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Diversity in modern heart failure trials: Where are we, and where are we going

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ABSTRACT

Over the last three decades, increased attention has been given to the representation of historically underrepresented groups within the landscape of pivotal clinical trials. However, recent events (i.e., coronavirus pandemic) have laid bare the potential continuation of historic inequities in available clinical trials and studies aimed at the care of broad patient populations. Anecdotally, cardiovascular disease (CVD) has not been immune to these disparities. Within this review, we examine and discuss recent landmark CVD trials, with a specific focus on the representation of Blacks within several critically foundational heart failure clinical trials tied to contemporary treatment strategies and drug approvals. We also discuss solutions for inequities within the landscape of cardiovascular trials. Building a more diverse clinical trial workforce coupled with intentional efforts to increase clinical trial diversity will advance equity in cardiovascular care.

1. Introduction

Blacks suffer disproportionate morbidity and mortality due to heart failure (HF) compared to other races in the US. Blacks have the highest prevalence of HF [74] and Blacks in The Multi Ethnic Study of Atherosclerosis (MESA) cohort developed HF at a higher rate (4.1 per 1000 person-years), compared to Hispanics (3.5) and Whites 2.4) [75]. These disparities continue to HF mortality as the age-adjusted death rates are highest in Black males at 120.9 per 100,000 compared to 71.5 in Hispanic males or 113.5 in White males [74], and unfortunately these disparities continue to widen. Although overall cardiovascular disease (CVD) mortality has decreased overall since the 1960s due to the advent of new drugs and invasive therapies, the rate of that decrease is significantly lower for Blacks compared to Whites [76]. This begs the question, why is the burden of HF more pronounced in Blacks? Are these therapies less effective?

Unfortunately, most pivotal trials in HF have not enrolled significant numbers of Blacks to address these questions. The NIH Revitalization Act in 1993 attempted to catalyze the elimination of healthcare disparities by establishing guidelines to include women and members of minority groups in clinical research trials, recognizing their pivotal role in improving disease outcomes. However, a quarter century after its inception, the representation of Blacks and other minorities in research trials is still lacking [2,3]. Subsequent action by the Food and Drug Administration (FDA) to improve minority inclusion in clinical trials by reporting demographic data on clinical trial participants has likewise

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resulted in little to no change in enrollment of Blacks in a growing number of non-cardiac trials [53,67,68]. However, this remains a priority of the FDA and NIH and should be for cardiologists and the medical community. The FDA's "Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry" published in 2020 states that clinical trials for new therapies should enroll and recruit a sample representative of the population in which the new therapy is to be used [79]. However, despite these recommendations, for the 53 novel drugs approved by the FDA in 2020, non-Whites which make up 40% of the population only comprised of 25% of clinical trial participants [80].

This review aims to evaluate the current state of and barriers to the recruitment of Blacks in HF research trials. Although efforts to enhance recruitment of women and other racial and ethnic minorities must increase, this paper will focus on Blacks for a variety of reasons. First Blacks have higher CVD and HF mortality rate than any other racial or ethnic group as mentioned above [74]. Second, one of the most infamous violations of ethical research conduct was perpetrated against Black men in the Tuskegee syphilis experiments. As such, mistrust of medical research in Blacks is highly prevalent. A 2002 study showed that 41.7% of black patients do not trust that their physician will fully explain research participation and 45.5% of black patients believe their physician would expose them to unnecessary risk [77]. Finally, with the recent spotlight on structural racism, it is imperative for medical researchers to engage Black communities with intentional proven strategies to help bridge the gap instead of widen the chasm.

In this review we will discuss the importance of adequate representation in clinical trials, review the enrollment patterns of 7 recent pivotal (landmark) (HF) trials and discuss strategies to improve enrollment based on empirical data and expert opinion. As the FDA recommends clinical trial samples should be representative of the population in which the therapy is to be used, and Blacks make up 13% of the population in the United States, we will define adequate representation within a clinical trial as a trial enrolling at least 13% Blacks. This in fact is a conservative number as we know that Blacks overrepresent HF prevalence, incidence and mortality. For international trials we will still use this conservative threshold although most data estimate a much a higher proportion of Blacks across the globe [4–7].

1.1. Impacts of underrepresentation

After controlling for socioeconomic factors, survival differences remain in varying racial populations for multiple diseases [81,82]. Clinical trials are necessary in generating evidence for efficacy and safety of therapies that target those maladies [1,12]. Most landmark cardiovascular trials are underpowered to detect efficacy in Blacks and other non-White racial/ethnic groups. For many clinical trials that have led to FDA approval of drugs or medical devices, their study population was composed of nearly 90% Whites [16]. This disparity means the majority of conclusions on the efficacy of new medical innovations in racial/ethnic minorities are based on extrapolation and the assumption that most drugs and innovations have the same homogenous effect on all populations; the results are less generalizable [17]. Applying trial results to patients who did not participate has been associated with harm [18]. Appropriate representation of patient populations is vital to discerning race and ethnicity-based differences in presentation, therapy response and prognosis [19].

Advances in cardiovascular genetics indicate interactions between common genetic variants and CVD [20]. As an example, salt excess is known to have pathological effects on vasculature [54], and epidemiological data suggest this plays a role in cardiovascular and renal morbidity and mortality [55]. Genetic variants contributing to salt sensitive hypertension exist within Black populations [64,65,66]. A review of salt sensitivity indicates endothelial dysfunction provoked by dysregulated nitric oxide (NO) production, decreased urinary kallikrein excretion, dysfunctional atrial natriuretic peptide (ANP) production, and higher aldosterone levels are several genetically based etiologies for salt sensitivity in non-Hispanic Blacks [63].

The Black community within the United States incorporates many subgroups: African Americans, Black immigrants from African nations, Caribbean nations, Central and South American nations and more. As such this community comprising of different ancestorial and even ethnic backgrounds is not a monolith. There is significant heterogeneity within race as well as between races. However as many disparities in healthcare are mediated by institutional and structural inequalities that were perpetrated via the social construct of race, it is not only reasonable but important to consider race in mitigation strategies like clinical research.

2. Evaluating landmark trials

2.1. The A-HeFT experience

A landmark trial that brought attention to the importance of diversity was the African American Heart Failure Trial (A-HeFT). This trial evaluated the use of isosorbide dinitrate and Hydralazine (ISDN-HYD) in Black patients with advanced systolic heart failure [21]. The A-HeFT study randomized 1050 Black patients with moderate to severe systolic heart failure (New York Heart Association [NYHA] Class III and IV) to fixed-dose ISDN-HYD therapy or placebo [21–23].

The study was terminated early as there was a 43% lower mortality in the ISDN-HYD group (6.2% intervention vs 10.2% placebo, $P = 0.02$). These findings established the use of ISDN-HYD as part of guideline directed medical therapy for management of heart failure in African Americans. The Genetic Risk Assessment in Heart Failure (GRAHF study) evaluated the NOS3 polymorphisms within the African American population and detected the Asp298 variant in approximately 80% of the patients [24]. The Asp298 variant had been previously associated with poor prognosis in White patients with heart failure [25]. These studies and others provide new insight into the relationship of genetic variants to outcomes of the African American population with systolic heart failure.

The aforementioned studies were initiated upon review of post hoc analyses of The Veterans Administration Cooperative Study (V-HeFT I and II) [26]. V-HeFT I and II initially suggested that enalapril was superior to ISDN-HYD therapy for improving survival in all heart failure patients (enalapril reduced mortality 28% more than the ISDN-HYD therapy) [27,28]. However, further analysis of the V-HeFT I and II trial demonstrated differential outcomes between Blacks and Whites. In V-HeFT I, there was a 47% reduction in mortality for Blacks receiving ISDN-HYD combination when compared with the Blacks in the placebo group (9.7% vs 17.3% respectively, $P = 0.04$). When the use of ISDN-HYD was compared to enalapril in African American patients from V-HeFT II, there was no significant difference in mortality (12.9% vs 12.8%, P=NS). However, the White patients had a 26% reduction in mortality with enalapril when compared with the White patients receiving ISDN-HYD therapy (11% vs 14.9% respectively, $P = 0.02$). These findings sparked the conversation about the remarkable response of African Americans to ISDN-HYD therapy leading to the hypothesis that relative nitric oxide deficiency present in African Americans may explain hypertension-related complications, concentric left ventricular hypertrophy and a distinct course of heart failure in the absence of ischemic heart disease [29,30]. Without pointed further evaluation of V-HeFT I and II trial the known mortality benefit of ISDN-HYD therapy in African Americans would not have been discovered.

2.2. Paradigm trial

Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) was a randomized trial on heart failure with reduced ejection fraction patients with NYHA Class II to IV heart failure comparing the angiotensin receptor-neprilysin inhibitors (LCZ696) to the ACE inhibitor, enalapril

for cardiovascular death and heart failure hospitalization [31]. In the PARADIGM-HF trial 8399 heart failure patients were randomized for treatment with sacubitril/valsartan or enalapril. Black patients enrolled were 5.1% of the study population. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure. Cardiovascular deaths and hospitalizations were reduced 20% overall in the trial compared with enalapril; in the Black patient subgroup, similar benefits were ascertained.

The Paradigm study is a great example of why it is important to understand differences in safety outcomes based on race, ethnicity and genetics. Within the double-blind period, the number of black and non-black patients that exhibited angioedema was 10 (1.79%) and 44 (0.44%) respectively. Of the 10 black patients with AAC-confirmed angioedema, one patient receiving sacubitril/valsartan was hospitalized. Due to the low recruitment of Blacks, it is difficult to make a conclusion if this is a true adverse effect or an incidental finding. Inadequate representation could impact quality of care as practitioners decide to prescribe this life saving therapy without clear insights into the true side effect potential in this large population(s). Without adequate representation, one is forced to make extrapolations. The lack of representation demonstrated in the Paradigm study is largely attributed to the potentially selective location of the included research sites. Despite the involvement of approximately 1200 research sites worldwide, among 5 geographic regions and inclusion of 47 countries, only 2 (Brazil and South Africa) have Black populations larger than that of the United States. As such although this commendable recruitment effort demonstrates significant diversity in participant region of origin, the representation of Blacks specifically is low at 5.1% [32].

2.3. Victoria trial

The Victoria Trial was a randomized trial that compared vericiguat to placebo for treatment of heart failure with reduced ejection fraction (NYHA Class II to IV). The primary outcome was cardiovascular death and heart failure hospitalization [34]. The Victoria trial randomized 5050 heart failure patients in 42 countries. The study enrolled 3239 White patients (64.1%), yet only 249 (4.1%) Black patients. Similar to the Paradigm study, of the 43 countries with study sites, only two (Brazil and South Africa) had Black populations larger than that of the United States.

In the vericiguat group, 27.4% of patients had a heart failure hospitalization. In the patients who received placebo, 29.6% had a heart failure hospitalization. In the subgroup analysis, Black patients had similar benefits. This study and Paradigm highlight how large international trials can enroll a diverse population, yet still lack in Black representation, often because there's no recruitment in the African continent.

2.4. Systolic heart failure treatment with the IF inhibitor ivabradine trial – SHIFT

SHIFT was a randomized, double-blind study that looked at the effects of ivabradine in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction. 3241 patients were randomized to ivabradine and 3264 patients were randomized to placebo. The primary endpoint (first event of hospitalization for worsening HF or CV mortality) occurred in 793 patients in the ivabradine group vs 937 patients in the placebo group (95% CI was [0.75, 0.90]; $P < 0.001$). Thus, ivabradine reduced cardiovascular mortality or hospitalization for worsening heart failure in patients with moderate to severe symptoms of CHF and reduced LVEF. Of the 6505 patients, 3241 were assigned to the ivabradine treatment group, while 3264 made up the placebo group. Within the ivabradine group, 2879 were White (88.8%) and only 32 (1.0%) were Black [39]. This international study (33 countries) whose distribution of patients does not include any patients from the United States, provides limited data ivabradine therapy in Black patients within the United States or elsewhere. It therefore functions as another example of a clinical trial that demonstrates how limited the development and evaluation of alternative solutions to heart failure management is within Black populations.

2.5. CRT-D (cardiac resynchronization therapy with defibrillation) therapy

CRT and ICD (implantable cardioverter-defibrillator) are medical innovations that have revolutionized the field of cardiology, providing significant survival advantage to heart failure patients, especially patients in the NYHA functional class (II and III). There has been known to be significant disparity in the application of this medical innovation to Black and Hispanic patients who meet criteria for treatment [35].

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial represents another landmark study with low recruitment of Blacks. Beginning in the December of 2004, the study assessed the effectiveness of CRT—D, as compared to implantable cardioverter defibrillator (ICD) therapy alone, in reducing the risk of heart failure or death and changes in cardiac volumes. There were 1638 (90%) White patients and 143 (7.7%) Black patients enrolled in MADIT-CRT [35,36]. A review that evaluated the racial differences in response to cardiac resynchronization therapy with defibrillator (CRT—D) concluded that both Black and White patients experienced similar and pronounced reductions in cardiac volumes with CRT-D therapy; risk reduction conferred by CRT-D therapy was found not to be significantly different between Blacks and Whites (HR = 0.78 and 0.60, respectively; $P = 0.44$). However, possibly due to sample size limitations the CRT-D versus ICD only adjusted risk for HF/death in Blacks was not statistically significant [35].

The use of CRT-D can significantly reduce re-hospitalizations and all-cause mortality while improving quality of life and functional status [37]. However, Black and Hispanic patients have historically been less likely to receive CRT-D than Whites [35,38]. Although data from the national NCDR registry showed that Blacks have the highest age-adjusted rates of sudden cardiac arrest; they remain significantly less likely than their White counterparts to receive an ICD [38]. A landmark 2007 observational study of over 13,000 patients illustrated that after adjustment for patient characteristics and hospital factors, the adjusted odds of ICD use were 0.73 (95% CI, 0.60–0.88) for Black men compared with White men [35]. These studies also demonstrate that when medical innovations are commercially available, there are still major factors limiting access to healthcare innovations in Blacks. While the trend of using CRT-D seems to be improving in the overall population, disparities in the use of CRT-D still remain within racial and ethnic subgroups [70].

2.6. Subcutaneous implantable cardioverter-defibrillator (S-ICD)

The Safety and Efficacy of a Totally Subcutaneous Implantable-Cardioverter Defibrillator Pre-market Investigational Device Exemption (IDE) trial is an example of a study which adequately enrolled Blacks (ie. ≥13% enrollment) within a heart failure population [40]. The transvenous leads of ICDs lead to frequent complications therefore subcutaneous implantable cardioverter-defibrillator (S-ICD) have been developed as an alternative system with hopes of less complications related to infection, perforation and other issues. The IDE trial was a prospective, nonrandomized, multi-center trial. It included adult patients with a standard indication for an ICD, who neither required pacing nor had documented pace-terminable ventricular tachycardia. The primary safety endpoint was the 180-day S-ICD system complication-free rate compared with a pre-specified performance goal of 79%. The racial demographics were 65% White and 24% Black.

In an analysis of 3717 S-ICD implants the percentage of Blacks that received S-ICD was about 27% (1004/3717) [36]. This was another trial which illustrated remarkable initiative in increasing participation of Blacks in clinical trials.

2.7. Haemodynamic-guided management of heart failure (GUIDE-HF)

This multicenter, single-blind study among 118 centers in the United States and Canada adequately enroll Blacks within a heart failure population. The study enrolled 86 (17%) black patients to the treatment group of 497 patients, and 93 (18%) black patients to the control group of 503. Designed to evaluate the potential remote pulmonary artery pressure monitoring holds in reducing heart failure events and mortality, this study showed hemodynamic-guided management allowed significant reduction in pulmonary artery pressure in the follow-up period for patients with chronic heart failure, despite a lack of reduction in mortality, heart failure hospitalizations and urgent heart failure hospital visits [83]. It is unclear what mechanisms were used to enroll such high proportion of Black patients. However, this study demonstrates that with a pointed effort, it is possible to have Blacks represented in large clinical trials.

3. Barriers and solutions

As demonstrated above several contemporary pivotal heart failure trials fail to recruit an adequate sample of Black patients (Table 1). Although the reasons behind this are complex, and multi-faceted, the following section will provide some insight into common etiologies and strategies to address them.

Table 1
Recent Landmark Clinical Trials tied with heart failure therapies for cardiovascular care, and Black patient representation.

Pivotal Trial*	Drug supported FDA approval date	Blacks in study, %	Drug benefit/function
A-HeFT trial	Bidil (Hydralazine Hydrochloride; Isosorbide Dinitrate) 2005	100%	Reduces the rate of mortality related to Heart Failure in African Americans
PARADIGM-HF	Entresto (Sacubitril, Valsartan) 2015	5%	Improved mortality related to Heart Failure
VICTORIA	Farxiga (Vericiguat) 2020	4.9%	Treatment of heart failure with reduced ejection fraction (NYHA II to IV)
SHIFT	Corlanor (Ivabradine) 2015	1.0%	Reduces the risk of being hospitalized for worsening heart failure
MADIT-CRT	Device: Cardiac Resynchronization therapy with Defibrillation (CRT—D) 2008	7.7%	Reduces rehospitalizations and all-cause mortality while improving quality of life and functional status in Heart Failure patients
S-ICD IDE	Device: Subcutaneous Implantable-Cardioverter Defibrillator 2012	23.7%	Senses ventricular arrhythmias and delivers successful rescue therapy to restore heart rhythm
GUIDE-HF	Device: CardioMEMS HF System 2014	17.9%	Wireless monitoring of pulmonary artery pressure and heart rate in recently hospitalized (NYHA Class III) heart failure patients

Abbreviations: A-HeFT trial, African-American Heart Failure Trial; CV, cardiovascular; PARDISGM-HF, Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction; NYHA, New York Heart Association; SHIFT, Systolic Heart Failure Treatment with the if Inhibitor Ivabradine Trial; MADIT-CRT, Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy; S-ICD, Subcutaneous Implantable Cardioverter Defibrillator; GUIDE-HF, Haemodynamic-GUIDEd management of Heart Failure *Phase III trials were considered as pivotal.

3.1. Failing to set black recruitment targets or disclose methods to achieve them

Demographics of participants within a clinical trial should be representative of the population in which the intended intervention or drug is to be used. Although Blacks have a disproportionately higher burden of cardiovascular disease in the U.S we still set a 13% threshold similar to their population make up as adequate. Although for international trials it is difficult to assess what percentage of that population is Black due to varying definitions of race, 16% of the world population is African. Although not all non-Africans are non-Black and not all Africans are Black, with these crude concepts in mind, a 13% target for international studies also appears reasonable and possibly conservative.

Unfortunately, many are not setting thresholds for Black recruitment or at least are not explicitly doing so. In a recent review by Prasanna et al. [78], of the 62 cardiovascular trials included in their paper from 2000 to 2017 only 13 (21%) specifically delineated goal recruitment parameters for underrepresented groups. There was an association of increased Black recruitment with trials that stated a goal although only one trial met the specified goal. It is also difficult to understand what study enrollment designs yield the highest likelihood of success in attaining target demographics if this is not reported. Once a target is set, a means to reach it should be considered as this will not occur passively or without deliberate action. If this is not considered and hence not reported there is less data available to evaluate the causes for success and failure. Another noteworthy conclusion is that there was no increase in Black recruitment in CVD trials included in this review over the nearly two-decade study period.

Setting goals is also important when assessing international trials. As we can see from Paradigm and Victoria, geographic diversity does not equate to ethnic and racial diversity. International trials need to set specific targets, ramp up Black recruitment in North America and Europe and harness the advancing health care infrastructure in Africa to increase Black enrollment. With the globalization of economies and technology there is no reason the entire continent of Africa should be repeatedly excluded in international trials.

3.2. Mistrust

Unfortunately, there is still a high level of mistrust between the Black community and the medical community. This mistrust may contribute to decreased minority patient enrollment in cardiovascular trials. This is compounded by inherent concerns about potential costs, time consumption, and perceived harms of participation [69,71]. To effectively recruit Blacks, the medical community has to reckon with our trustworthiness that has impacted the attitudes and beliefs of Blacks towards the medical community and research [58]. These were captured in an investigation focused on identifying patient-level reasons behind why Blacks are reluctant to participate in clinical trials [60,61]. All participants expressed suspicion about the motives of physicians conducting human research. They had the impression that medical research trials were more so to gain prestige for the investigator rather than for patient benefit. All patients agreed that if they trust the doctor, they would be more willing to participate in research. One of the most prominent findings was that most patients perceived the consent process as a legal process set up to protect the researchers rather than an informative tool about the proposed trial. The investigation also found that doctors viewed consent as a legal requirement rather than an avenue to improve the patient's understanding. This demonstrated how mistrust and lack of communication can affect patient participation in crucial clinical trials.

Several incidences in the past decades have fostered this "seed of mistrust" between the medical community and minorities. A vivid example was the Tuskegee syphilis experiment performed in Macon County, Alabama by the US Public Health Service (USPHS) in 1932 [42]. This study unethically observed the progression of untreated syphilis in Black men and examined whether the disease course differed by race. As

the USPHS had reports on treatment and management of syphilis published in 1932 and 1933 and it was already known that progression to symptomatic, tertiary syphilis occurred in 2% to 5% of the treated group and 20% to 30% of the untreated group [42,43]. Such dark parts of American history still reverberate in the minds of Blacks about the potential for abuse especially in patients that are from disadvantaged backgrounds. These thoughts are still continued in present day as Blacks face prejudice in the healthcare system. They experience subtle differences in treatment (i.e. first name usage, use of stereotypical slang, decreased amounts of prescribed pain meds, long wait times in the ER, and decreased referral to clinical trials) [62].

3.3. Diversity

Black people make up about 13% of the US population but make up less than 5% of the racial demographics in most cardiovascular research trials [59]. One in three Blacks will die from CVD, but only 2% of cardiologists in the United States are Black [44]. Lack of diversity among healthcare workers can foster an atmosphere dictated by implicit bias [45]. Implicit bias limits a fruitful relationship between patients and physicians. A recent study showed that only 5% of cardiologists realize that implicit bias may exist in their own practice and only about 35% of cardiologists believe that disparities exist in terms of overall care provided to patients in the United States [46]. Thus, Implicit bias may contribute to varying approaches in recruiting minorities to enroll in clinical trials.

Studies have shown that areas that have poor clinician diversity have a lower rate of minority enrollment in clinical trials. This is likely due to patients seeking out physicians with shared cultural similarities [47]. When trials lack diversity, outcomes are not generalizable and important genetic or environmentally influenced adverse effects may be missed. Despite the NIH Revitalization Act of 1993, still less than 2% of NIH principal investigators on research project grants are Black; underrepresented racial/ethnic minorities comprise only 10% and 10.9% of NIH study section reviewers in 2000 and 2013, respectively [48].

In a study aimed at increasing participation in clinical trials among racially and ethnically diverse underserved communities, a research group at Georgetown-Lombardi Comprehensive Cancer Center used tenets of community based participatory research principles [49], and the socio-ecologic model [50], to analyze the components within clinical trials that obstruct trials from having an ethnic disposition more demonstrative of the average US population. The basic premises underlying community capacity-building and clinical trial cancer recruitment strategy were: (1) the importance of physical proximity of cancer prevention programs and trial interventions within a given community; and (2) cultural competence of the program design, faculty, and staff together with the respect and trust they build and share with clinical trial participants and the community [51].

3.4. Rebuilding trust and increasing recruitment

An effective way to gradually improve racial/ethnic minority enrollment in research trials is to rebuild trust, focus on location/proximity to a given community, and ensure the cultural competence of the program design, it's faculty and staff. Effective communication may help to unearth the seeds of mistrust planted in the past. Increasing community trust involves collaborative community engagement and partnership [72]. Ideas for engagement include holding monthly meetings with the local Black medical society (e.g the local National Medical Association chapter or Student National Medical Association) to engage in discussion regarding community willingness to be involved in research and strategies to increase recruitment. Monthly meetings can also serve as a means of educating community leaders on the current trials and criteria to be involved. Involving racial/ethnic minority health care providers from the same communities as the underrepresented participant groups may help increase the level of awareness, trust and therefore participation in cardiovascular clinical trials.

Additionally, stronger partnerships between smaller community hospitals and tertiary academic medical centers are needed to improve recruitment of diverse participants. For example, in NYC Blacks are 50% less likely to receive care at an academic institution compared to their White counterparts [52]. Academic centers are generally more equipped to provide specialized care and engage patients in clinic trial enrollment. With unequal access to academic institutions, the community as a whole, is less likely to engage in clinical trials receive specialty care. Historical redlining and residential segregation may contribute to the fact that academic hospitals' Black patient population constitute 18% of their patients compared to 33% of patient populations at community hospitals [52].

Collaboration between community hospitals and academic hospitals/medical societies can help to equip clinics in underserved and underinvested communities with the resources to effectively recruit diverse participants which may decrease the burden of access to academic institutions. As an example, among academic medical centers, the Johns Hopkins Clinical Research Network (JHCRN) – founded in 2010 - has spearheaded a drive towards integrating clinical research with community-based healthcare delivery systems by creating collaborations that link its academic center with a diverse network of regional health systems. Similarly, Trillium Health Partners (THP), linked to the University of Toronto, formed the Institute for Better Health in 2014 in-part to mitigate inequity, with a focus on providing oversight and management of clinical research/trials across its three sites.

Creating platforms for community and clinical trial engagement, involves increasing racial/ethnic minority group representation on both sides of the study team. Black faculty ideally would include both academic physicians and community physicians. Having a larger amount of Black faculty and physicians will help to bridge the gap between the academic centers and smaller community hospitals, which may serve a large population of Black patients. This would help provide a different perspective and approach towards recruiting community patients who may not have access to large academic institutions.

4. Conclusion

Underrepresentation is a common challenge in heart failure trials. This review sheds light on the persistent and pervasive nature of this impactful issue, yet also provides insightful practical tools to increase involvement of Blacks in clinical trials. Failure to achieve adequate Black representation results in unclear safety and efficacy of emerging and established therapies; a gamble we can't wager in a group already suffering disproportionately at the hands of HF and CVD. Addressing and surmounting this obstacle will undoubtedly be a critical element in improving heart failure outcomes over the coming decade.

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All person who meets authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *International Journal of Cardiology*.

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