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## Racial and Ethnic Minority Groups Are Under-Represented and Under-Reported in Guideline-Informing Heart Failure Clinical Trials

Gerardo Gamino

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Honors Thesis

RACIAL AND ETHNIC MINORITY GROUPS ARE UNDER-REPRESENTED  
AND UNDER-REPORTED IN GUIDELINE-INFORMING HEART FAILURE  
CLINICAL TRIALS

by  
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Submitted to Brigham Young University in partial fulfillment of graduation  
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## ABSTRACT

### RACIAL AND ETHNIC MINORITY GROUPS ARE UNDER-REPRESENTED AND UNDER-REPORTED IN GUIDELINE-INFORMING HEART FAILURE CLINICAL TRIALS

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Bachelor of Sciences

Heart failure (HF) is a common cause of morbidity and mortality in the United States (U.S.) that may disproportionately affect certain racial/ethnic groups.<sup>1,2</sup> Compared with White individuals, HF may affect Black individuals at a younger age with less favorable prognosis, and this excess risk may be partially explained by differences in HF risk factor burden.<sup>3</sup> It is crucial for guideline informing HF clinical trials to adequately reflect the racial/ethnic diversity in the population. We assessed the extent of reporting and representation of race/ethnicity in HF clinical trials referenced in the 2013 American College of Cardiology (ACC) Foundation/ American Heart Association (AHA) Guideline for the Management of Heart Failure and the 2017 ACC/AHA/Heart Failure Society of America (HFSA) Focused Update.<sup>2,4</sup> All randomized clinical trials referenced in these guidelines were included. The prevalence of reporting of race/ethnicity, the proportions of racial/ethnic subgroups enrolled, and subgroup analysis based on intervention type – pharmacologic, device, and other – were evaluated. A total of

265 trials (547,353 subjects) were included in the study which were published between 1950 and 2018. Among these, only 99 trials reported any race/ethnicity (37.4%), 97 reported white race (36.6%), 57 reported Black race (21.5%), 15 reported Hispanic ethnicity (5.7%), and 24 reported Asian race (9.1%). In trials reporting white, black, Hispanic, and Asian race/ethnicity respectively, 77.8% (n = 248,321/319,070) of patients were white, 12.3% (n = 29,353/239,192) of patients were black, 11.0% (n = 8,374/76,099) of patients were Hispanic, and 9.7% (n = 15,063/155,577) of patients were Asian. Stratification by intervention type demonstrated that no device trials referenced in the guidelines report Asian race of Hispanic ethnicity, and just a single trial reported Black race. Clinical trials that dictate clinical care of patients with HF through informing contemporary ACC/AHA HF guidelines under-represent Black and Hispanic populations. Additionally, two-thirds of trials fail to report any race/ ethnicity at all. Guideline and practice-informing clinical trials need to improve the representation of minority populations to provide clinicians with generalizable data.



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## INTRODUCTION

Among cardiovascular diseases, heart failure (HF) is the number one cause of cardiovascular related hospitalization in the U.S., and it is the fifth leading cause of hospitalization overall.<sup>5</sup> This is problematic for the increasing population of racial/ethnic minority groups who carry an uneven burden of this disease. African Americans are one such group that has a higher incidence rate of congestive HF.<sup>1</sup> From 2013-2016, the prevalence of HF in males older than 20 years for Blacks/African Americans and Hispanics was 3.5% and 2.5% respectively.<sup>6</sup> In the MESA study, Blacks had the highest risk of developing HF followed by Hispanics and Whites at 4.6, 3.5, 2.4 per 1000 person-years, respectively.<sup>7</sup> These higher rates have been connected to higher comorbidity rates of hypertension, diabetes mellitus, and obesity linked to poverty and other environmental factors.<sup>1,6</sup>

The Federal Drug Administration's (FDA) Office of Minority Health has recognized the disproportionate effect cardiovascular diseases have on ethnic minorities and have organized a dedicated effort to improve the production of medical products that represent the general population.<sup>8</sup> This disparity can be attributed in part to lifestyle and socioeconomic factors, however differences in patients can also result from genetic variants that are more common in specific subpopulations. Regarding variations between races and ethnicities, there are many documented differences in drug metabolism, toxicity in chemotherapy, immunosuppressants, and cardiovascular drugs.<sup>8</sup> Proper representation of diverse patient populations in clinical trials will promote proper inclusion of

genetic variation across racial and ethnic groups, thereby improving the heterogeneity of trial results.

Although there is a general push to increase the amount of racial/ethnic minority patients included in clinical trials, there are several reports that conclude that racial/ethnic minorities are underrepresented in clinical trials. HF clinical trials are no exception to this problem as elderly patients, women, and racial minority groups have been found to be underrepresented in HF clinical trials.<sup>9</sup> Apart from hindering the generalizability of trial results, the lack of proper representation affects the clinical practice guidelines that use trials as their primary evidence base. Clinical trials used to formulate standard guidelines for the management of disease have an added degree of importance because of their impact on the treatment of patients.

The African American HF trial (A-HeFT) took into account a specific variation among African American HF patients and found a 40% reduction in all-cause mortality and a 33% reduction in first hospitalizations in this population by using a certain combination of therapeutic agents.<sup>10</sup> This trial helped shape a portion of the 2013 ACC/AHA HF guidelines and it exemplifies the importance of clinical trials that include sufficient racial and ethnic minorities in their patient populations. However, if clinical trials do not adequately represent these groups, then clinical practice guidelines will not have the needed evidence to properly outline the best management for specific populations.

As mentioned above, there is a general lack of representation of racial/ethnic minorities in clinical trials, and this project hypothesizes that there is

an underrepresentation and underreporting of racial/ethnic minorities in the HF clinical trials cited in clinical guidelines compared to U.S. Census and HF proportions.

## METHODS

### *Data Collection*

Two authors (J.P, G.G) performed a review of the 2013 ACC/AHA HF guidelines and the 2017 focused update to identify all cited randomized clinical trials. Only primary manuscripts, the first full report of the primary outcomes of a trial, were included in the review regardless of trial size. Secondary reports, including follow-up studies, meta-analyses, and observational studies were excluded. The range of publications dates spanned from 1950 to 2018 which was selected to encompass all clinical trials cited in the HF guidelines. The following data were abstracted from the manuscripts: (1) trial name; (2) year of publication; (3) journal name; (4) type of intervention (drug, device, procedure, laboratory test, or other); (5) first year of enrollment (6) total sample size; (7) funding source; and (8) race and ethnicity (if reported). When examining the manuscripts and their associated supplemental materials (figures and tables) for the reporting of enrollment by race/ethnicity, the following racial/ethnic groups were included: White, Black, Hispanic/Latinx, and Asian. Racial/ethnic groups were defined according to the racial/ethnic categories described in the Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity.<sup>11</sup> White race was defined as a person having origins in any of the original peoples of Europe, the Middle East, or North Africa. Black race was defined as a person having origins in any of the black racial groups of Africa. Hispanic ethnicity was defined as a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin. Asian race was defined as a person

having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent. Patients were divided into these categories according to the information reported in the trials themselves. Due to reporting limitations, White and Black categories included subjects with (“non-Hispanic”) or without an indicated ethnicity (ie “White” or “Black”).

### *Statistical Comparison*

For each racial/ethnic group, we determined the median enrollment rates across trials that reported each race/ethnicity. This was compared with U.S. Census proportions (2018) and estimates of race/ethnicity specific prevalent HF population proportions (2016). We then pooled all subjects and determined whether proportions differed significantly from that expected based on U.S. Census proportions or HF proportions using two-proportion z-tests. Trials were stratified by intervention type to determine the number of trials reporting race/ethnicity by trial type. Further demographic descriptions, including sex and age were not included in the study because past research has established the underrepresentation of women and the elderly in HF trials.<sup>9</sup> Other races such as Native American, Alaskan Native, Hawaiian or pacific Islander were not included in the study because of insufficient and inconsistent reporting of these categories in included trials. Data on the levels of awareness for clinical trials among racial/ethnic groups, access to health care services, level of education, and disease severity were not included in the study as only data included in the trials was considered.

## RESULTS

### *Reporting and Representation*

We identified 265 trials (547,353 subjects total, median trial size 448 subjects) published between 1950 and 2018. Among these, 99 trials reported any race/ethnicity (37.4%). White race, Black race, Hispanic/Latinx ethnicity, and Asian race were reported in 97 (36.6%), 57 (21.5%), 15 (5.7%), and 24 trials (9.1%), respectively. Compared to U.S. Census data, we found an overrepresentation of White subjects (Trial median: 85.6%, Census: 72.2%, HF population: 61.8%) and underrepresentation of Black (Trial median 8.9%, Census: 12.7%, HF population: 22.4%), Hispanic/Latinx (Trial median 6.9%, Census: 18.3%, HF population: 15.8%), and Asian subjects (Trial median: 3.0%, Census proportion: 5.6%) (Figure 1).

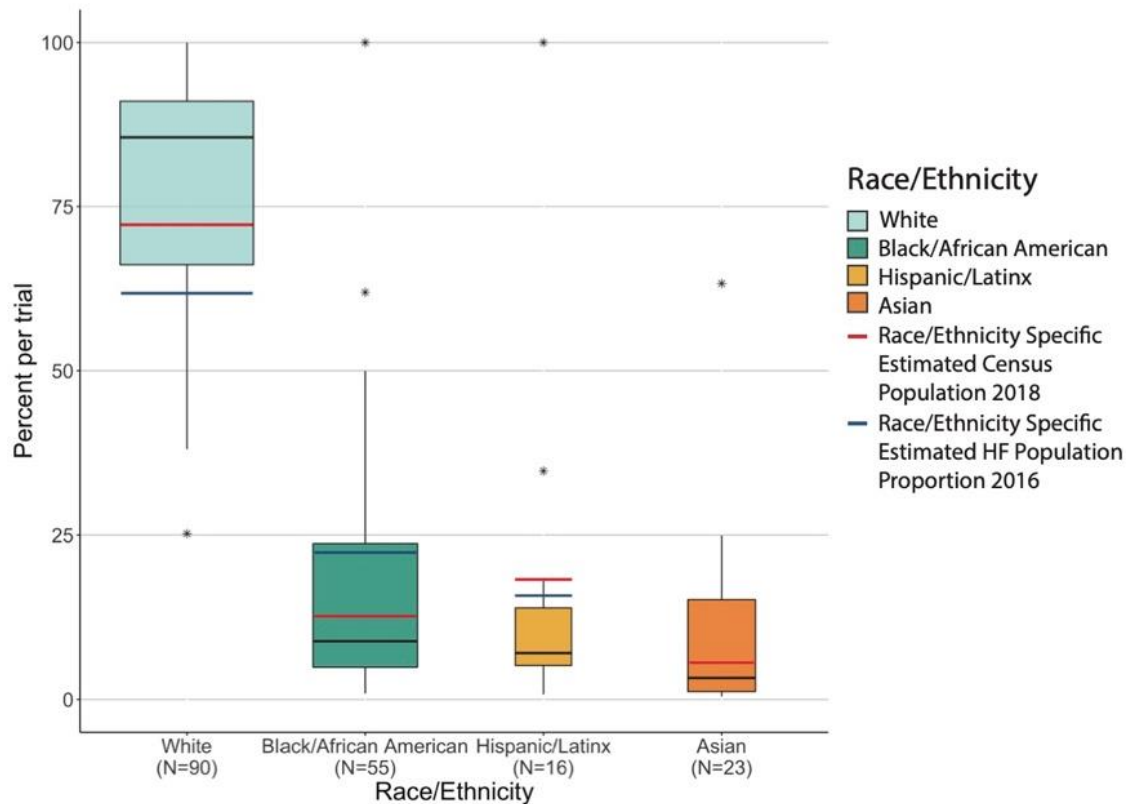
### *U.S. Census and HF Proportions Comparison*

In pooled analysis of trials reporting White, Black, Hispanic/Latinx, and Asian participation respectively, 77.8% (248,321/319,070) of subjects were White, 12.3% (n = 29,353 of 239,192) of subjects were Black, 11.0% (8,374/76,099) of subjects were Hispanic, and 9.7% (15,063/155,577) of subjects were Asian. With exclusion of the ALLHAT trial, a marked outlier in Black subject enrollment, just 9.1% of participants were Black. Pooled race/ethnicity specific trial proportions were significantly different from Census and HF population proportion estimates ( $p < 0.0001$  for all). Stratification by intervention type



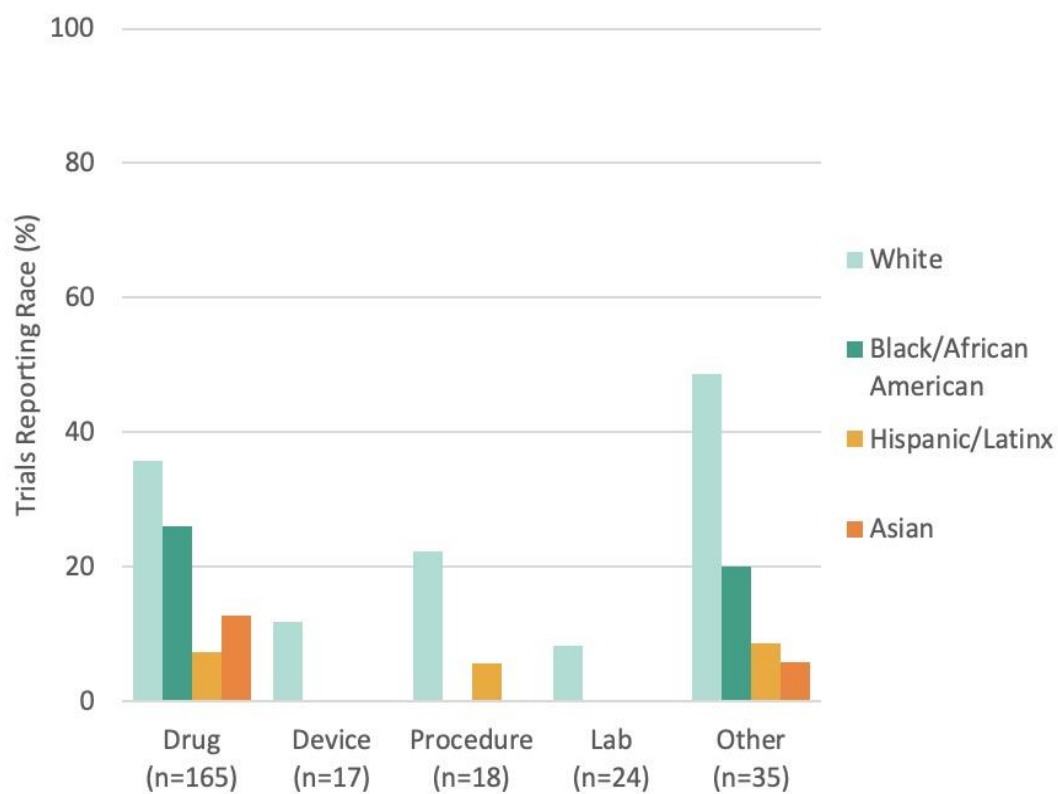
demonstrated that no device trials referenced in the guidelines report Asian race or Hispanic ethnicity, and just a single trial reported Black race (Figure 2).

**Figure 1.** Clinical trial reporting and enrollment of racial/ethnic groups.



Percent of subjects enrolled from each racial/ethnic group in trials reporting any race/ethnicity of subjects. Black line – indicates the median. Red line – indicates Census estimate of population proportion of each racial/ethnic group. Blue line – indicates estimate of heart failure population proportion of each racial/ethnic group. The upper and lower bounds of boxes indicate the 75th and 25th percentiles; whiskers represent the 97.5th and 2.5th percentiles; asterisks indicate outliers beyond the bounds of the whiskers. The width of boxes indicates the relative number of included trials.

**Figure 2.** Percent of trials reporting each racial/ethnic subgroup stratified by the type of intervention



## DISCUSSION

Our study aimed to examine the extent of reporting and representation of racial/ethnic minority groups in high-impact HF clinical trials used to establish clinical practice guidelines. Among trials included in the 2013 and 2017 ACC/AHA HF guidelines, we found infrequent, heterogeneous reporting of race/ethnicity of study participants. Black and Hispanic/Latinx participants were significantly underrepresented in trial populations based on US Census and HF prevalence proportion estimates. This data reflects the general underrepresentation of racial/ethnic minority groups in high impact clinical trials found in other studies.<sup>9,12,13</sup> Additionally, it suggests the need for diversity enrollment targets for clinical trials as emphasized by the FDA and NIH.<sup>8,14</sup>

Adequate reporting of racial/ethnic group representation in clinical trials is of paramount importance to evaluate the generalizability of trial results and assess recruitment gaps. For trials used to establish the standard of clinical practice via guidelines, appropriate reporting is especially consequential. A review of enrollment in recent (2001 to 2016) HF clinical trials with more than 400 subjects found that race/ethnicity was reported in only 55% of trials.<sup>7</sup> However, there has been no evaluation of the representation and reporting of racial/ethnic minority groups in HF clinical trials cited in HF guidelines. We now show that high-impact clinical trials used to inform treatment practices through inclusion in the 2013 and 2017 ACC/AHA guidelines have lower rates of reporting.

Among trials reporting their enrollment, Black and Hispanic participants were significantly underrepresented. Trial underrepresentation affects

generalizability and may exacerbate racial/ethnic disparities. Disproportionate enrollment by race/ethnicity requires extrapolation of trial results to underrepresented populations despite baseline HF risk factor differences (such as hypertension) that may contribute to disproportionate HF risk, and social, cultural, and environmental differences that may inform outcomes.

The foundational Studies of Left Ventricular Dysfunction (SOLVD) trial evaluating enalapril versus placebo did not demonstrate equivalent effects in African American participants compared with White participants; and isosorbide dinitrate/hydralazine remains a Class I ACC/AHA HF recommendation for self-described Black patients based on a dedicated trial.<sup>3</sup> While guideline-directed HF therapy should be used consistently across groups for outcome benefit, ensuring broad efficacy through adequate trial representation may be an important link in addressing HF health disparities.

Our study was subject to several limitations which should be noted. A lack of standardized categories of racial/ethnic groups for reporting in the trials resulted in the inclusion of subjects with (“non-Hispanic”) or without an indicated ethnicity (i.e. “White” or “Black”) into the White and Black race categories. Although the effects of this decision on the study results should be minor, there is the possibility for some discrepancies. The inclusion of publications from 1950 to 2018 was based on the range of trials cited in the ACC/AHA guidelines. This broad range allowed for the inclusion of older trials that were not conducted in a period where racial/ethnic reporting was considered beneficial. However, because these select trials are still cited in contemporary HF guidelines, their

influence on clinical practice continues. Therefore, we believed that the inclusion of these trials was relevant for the aims of this study. Despite these limitations, we are confident in our results and expect that future studies would find similar results.

To address the lack of standardized reporting of racial/ethnic categories in HF trials and clinical trials in general, we propose that all clinical trials registered in the U.S. be required to report the same set of racial categories (White, Black/African American, Asian, Native American, Pacific Islander, etc.). Hispanic ethnicity reporting should also be required, however, a more descriptive and inclusive categorization of Hispanic ethnicity should be included to reflect the diverse subgroups that identify as Hispanic.

In conclusion, we found significant underreporting and underrepresentation of major racial/ethnic groups in guideline-informing HF clinical trials, which may affect trial generalizability, be reflective of contemporary structural bias, and should spur enduring efforts to standardize reporting and correct underlying barriers to diverse trial enrollment.

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