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Racial differences in mortality in patients with advanced systolic heart failure: Potential role of right ventricular ejection fraction

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ABSTRACT

In Beta-Blocker Evaluation of Survival Trial (BEST) bucindolol significantly reduced mortality among Caucasians with systolic heart failure (HF) but not among African Americans. Whether this differential effect can be explained by racial differences in baseline characteristics has not been previously examined. Of the 2708 BEST participants, 627 were African Americans. Because African Americans were more likely to be younger and women, we used age–sex-adjusted hazard ratios (HR) and 95% confidence intervals (CI) to estimate their outcomes (vs. Caucasians). A step-wise multivariable-adjusted model using 24 baseline characteristics was used to identify variables associated with between-race outcome differences and propensity-matching was used to determine independence of associations. Age–sex-adjusted HR for all-cause mortality for African Americans during 2 years of mean follow-up was 1.27. African Americans were more likely to have lower right ventricular ejection fraction. African Americans had no association with mortality among propensity-matched patients. The higher risk of death among African Americans in BEST may in part be due to their lower RVEF which may in part explain the lack of response to bucindolol among these patients. Future studies need to examine the role of low RVEF on the effect of beta-blockers in patients with systolic HF.

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1. Introduction

Population-based studies have suggested that African American patients with heart failure (HF) have a higher mortality rate than Caucasians with the same condition [1]. This finding has been attributed to differences in the severity, causes and management of HF, the prevalence of coexisting conditions and, also to socioeconomic factors [2,3]. Moreover, in equally treated patients it has been shown that racial differences may still exist [4]. Whether differences in the cardiac intrinsic or modulated functions or response to drug treatment contribute to these disparities has been incompletely assessed. In fact, African-American patients with HF respond less to angiotensin modulating agents [5] while the use of a direct vasodilator treatment with the combination of hydralazine–nitrates has shown to be effective in these patients [6–8].

Although bucindolol had no overall mortality benefit in the Beta-Blocker Evaluation of Survival Trial (BEST), in a subgroup analyses, Caucasian patients exhibited a significant survival benefit to treatment while African-American yielded no significant differences in mortality (P for interaction, 0.02) [9]. Whether these results could be related to chance or a decreased effectiveness of beta-blockers in African American patients remains unanswered [10]. Furthermore, whether if this racial difference in response to bucindolol therapy can be explained by racial differences in baseline characteristics has not been previously examined. In particular, the BEST was unique among beta-blocker trials in HF because data on right ventricular ejection function (RVEF) were collected. Therefore, the objective of present study is to determine the association between race and outcomes in the BEST, and examine if

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racial differences in various baseline characteristics, in particular, RVEF, may help explain a racial difference in outcomes.

2. Methods

2.1. Study design and patients

The BEST was a multicenter randomized placebo-controlled clinical trial of bucindolol, a non-selective beta-blocker in patients with chronic advanced systolic HF [9]. The rationale, design and results of the BEST have been published in the past [11,12]. Briefly, 2708 HF patients with systolic dysfunction (left ventricular ejection fraction {LVEF}; <35%) and New York Heart Association (NYHA) class III–IV symptoms were randomized to receive bucindolol or placebo between May 31, 1995 and December 31, 1998 from 90 different sites across the United States and Canada. Over 90% of these patients were receiving angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digitalis. For the purpose of the current study, we used a public-use copy of the BEST dataset, available with 2707 patients (one did not consent to be included in the de-identified public-use copy of the data) obtained from the National Heart, Lung, and Blood Institute (NHLBI), which also sponsored the BEST along with the Department of Veterans Affairs (VA).

The trial was terminated early by study sponsors (NHLBI and VA) at the recommendation of the data and safety monitoring board after the 7th interim analysis due to the "totality of evidence regarding the usefulness of beta-blocker treatment derived from the BEST and other studies" and a report based on data collected through July 26, 1999 demonstrated that there was no significant mortality difference between the two treatment groups. All-cause mortality occurred in 33% (n = 449) of patients in the placebo group and 30% (411) of patients in the bucindolol group (hazard ratio (HR), 0.90; 95% confidence interval (CI), 0.78–1.02; P = 0.10). However, a subgroup analysis suggested that bucindolol significantly reduced the risk of total mortality among non-black patients (HR, 0.82; 95% CI, 0.70–0.96; P = 0.01) but not among African Americans (HR, 1.17; 95% CI, 0.89–1.53; P = 0.27; interaction P = 0.02).

Because of smaller number of participants with other race, we excluded 185 Hispanic or other race participants. Thus, the final sample size for the current study was 2522 participants including 627 African-Americans and 1895 Caucasians.

2.2. Study outcomes

The primary outcome of interest for current analysis was all-cause mortality. Secondary outcomes included cause-specific mortality and hospitalizations. All outcomes were centrally adjudicated.

2.3. Assembly of a balanced study cohort

To reduce significant imbalances in baseline characteristics between patients with African American and Caucasians (Table 1), we used propensity score matching to assemble a balanced cohort. We estimated propensity scores for each of the 2522 patients using a non-parsimonious multivariable logistic regression model, in which African American was the dependent variable and other baseline characteristics displayed in Fig. 1 were used as covariates [13,14]. Then we used a greedy matching protocol to match 276 African Americans with another 276 Caucasians who had similar propensity scores [15–17]. Absolute standardized differences were estimated to assess the effectiveness of propensity score model and presented as a Love plot (Fig. 1) [18,19]. An absolute standardized difference of 0% would indicate no residual bias and values <10% are considered inconsequential.

2.4. Statistical analyses

For baseline characteristics, Pearson's Chi-square and Wilcoxon rank-sum tests for pre-match, and McNemar's test and paired sample t-test for post-match comparisons, as appropriate (Table 1). Kaplan–Meier plots were used to determine the associations of African Americans with outcomes during mean follow-up of 2 years. We examined the association of race with outcomes among pre-match participants using bivariate and step-wise multivariable Cox regression hazard models. Because measure baseline characteristics are balanced in propensity-matched cohorts, we also used bivariate Cox proportional hazard models to determine the associations of race with outcomes among matched participants. A formal sensitivity analysis was conducted to estimate the degree of hidden bias that could potentially explain away a significant association among matched patients [20]. All statistical tests were two-tailed and P value <0.05 was considered as statistically significant. SPSS for Windows version 20 was used for data analysis.

3. Results

Matched patients (n = 552) had a mean age of 56 years, and 25% were female. Baseline characteristics pre-match imbalances and post-match balances are presented in Table 1 and Fig. 1. Before matching, African American HF patients were more likely to be younger, female and smoker and had higher prevalence of diabetes and hypertension. They also had lower LVEF (22% vs. 23% for Caucasians) and right ventricular ejection fraction (RVEF; 32% vs. 36% for Caucasians). They were more likely to receive diuretic but less likely to receive statin. There were no differences in other key HF medications such as beta-blocker, ACE inhibitor, angiotensin receptor blockers or digitalis. After matching, we were able to achieve a balance cohort.

3.1. Outcomes

All-cause mortality occurred in 33% of African American and 32% of Caucasian HF patients before matching (unadjusted hazard ratio {HR}, 1.10; 95% confidence interval {CI}, 0.94–1.29; P = 0.228; Table 2 and Fig. 2 left panel). After adjustment with age and sex, the association became significant (HR, 1.27; 95% CI, 1.08–1.50; P = 0.003; Table 2 right panel). Similar association was observed in full model after including LVEF with other covariates (HR, 1.20; 95% CI, 1.01–1.43; P = 0.043) but lost significantly when RVEF was added either into full model (HR, 1.17; 95% CI, 0.98–1.39; P = 0.089) or to the age–sex-adjusted model (HR, 1.15; 95% CI, 0.98–1.36; P = 0.093; Table 2). In matched cohort, all-cause mortality occurred in 33% and 36% of African American and Caucasian HF patients, respectively (HR, 0.86; 95% CI, 0.65–1.15; P = 0.316; Table 2). Pre- and post-match associations of African American race with other outcomes are displayed in Table 3.

4. Discussion

Findings from the current study demonstrate that among patients with advanced systolic heart failure enrolled in the BEST, African Americans were younger and more likely to be women compared to Caucasians. These facts could explain the lack of differences in age–sex-adjusted mortality between the two races. African Americans had a significantly lower mean RVEF. When adjusted for the full model including 23 baseline characteristics but excluding RVEF the association remained significant. However, when adjusted for RVEF alone or RVEF added to the full model, the association lost its significance, suggesting that the lower RVEF among African Americans may also underlie the high mortality among these patients. These findings suggest that African American patients with advanced HF may be characterized by a low RVEF, which may explain their higher mortality, which in turn may modulate their response to beta-blocker therapy.

The absence of mortality benefit of beta-blockers in African American patients showed in the BEST may be explained by differences in baseline characteristics, in particular a lower mean RVEF among African Americans. Racial difference in neurohormonal modulation as demonstrated by a relatively less response to renin–angiotensin–aldosterone blockade and lesser sympathetic nervous activation may also be associated with a decrease response to beta-adrenergic blockade [21]. Another investigation has reported that black patients could have lesser beta-adrenoceptor sensitivity than Caucasians [22]. This study would be in agreement that despite some beneficial effect of chronic beta adrenergic blockade in both Caucasian and African-American populations [23], the efficacy of beta-blockers could be higher in Caucasian [24,25]. Other potential mechanisms include an increased oxidative stress which may be related to an increase rate of hypertension and diabetes in African-Americans [26]. In addition, previous studies have shown a marked impairment in endothelial vasomotor function in black patients with hypertension [27], explaining the beneficial clinical effect of increasing the biodisponibility of nitric oxide in this population [28].

Differences in baseline characteristics between Caucasians and African-Americans in the BEST could also contribute to disparities in the results. In accordance to previous publications in the BEST [29,30], black population had more incidences of hypertension and diabetes. Also, black patients in that trial represented a population with major incidence of cardiovascular risk factors, with more signs of congestion and a greater need for diuretic treatment suggesting a less compensated state of HF in this population [3]. Nevertheless, the proportion of

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