Representation of black patients in randomized clinical trials of heart failure with reduced ejection fraction

Lonnie T. Sullivan, II, BS,[a,c] Tiffany Randolph, MD,[b] Peter Merrill, PhD,[c] Larry R. Jackson, II, MD,[a,c] Chidiebube Egwim, MD, MPH,[a] Monique A. Starks, MD, MHS,[c] and Kevin L. Thomas, MD[a,c] *Durham, and Greensboro, NC*

Background Black individuals have a disproportionately higher burden of heart failure with reduced ejection fraction (HFrEF) relative to other racial and ethnic populations. We conducted a systematic review to determine the representation, enrollment trends, and outcomes of black patients in historic and contemporary randomized clinical trials (RCTs) for HFrEF.

Methods We searched *PubMed* and *Embase* for RCTs of patients with chronic HFrEF that evaluated therapies that significantly improved clinical outcomes. We extracted trial characteristics and compared them by trial type. Linear regression was used to assess trends in enrollment among HFrEF RCTs over time.

Results A total of 25 RCTs, 19 for pharmacotherapies and 6 (n=9,501) for implantable cardioverter defibrillators, were included in this analysis. Among these studies, there were 78,816 patients, 4,640 black (5.9%), and the median black participation per trial was 162 patients. Black race was reported in the manuscript of 14 (56.0%) trials, and outcomes by race were available for 12 (48.0%) trials. Implantable cardiac defibrillator trials enrolled a greater percentage of black patients than pharmacotherapy trials (7.1% vs 5.7%). Overall, patient enrollment among the 25 RCTs increased over time ($P = .075$); however, the percentage of black patients has decreased ($P = .001$). Outcomes varied significantly between black and white patients in 6 studies.

Conclusions Black patients are modestly represented among pivotal RCTs of individuals with HFrEF for both pharmacotherapies and implantable cardioverter defibrillators. The current trend for decreasing black representation in trials of HF therapeutics is concerning and must improve to ensure the generalizability for this vulnerable population. (Am Heart J 2018;197:43-52.)

Racial and ethnic variations in disease pathogenesis, prevalence, and approach to treatment have been described for a variety of conditions,[1-4] most notably heart failure (HF).[5,6] HF affects over 5.7 million adults in the United States,[7] and this number is expected to increase to over 8 million by 2030.[8] Among all racial/ethnic groups, black individuals have the highest incidence of HF (3%) in the United States.[5,9,10] The Multi-Ethnic Study of Atherosclerosis estimates that the incidence of HF among blacks is 4.6 per 1,000 person-years as compared with 3.5 and 2.4 per 1,000 person-years for Hispanic and white individuals, respectively.[5] The unique pathogenesis of HF in black patients in part explains the high incidence of HF among these individuals. For nonblack individuals, HF typically develops as a result of myocardial ischemia secondary to coronary artery disease.[11,12] Conversely, long-standing and poorly controlled hypertension is the provocateur for most black patients resulting in systolic dysfunction.[13] These racial differences in HF etiology may have significant implications when considering treatment.

Racial and ethnic minority populations are often underrepresented in randomized clinical trials (RCTs). The generalizability of cardiovascular treatment guidelines to underrepresented racial and ethnic populations remains uncertain based on the dearth of these populations in RCTs that inform national cardiovascular guidelines.[14-16] Prior reviews have examined the inclusion of black individuals in RCTs for chronic systolic HF,[9,13] but there is a paucity of data on how the enrollment of black patients has changed over time. Furthermore, the representation of black patients with chronic heart failure with reduced ejection fraction (HFrEF) in implantable cardioverter defibrillator (ICD)

From the [a]Duke University Medical Center, Durham, NC, [b]Cone Health Medical Group, Greensboro, NC, and [c]Duke Clinical Research Institute, Durham, NC.
Javed Butler, MD, MPH served as guest editor for this article.
Submitted April 30, 2017; accepted October 30, 2017.
Reprint requests: Kevin L. Thomas, MD, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC 27705.
E-mail: kevin.thomas@duke.edu
0002-8703

https://doi.org/10.1016/j.ahj.2017.10.025

trials relative to pharmacotherapy trials is unknown. The objectives of this review are (1) to characterize black representation among RCTs of pharmacotherapies and ICDs for chronic HFrEF that have demonstrated improvements in morbidity and mortality; (2) to describe enrollment trends for all patients relative to black patients; and (3) to assess outcomes by race when reported for these trials.

Methods

Study selection

Randomized clinical trials for HFrEF pharmacotherapies and ICDs or cardiac resynchronization therapy defibrillators (CRT-Ds) were included in this review. Other inclusion criteria included the following: trials with improvement in mortality and/or decreased hospitalizations and included at least 1 site in North America. Trials not published in English, those examining acute HFrEF in the setting of myocardial infarction, HFpEF, or post hoc analyses of larger RCTs were excluded.

Search strategy

The coauthors and a trained medical librarian designed the search strategy used for this analysis. We searched the online databases *PubMed* and *Embase* to identify HF pharmacotherapy trials. Our search strategy was comprised of MeSH terms including specific drug classes known to improve mortality and hospitalizations among individuals with HFrEF. We searched the following: (heart failure) AND (mortality OR hospitalization) AND (angiotensin-converting enzyme inhibitor OR beta blocker OR angiotensin receptor blocker OR mineralocorticoid receptor antagonist OR vasodilator agents OR ivabradine OR digoxin). Given the small number of RCTs of ICDs/CRT-Ds for primary prevention indications, we identified relevant cardiac device trials by directly extracting them from the HF treatment guidelines and reviewing the references of their primary manuscripts.[17,18] The final search strategy was approved by the principal investigator (K. T.).

The initial search yielded 1,781 unique citations from 1966 to 2017. These citations were exported into an Endnote library and screened by 2 independent reviewers (K. T. and L. S.). Of the identified 1,781 citations, 1,583 were rejected by title and abstract. The 198 remaining studies were examined by abstract and manuscript, and an additional 178 citations were rejected for not meeting our inclusion criteria (Figure 1).

Statistical analysis

Descriptive statistics were used to calculate racial demographic data. Numerical data were represented as whole numbers (n) or percentages (%). We calculated the total number of participants for each trial and which trials reported racial demographics. For trials that reported race, we calculated the total number of black study participants for each trial. We chose to focus only on black race due to the burden of HF, poor outcomes, and large body of data demonstrating disparities of care and outcomes in this population. If race was not characterized in the primary manuscript, we queried *PubMed* and *Google Scholar* for post hoc analyses or additional publications for demographic information.

We further extracted trial characteristics, including New York Heart Association (NYHA) functional class, number of sites and countries, and funding source. We excluded the African American Heart Failure Trial (A-HeFT) from our statistical analyses; it was a trial of all-black participants and would skew results. The data were stratified by treatment type (pharmacotherapy vs ICD), and the results were tabulated.

Outcomes for black subgroups were ascertained from either the primary manuscript or post hoc analyses. Trends for total and black patient enrollment over time were determined using regression analysis. P values $< .05$ were considered statistically significant. These calculations were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

The authors were solely responsible for the design and conduct of this study, including the study analyses, the drafting and editing of the paper, and its final contents. No extramural funding was used to support this work.

Results

Search results

Our search yielded 26 RCTs: 20 for HFrEF pharmacotherapies and 6 for ICDs. The 26 trials included 79,866 total patients: 70,365 in pharmacotherapy trials and 9,501 in device trials (Table I). After excluding A-HeFT, a total of 25 RCTs (N = 78,816) remained for analysis.

Trial characteristics

Most commonly, trials included HFrEF patients who had NYHA functional class II, III, or IV (40.0%) or NYHA functional class I, II, or III (28.0%) HF. The median time for recruitment was 32 months among all trials. Trials of ICD therapy had longer median recruitment (43 months) compared with pharmacotherapy trials (30 months). The median number of enrolling centers among all trials was 195 with a median of 15 different countries. Most RCTs had at least 1 enrolling center outside of North America (Table II).

Black enrollment

Black race was reported in the primary manuscript in 14 of the 25 RCTs (56.0%). Racial demographics were much more likely to be reported in pharmacotherapy trials as compared with ICD trials (68.4% vs 16.7%). Among all study participants, there were 4,640 (5.9%) black patients, and the median black patient enrollment per study was 162. Trials for ICDs enrolled a larger