Association of β-Blocker Exposure With Outcomes in Heart Failure Differs Between African American and White Patients

David E. Lanfear, MD, MS; Tara N. Hrobowski, MD; Edward L. Peterson, PhD; Karen E. Wells, MS; Tanmay V. Swadia, MD; John A. Spertus, MD, MPH; L. Keoki Williams, MD, MPH

Background—β-Blockers (BB) are a mainstay of heart failure (HF) treatment, yet there are 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 6-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 1094 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 (hazard ratio, 0.40; 95% confidence interval, 0.27, 0.60; \( P < 0.001 \)) compared with African American individuals (hazard ratio, 0.67; 95% confidence interval, 0.48, 0.94; \( P = 0.024 \)). A formal test for interaction indicated that the protection association for BB exposure differed by race (\( P = 0.098, \beta = 0.40 \)). 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 compared with white individuals. Further study is needed to better understand BB effectiveness in African Americans with HF. (Circ Heart Fail. 2012;5:202-208.)

Key Words: heart failure ■ β-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 more than 500 000 new cases annually.1 β-Adrenergic antagonists (BB) are a cornerstone of therapy for systolic HF with morbidity and mortality benefits demonstrated in multiple randomized, clinical trials.2–4 However, the consistency of this benefit across racial-ethnic subgroups is not clear and warrants further investigation.5 Whereas 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,6,7 even in a pooled analysis,8 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.9,10 Although it is possible that this difference in efficacy by race is specific to bucindolol, (which has unique pharmacological properties distinct from other members of the class),11,12 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 reassess the effectiveness of commonly used BB in African Americans with HF, as there are limited data in this group.

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Existing observational studies that 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 (ie, 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 6-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 that 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 that were queried for this study. For the subset of patients enrolled in the HMO, the data include 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 before 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 and others to be a highly specific claim signature for HF (specificity, 95–100%). Patients were followed until they reached a study end point (ie, death or rehospitalization) 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 (ie, coded diagnoses, procedures, and prescription fills; see online-only Data Supplement Appendix for codes used) occurring both within and outside the health system. A master patient index contained demographic data (ie, 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/health care staff who registered the patient. We have previously found excellent agreement between self-reported race-ethnicity and that 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 were queried with patients’ social security numbers to identify deaths. Left ventricular EF was abstracted from the medical record using the clinical test that reported it (ie, 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 BB Exposure

To be able to examine medication exposure across the BB class of agents (ie, 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 (eg, atenolol). Specifically these target/maximal daily doses were 50 mg for carvedilol, 200 mg for metoprolol (for both long-acting and short-acting formulations), 10 mg for bisoprolol, 100 mg for atenolol, and 600 mg for labetalol. For example, 25 mg of carvedilol per day (ie, 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 (ie, 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 (eg, 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, sex, and baseline comorbidities (atrial fibrillation, diabetes, hypertension, vascular disease, stroke, preexisting 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 because adherence is known to affect outcomes regardless of treatment modality including placebo. Except for 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 before the index hospitalization date. Hypertension required 2 claims with the relevant ICD-9 diagnostic codes from any clinical setting, or at least 1 primary diagnosis from a hospitalization in the baseline year. A diagnosis of diabetes mellitus required 2 claims from any clinical setting, or 1 primary diagnosis from a hospitalization in the baseline year, or at least 1 prescription filled for a diabetic medication in the baseline year (see online-only Data Supplement 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.
End Point Assessment

The primary end point was the time to death or rehospitalization for any cause. Hospital readmissions 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 end points were analyzed as a time-to-event, using proportional hazards regression (see Statistical Analysis below for details); therefore, associations with repeated hospitalizations (beyond the first readmission) or the total number of hospitalizations were not tested. As stated above, because 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 by means of either χ² tests for categorical variables or 2-sample Student t tests for continuous variables. Those variables that were not distributed normally were compared using a 2-sample Mann-Whitney test. Proportional hazards regression models were used to assess the relationship of BB exposure with the composite end point of mortality or rehospitalization after 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 variables. Those variables that were not distributed normally were tested for association the combined event of death or hospitalization. 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 individuals and white individuals separately. This illustrates the magnitude of the beneficial effect of greater BB exposure within the 2 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 end points 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 2 race groups (HR, 0.30 for white patients versus 0.24 for African American patients; P=NS). 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 (HR, 0.37; 95% CI, 0.26–0.57) and African American patients (HR, 0.65; 95% CI, 0.39–0.95) were very similar to that seen for all-cause hospitalization. Additional analyses were performed on the basis of oral BB 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% versus 38.1%, respectively; P=0.285). Furthermore, there was not a significant interaction between type of BB (recommended in systolic HF versus not), BB exposure, and outcomes (P interaction >0.9). Finally, we excluded patients who predominantly received the nonrecommended 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), whereas 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 because of smaller sample size, though the effect size in terms of the β-coefficient was similar (β=0.41).

We also performed an analysis excluding patients who had no fills of any heart failure medicine (ie, 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 nonsignificant 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. Although 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 end point of death or rehospitalization. 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 included few African American participants, and, although subgroup analyses are consistent with a similar benefit by race, this effect did not reach statistical significance, even in a meta-analysis pooling these data. Our observations somewhat contrast with these by...
suggesting a reduced benefit of BB in African Americans with HF compared with 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 with clinical trial findings, it is 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 that have been subject to significant methodological limitations. Because 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. Because of 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,22 which performed a pre-post analysis of patients initiating carvedilol treatment. This study included 523 African Americans and showed a similar reduction compared with whites in symptoms and hospitalizations (58% and 56% reduction in hospitalization compared with the year before 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, sex, and age. The study design also included historical control, which has inherent limitations. Our data contrast with the COHERE findings, possibly because of 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 a recent study from Cresci et al.,23 a 2-center HF registry that 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 (ie, no knowledge of dose or adherence) and the vast majority of patients were (appropriately) treated with BB. Thus, the number of African American 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 end point, but alternatively could indicate that these end points 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 believe they are also unlikely to explain race-based differences in BB effectiveness. Finally, because 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 composed 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

Table 2. Results of Multivariable Proportional Hazards Regression Modeling

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome</th>
<th>African American</th>
<th>P Value</th>
<th>White</th>
<th>P Value</th>
<th>Interaction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>Death or hospitalization, HR (95% CI)</td>
<td>0.67 (0.48–0.94)</td>
<td>0.021†</td>
<td>0.40</td>
<td>&lt;0.001†</td>
<td>0.40†</td>
<td>0.098†</td>
</tr>
<tr>
<td></td>
<td>Death, HR (95% CI)</td>
<td>0.24 (0.13–0.45)</td>
<td>&lt;0.001†</td>
<td>0.30</td>
<td>0.16–0.56</td>
<td>0.001†</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>All hospitalization, HR (95% CI)</td>
<td>0.67 (0.47–0.95)</td>
<td>0.020†</td>
<td>0.40</td>
<td>0.26–0.60</td>
<td>0.001†</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>HF hospitalization, HR (95% CI)</td>
<td>0.65 (0.45–0.93)</td>
<td>0.019†</td>
<td>0.37</td>
<td>0.24–0.57</td>
<td>0.001†</td>
<td>0.47</td>
</tr>
<tr>
<td>Approved BB only*</td>
<td>Death or hospitalization, HR (95% CI)</td>
<td>0.66 (0.83–1.05)</td>
<td>0.078†</td>
<td>0.38</td>
<td>0.21–0.69</td>
<td>0.002†</td>
<td>0.41</td>
</tr>
<tr>
<td>Excluding subjects w/o fills</td>
<td>Death or hospitalization, HR (95% CI)</td>
<td>0.63 (0.45–0.89)†</td>
<td>0.009†</td>
<td>0.39</td>
<td>0.26–0.59</td>
<td>0.001†</td>
<td>0.32</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; HF, heart failure; BB, β-blocker.
*Approved BB are carvedilol, metoprolol succinate, and bisoprolol; patients receiving other agents were excluded.
†Statistically significant findings (P<0.05 for main effect, P<0.1 for interactions).
of the larger metropolitan population from which it is derived.24

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 because 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.

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Disclosures
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