining the benefit of BB in African American individuals with HF has been a difficult research challenge. While the magnitude of benefit of BB in African American individuals with HF remains incompletely defined (requiring additional randomized data), our findings provide important insights on the relative effectiveness of BB therapy in African American individuals with HF in comparison to white patients. These data clearly indicate a reduced benefit for preventing the composite endpoint of death or re-hospitalization. However, it is very important to note that BB exposure was still associated with improved outcomes among African Americans, and consequently these data do not conflict with the current standard of care for African Americans with HF as codified in guidelines. Instead they underscore the need for further research to better understand the risk: benefit ratio of BB in African Americans, to determine the mechanism underlying these racial differences, and ultimately to improve outcomes for African American HF patients.

Early BB trials\(^3,4,6,21\) included few African American participants, and while subgroup analyses\(^6,7\) are consistent with a similar benefit by race, this effect did not reach statistical significance, even in a meta-analysis pooling these data.\(^8\) Our observations somewhat contrast with these by suggesting a reduced benefit of BB in African
Americans with HF compared to whites. However, they could both be viewed as congruent with a net benefit of BB in African Americans, but less so than for whites, and that this relative difference is simply missed in the clinical trial data due to our greater granularity of exposure, or because hospitalizations were not analyzed (which is primarily what drove our findings). When comparing our results to clinical trial findings, its also worth noting that our effect sizes are expectedly greater in magnitude. This is because our methods account for adherence and exposure, so that the impact is comparing perfect exposure to none, rather than the average exposure in a group of treated patients (as in a clinical trial).

Other efforts to examine BB effectiveness across race have been limited to observational datasets which have been subject to significant methodological limitations. Since BB treatment is a performance measure in HF, there are often few subjects truly unexposed to BB in such studies. Adding to this is that adherence behaviors, variability in medication dosing, and changes in dose or adherence over time, have generally not been accounted for. Due to these factors, much of the variability in actual medication exposure is lost, leaving these studies underpowered. One of the larger such analyses came from the COHERE registry, which performed a pre-post analysis of patients initiating carvedilol treatment. This study included 523 African Americans and showed a similar reduction compared to whites in symptoms and hospitalizations (58% and 56% reduction in hospitalization compared to the year prior to carvedilol initiation in whites and African Americans, respectively). However this study did not adjust for potentially important confounders that were drastically different between race groups including coronary disease, gender, and age. The study design also included historical control,
which has inherent limitations. Our data contrast with the COHERE findings, possibly due to these important design differences. Specifically, our study accounted for these key confounders and quantified drug exposure continuously. Thus our approach may better assess the risk reduction specifically attributable to BB exposure and how this varies between population groups.

On the other hand our data are in agreement with the trend suggested in recent study from Cresci and colleagues, a two center HF registry which included roughly 600 African Americans. This study suggested reduced BB benefit in African Americans but was not conclusive, in part because BB exposure was characterized as either present or absent (i.e. no knowledge of dose or adherence) and the vast majority of patients were (appropriately) treated with BB. Thus the number of African Americans subjects deemed to have not received BB therapy was very small (n=98). The enhanced detail of drug exposure collected in our study allowed a significant difference to be discerned despite the number of African American patients being similar. An interesting facet is that the outcome differences seen in our study appear to be driven by rehospitalization, whereas the BB-associated reduction in mortality appeared similar across racial groups. This may be explained by insufficient power for this less common endpoint, but alternatively could indicate that these endpoints are determined by different factors or that mortality protection is not different by race.

The mechanism underlying race differences in BB effect remains an open question, though our data do help in making a few potential explanations less likely. First, medication adherence has repeatedly been shown to be lower among African Americans and thus might have been suspect. However, our analysis accounts for
differences in adherence and still showed differential BB-associated outcomes. Differences in comorbidities such as ischemic heart disease or diabetes were accounted for, so we feel they are also unlikely to explain race-based differences in BB effectiveness. Finally, since the overall BB exposure was similar in African Americans and whites, possible differences in physician tendency to prescribe BB or to reach target dosing are also unlikely to be involved. The fact that our study population was comprised of patients with health insurance would seem to make differences in access to care an unlikely explanation, but additional studies examining possible racial differences in thresholds for admitting patients to the hospital or with better accounting for socioeconomic factors may be worthwhile.²⁴

Several other unmeasured variables associated with race or ethnicity may exist including environmental influences and/or genetic and biological differences that may explain the differential response to BB. For example, there are several genetic variants in the adrenergic pathway that appear to impact BB-related outcomes.²³,²⁵,²⁶ However, this association has been most clearly demonstrated with bucindolol, and is much less clear in the setting of clinically used BB agents. Furthermore, it has been challenging to identify ancestry-specific pharmacogenomic determinants of BB response, in part due to the difficulty in separating race and genetics; the relatively low numbers of African Americans studied; the high proportion of HF patients already treated with BB (i.e., lack of variation in treatment); and the heretofore failure to capture and account for the true range of BB medication exposure.

Our study has limitations that should be considered when interpreting the findings. First, it was based predominantly on electronic data sources. While this enables large
numbers of patients to be studied, certain variables may not be available, and diagnostic misclassification can occur. For example blood pressure and NYHA class at admission were not available. Diagnostic misclassification is less likely because a primary discharge diagnosis of HF (part of our inclusion criteria) has been shown to have 95% -100% specificity for patients meeting the Framingham definition of HF,17, 27 and the diagnostic and procedure codes that we used have been previously demonstrated to be valid.28 Secondly, medications could have been obtained without an insurance claim via our system, and thus have been missed by our methods. While we cannot rule this out, recent work from our group suggest that pharmacy fills via other insurers occurs very infrequently in our HMO population (<1% of the time).29 Another concern is that data was combined across a variety of BB agents in order to maximize power and reflect ‘real world’ treatment of patients. Importantly, the use of BB agents not approved for HF treatment (e.g. metoprolol tartrate) was similar across race groups (in fact African Americans showed slightly higher rates of receiving appropriate agents), and our secondary analyses excluding patients on unapproved agents showed similar results to the primary analysis. While our dose equivalency conversions are likely imperfect, any impact of this should affect groups similarly and thus would not be expected to unduly bias our results. Another potential limitation is that we did not use propensity scores or propensity matching in this analysis. These approaches have been used to account for confounders associated with treatment choice,30-32 which could be relevant here due to the retrospective nature of the study and imbalance of some baseline characteristics. However, even these methods do not always adequately account for unmeasured confounders and an earlier study by us suggested that propensity scores may not be
necessary when the analytic model accounts for the most relevant variables. Finally, all data come from a single center and included insured patients, potentially limiting generalizability. However, our health system population has been shown to be representative of the larger metropolitan population from which it is derived.

Conclusions

In this observational data set, BB exposure appeared less protective among insured African Americans with HF and reduced EF in terms of preventing death or readmission when compared with Whites. The potential mechanisms of reduced BB effectiveness in African Americans are unknown and may include pharmacogenetic variations associated with race, and differences in environmental exposures or socioeconomic factors. The awareness of racial differences in response to therapy is important as it underscores the need to identify additional opportunities to improve the outcomes of all patients, but particularly African Americans, and to reduce outcome disparities. Additional study is needed to better understand this phenomenon, define the risks and benefits of BB in African Americans with HF, and develop improved targeting of current treatment strategies.
Disclosures

Dr. Lanfear is the PI of an NIH grant relevant to this topic, on which Dr. Williams is a collaborator and Dr. Spertus a consultant.

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References


patients at risk for 30-day readmission or death using electronic medical record data. Med Care. 2010;48:981-988.


Table 1. Baseline Characteristics of Patients by Race

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>African American (n=618)</th>
<th>White (n=476)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.4 ±14.1</td>
<td>71.5 ±11.7</td>
<td>0.001</td>
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<tr>
<td>Female, n (%)</td>
<td>272 (44%)</td>
<td>179 (38%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Pre-existing heart failure, n (%)</td>
<td>290 (47.1%)</td>
<td>254 (53.4%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>244 (40%)</td>
<td>199 (42%)</td>
<td>0.437</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>173 (28%)</td>
<td>175 (36.8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>114 (18.5%)</td>
<td>167 (35.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>72 (11.7%)</td>
<td>68 (14.3%)</td>
<td>0.199</td>
</tr>
<tr>
<td>Cerebrovascular accident, n (%)</td>
<td>85 (13.8%)</td>
<td>64 (13.5%)</td>
<td>0.874</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>390 (63.2%)</td>
<td>278 (58.4%)</td>
<td>0.106</td>
</tr>
<tr>
<td>Ejection Fraction, %</td>
<td>27.5 ±11.0</td>
<td>30.1 ±11.4</td>
<td>0.001</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>1.31 ±0.62</td>
<td>1.29 ±0.51</td>
<td>0.849</td>
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<td>Hemoglobin, g/dl</td>
<td>12.4 ±1.9</td>
<td>12.4 ±2.1</td>
<td>0.943</td>
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<td>Sodium, meq/dl</td>
<td>140.3 ±3.7</td>
<td>138.7 ±4.5</td>
<td>0.001</td>
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<td>B-type natriuretic peptide, pg/ml</td>
<td>1044 ±995</td>
<td>1048.1 ±992</td>
<td>0.996</td>
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<td>Mean BB exposure</td>
<td>0.24 ±0.27</td>
<td>0.25 ±0.27</td>
<td>0.74</td>
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<tr>
<td>Mean ACE-Inhibitor exposure</td>
<td>0.25 ±0.26</td>
<td>0.28 ±0.28</td>
<td>0.1</td>
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<td>Any BB exposure, n (%)</td>
<td>497 (80.4%)</td>
<td>377 (79.2%)</td>
<td>0.618</td>
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<td>Target/Maximum dose (at any time), n (%)</td>
<td>151 (24.4%)</td>
<td>110 (23.1%)</td>
<td>0.610</td>
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<td>BB approved for heart failure*, n (%)</td>
<td>260 (42.1%)</td>
<td>185 (38.9%)</td>
<td>0.285</td>
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<tr>
<td>Rehospitalization within 2 years</td>
<td>207 (33.5%)</td>
<td>187 (39.3%)</td>
<td>0.048</td>
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<tr>
<td>Death within 2 years</td>
<td>136 (22.0%)</td>
<td>140 (29.4%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Approved BB include bisoprolol, carvedilol, and metoprolol succinate.
Statistically significant variables (p<0.05) in **Bold** typeface.
Table 2. Results of multivariable proportional hazards regression modeling

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome</th>
<th>African American</th>
<th>P</th>
<th>White</th>
<th>P</th>
<th>β-coefficient BB*Race interaction</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cohort</td>
<td>Death or Hospitalization, HR (95%CI)</td>
<td>0.67</td>
<td>0.021</td>
<td>0.40</td>
<td></td>
<td>0.40</td>
<td>0.098</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.48 - 0.94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death, HR (95%CI)</td>
<td>0.24</td>
<td>&lt;0.001</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>-0.21</td>
<td>0.808</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.13 - 0.45)</td>
<td></td>
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<tr>
<td></td>
<td>Hospitalization (all), HR (95%CI)</td>
<td>0.67</td>
<td>0.020</td>
<td>0.40</td>
<td>&lt;0.001</td>
<td>0.37</td>
<td>0.134</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.47 - 0.95)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>HF hospitalization, HR (95%CI)</td>
<td>0.65</td>
<td>0.019</td>
<td>0.37</td>
<td>0.001</td>
<td>0.47</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.45 – 0.93)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Approved BB only*</td>
<td>Death or Hospitalization, HR (95%CI)</td>
<td>0.66</td>
<td>0.078</td>
<td>0.38</td>
<td>0.002</td>
<td>0.41</td>
<td>0.224</td>
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<tr>
<td></td>
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<td>(0.83 -1.05)</td>
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</tr>
<tr>
<td>Excluding subjects w/o fills</td>
<td>Death or Hospitalization, HR (95%CI)</td>
<td>0.63</td>
<td>0.009</td>
<td>0.39</td>
<td>0.001</td>
<td>0.32</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
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<td>(0.45 - 0.89)</td>
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</tbody>
</table>

Statistically significant findings (p<0.05 for main effect, p<0.1 for interactions) in **Bold** typeface.

*Approved BB are carvedilol, metoprolol succinate, and bisoprolol; patients receiving other agents were excluded.
Figure Legends

Figure 1. Schematic of Study Timeline

Figure 2. Time to Death or Hospitalization in African American and White Patients for high and low BB Exposure (from proportional hazards regression model). High BB exposure was set at the 75 percentile while low exposure was set at the median.
FIGURE 1

- Index Hosp.
- First Exposure Estimate
- BB Exposure Re-Calculated Daily
- Observation Period 1 year
- Time Zero
- 6 mo
Association of Beta Blocker Exposure with Outcomes in Heart Failure Differs Between African American and White Patients

David E. Lanfear, Tara Hrobowski, Edward L. Peterson, Karen Wells, Tanmay Swadia, John A. Spertus and L. Keoki Williams

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