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# Improving the enrollment of women and racially/ethnically diverse populations in cardiovascular clinical trials: An ASPC practice statement

Erin D. Michos[a,*], Tina K. Reddy[b], Martha Gulati[c], LaPrincess C. Brewer[d], Rachel M. Bond[e,f], Gladys P. Velarde[g], Alison L. Bailey[h], Melvin R. Echols[i], Samar A. Nasser[j], Harold E. Bays[k], Ann Marie Navar[l], Keith C. Ferdinand[b]

[a] Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD USA
[b] Tulane University Heart and Vascular Institute, Tulane University School of Medicine, New Orleans, LA USA
[c] Division of Cardiology, University of Arizona College of Medicine-Phoenix, Phoenix, AZ USA
[d] Division of Preventive Cardiology, Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN USA
[e] Internal Medicine, Creighton University School of Medicine, Chandler, AZ USA
[f] Women's Heart Health, Dignity Health, AZ USA
[g] Division of Cardiology, University of Florida Health, Jacksonville, FL USA
[h] Centennial Heart, Chattanooga, TN USA
[i] Division of Cardiology, Morehouse School of Medicine, Atlanta, GA USA
[j] Division of Clinical Research and Leadership, George Washington University School of Medicine, Washington, DC USA
[k] Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY USA
[l] Division of Cardiology, UT Southwestern Medical Center, Dallas, TX USA

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of death for both women and men worldwide. In the United States (U.S.), there are significant disparities in cardiovascular risk factors and CVD outcomes among racial and ethnic minority populations, some of whom have the highest U.S. CVD incidence and mortality. Despite this, women and racial/ethnic minority populations remain underrepresented in cardiovascular clinical trials, relative to their disease burden and population percentage. The lack of diverse participants in trials is not only a moral and ethical issue, but a scientific concern, as it can limit application of future therapies. Providing comprehensive demographic data by sex and race/ethnicity and increasing representation of diverse participants into clinical trials are essential in assessing accurate drug response, safety and efficacy information. Additionally, diversifying investigators and clinical trial staff may assist with connecting to the language, customs, and beliefs of study populations and increase recruitment of participants from diverse backgrounds. In this review, a working group for the American Society for Preventive Cardiology (ASPC) reviewed the literature regarding the inclusion of women and individuals of diverse backgrounds into cardiovascular clinical trials, focusing on prevention, and provided recommendations of best practices for improving enrollment to be more representative of the U.S. society into trials.

## Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the United States (US) and worldwide [1]. Randomized clinical trials (RCTs) serve as the primary evidence base that shape guidelines and clinical practice. However, historically, there have been scientific, institutional, socioeconomic, and cultural barriers that have restricted the adequate inclusion of women and racial/ethnic minority populations in clinical trials. Providing comprehensive demographic data by sex/gender and race/ethnicity and increasing representation of diverse participants into clinical trials are essential in assessing accurate drug response, safety and efficacy information. The lack of diverse participants is not only a moral and ethical concern, but a scientific one as well, as it can seriously limit the applicability of future therapies. Clinical trials which underrepresent demographic diversity, especially for populations most affected by certain diseases, may lead to findings which cannot be generalizable. Additionally, diversifying investigators and clinical trial staff may assist with connecting to the language, customs, and beliefs of study populations and increase recruitment of participants from different backgrounds.

* Corresponding author at: Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD USA
*E-mail address:* edonnell@jhmi.edu (E.D. Michos).

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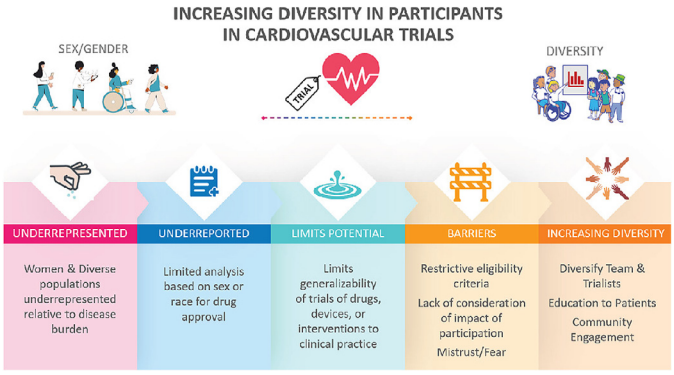
In this practice statement, a working group for the American Society for Preventive Cardiology (ASPC) has reviewed the literature regarding the inclusion of women and members of racial/ethnic groups into cardiovascular (CV) clinical trials, focusing predominantly on prevention trials, and discusses best practices for improving enrollment of diverse populations into trials (**Central Illustration**).




## Enrollment of women in clinical trials

### *Background*

Despite decades of progress in the understanding of CVD risk factors and preventive therapeutics, CVD rates have recently been on the rise among younger to middle-aged women [2–4], with a decline in awareness that heart disease remains the leading cause of death [5]. This under-recognition of the importance of heart disease in women is not due to a lack of contact with the health care system. Rather, women have greater utilization of health care services than men [6]; however, they have been under-enrolled in CV clinical trials, even after adjusting for the population prevalence of the specific CVD [7–14]. Beyond the high prevalence of CVD in women, evaluating the impact of CV therapies in women is of further importance due to potential biological differences between men and women that may impact both safety and efficacy of therapies. There are sex-based differences in the pharmacokinetics and pharmacodynamics of drugs [15], and women may be at greater risk for adverse safety concerns compared to men [16]. Ensuring adequate representation of women in clinical trials is critical to allow for sufficient data generation regarding both safety and efficacy of CV interventions in both men and women.

Unfortunately, historically early-phase drug trials have excluded women of child-bearing age due to concerns of safety for the mother and fetus if the woman was to become pregnant during trial [10,17,18]. Due to fluctuating hormone levels, women were also considered to be more challenging to study a drug's biological effect. On the other hand, men were considered to be the normative population, while women were assumed to have a similar response as men [17,19,20]. Consequently, there was a large gap in the understanding of sex-based differences in CVD and response to therapeutic and preventive interventions [21].

Recognizing this, in 1986, the National Institute of Health announced a policy recommending that grant applications include women in their study populations [22]. Over decades, the Food and Drug Administration (FDA) has also evolved in their guidance regarding reporting of sex in trial results [23]. However, the uptake of both of these recommendations has been slow and remains suboptimal [14]. For example, a recent analysis examining 10-year trends in pivotal randomized clinical trials (RCTs) that were used to support FDA approval for 35 novel cardiometabolic drugs found that women only represented 36% of trial participants [9]. In another study of patients with acute coronary syndrome (ACS), women only consisted of 27% participants [11].

While women may have a lower prevalence of CVD, such as coronary heart disease (CHD) and ACS relative to men, particularly at younger and middle ages, studies have shown that they still remain underrepresented relative to their disease burden in the population [7–10,14]. The approximate enrollment disparity difference between the proportion of women with prevalent disease and the proportion of women enrolled in the RCTs was -9% for lipid-lowering therapy trials [10], -16% in heart failure (HF) trials [12], -18% for ACS trials, -2% in arrhythmia trials [7], -10% in hypertension trials [7] and -5% for stroke trials [8]. Thus, women continue to be inadequately represented in CV clinical trials relative to their disease burden. This may have important implications in determining efficacy and safety of these CV preventive therapies among women, and may impair generalizability of trial results to routine clinical practice. Practical steps should be undertaken to develop new strategies to achieve optimal recruitment so that the proportion of trial participants is representative of the proportion with the disease in the population.

In addition to improving enrollment, another critical issue is to develop strategies to foster retention of women participants. One analyses of participants enrolled in the Thrombolysis in Myocardial Infarction (TIMI)-study group CV trials found that female participants were more likely to discontinue study drug and withdraw consent from the trials compared to male participants [24].

### *Women as trial investigators*

One way to improve the enrollment and retention of women in RCTs is to ensure that the study leadership, including the study executive committee and site investigators, are diverse. There is a greater likelihood of a study reporting a sex/gender specific analysis as the number of women study authors increased, and when the first or senior author was a woman [25]. Additionally, studies have demonstrated a direct correlation between the number of women trial investigators/authors with a greater proportion of women participants enrolled in the trials [13,26,27].

Unfortunately, there is a dearth of women among CV clinical trial leadership. In a recent analyses of CV RCTs published in leading medical journals over the past 4 years, only 10.1% of clinical trial leadership committees were women, and more than half of the trials had no women as part of the trial leadership team [28]. Furthermore, only ~10% of these publications had a woman in the first or last author position [28]. Specifically related to trials in CVD prevention, previous work has demonstrated that women comprised less than 20% of all authors in large RCTs in lipid-lowering therapies [29]. In another analysis of 107 HF trials that listed their steering committee members, only 11.% of trial leadership members were women, with no change between the years of 2000 to 2019 [30]. Thus, efforts to recruit and retain women trial investigators may be a critical mechanism to help lessen the disparities in both areas (i.e. trial leadership and trial participants).

Journals who publish these trial results should make it a requirement that the authorship (thus reflecting the trial's leadership) is diverse [31]. New initiatives such as the American College of Cardiology (ACC)'s "Clinical Trial Research: Upping Your Game" program have been specifically designed to help develop and train the next generation of a diverse clinical trials workforce by fostering the development of women and individuals from under-represented backgrounds as clinical trialists [32].

### *Barriers to female patient enrollment*

Data regarding reasons why women are under-enrolled in CV RCTs are limited, but many factors have been speculated. Women tend to present with CVD at older ages, and older adults are less likely to be enrolled in clinical trials [10–12]; however, in many cases exclusion criteria that limit older adults' participants have been poorly justified [33]. Women patients may be less likely to be considered at risk for CVD [34], and thus less often referred to specialists who may have awareness and access to on-going RCTs. A survey analyzing sex differences in participant's willingness to participate in clinical trials indicated that women

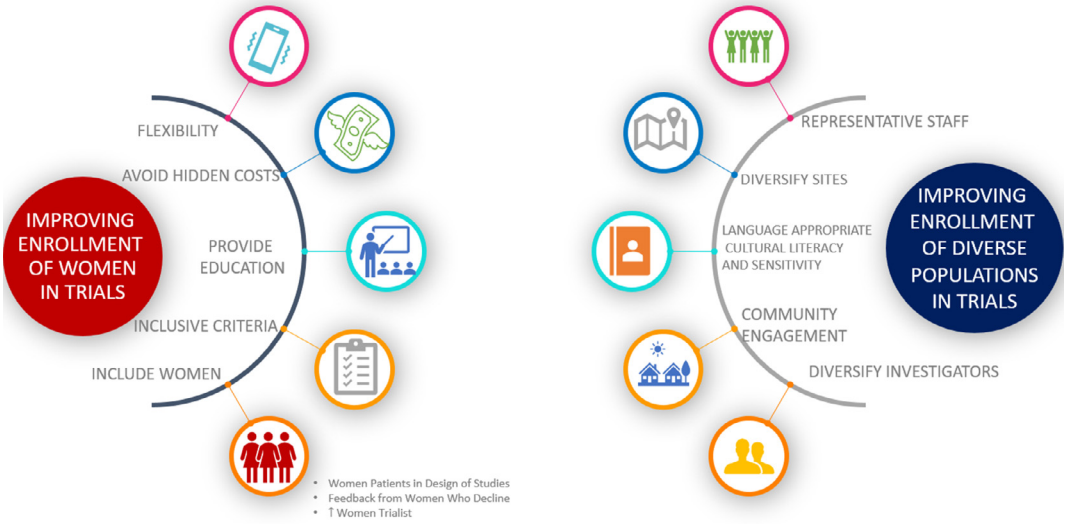



**Fig. 1.** Improving Diversity in Enrollment.

are more likely to perceive harm from trials; however, they were more influenced by monetary incentives [35]. Another survey found that reasons that favorably influenced women's decisions to participate in trials were trust in their clinicians and belief of benefit for others or themselves [36].

Beyond improving the diversity of trial investigators, other suggestions to improve enrollment of women in trials include designing the study visit schedule to accommodate barriers to trial participation (Fig. 1). This involves more flexible visit schedules (i.e., on weekends, via apps, by phone/virtually, or with a local primary care provider) and avoiding or offsetting hidden costs of participation (i.e., transportation, care-giver arrangement costs, time off work). Study inclusion criteria should also be evaluated for the potential to impact enrollment of women [37]. This may include avoiding certain female-specific exclusion criteria (i.e. women of child-bearing age with adequate contraception plan should not be excluded out of fear of possible pregnancy). In addition, there should be efforts to overcome more subtle criteria that may disproportionately identify men, for example using risk scores to identify eligible patients that includes male sex as a variable or coronary artery calcification which may be more prevalent in men vs. women [38,39]. Ensuring that the inclusion criteria are not based on male-centric presentations could also assist in increased inclusion of women.

Furthermore, the perspective of women participants should be incorporated into the design and conduct of the study to identify potential barriers and recruitment strategies that may target women. Study coordinators and sites should also be provided adequate resources regarding the trial to allow for appropriate education of potential participants about the benefits of the research and to dispel misconceptions. Finally, to guide future recruitment efforts, feedback should be elicited from both men and women, who were approached, but declined to participate, in order to understand and ultimately fix barriers to equity in enrollment.

Augmenting women's enrollment in trials also necessitates studying diseases that are relevant to women, including understanding that mechanisms and risk factors underpinning CVD can be different in women [38,40,41]. For example, women are more likely to experience ischemia with non-obstructed coronary arteries than men, who are more likely to have obstructive disease in a setting of angina. Furthermore, women also have unique risk factors throughout their lifespan related to pregnancy, hormones, and menopause that men do not experience [42,43]. There needs to be further insight of how these female-specific factors across a lifespan contribute to CVD and impact response to preventive interventions.

With respect to data collection and reporting, it is imperative that all trials report sex/gender stratified outcomes for both efficacy and adverse events. This will allow for recognition of signals of differences in outcomes based on the intervention of the clinical trial. An important final consideration with respect to representation of women in clinical trials is the emerging recognition of the need to also include transgender, gender-nonconforming, and non-binary individuals in clinical trials. The first step is ensuring that data collection forms and inclusion/exclusion criteria appropriately collect data on both sex and gender, providing sufficient options for patients beyond binary male/female and man/woman. Inclusion/exclusion criteria, when sex- or gender-specific, should also be worded appropriately as to not unnecessarily exclude adults who do not identify as cis-gendered men or women.

## Enrollment of racial/ethnic minority populations

### *Background*

There are significant disparities in CV risk factors and CVD outcomes among U.S. racial and ethnic minority groups, for whom some populations have the highest CVD incidence and mortality [1]. Black adults share a disproportionate burden of CV risk factors (hypertension, diabetes, and obesity – especially in women), experience an earlier onset of atherosclerotic cardiovascular disease (ASCVD), and have a shorter life-expectancy compared to White adults [1,44]. The 2016 CVD mortality rate among non-Hispanic Black individuals in the U.S. was 211.6 per 100,000 which was higher than all other racial/ethnic groups [1].

Despite their greater disease burden, Black, Indigenous, and People of Color (BIPOC) remain underrepresented in CV outcome trials. For example, a recent analysis examining a 10-year trend in pivotal RCTs used to support FDA approval of 35 novel cardiometabolic drugs found that non-Hispanic White adults consisted of 81% of trial participants, compared to only 4% Black, 12% Asian, and 11% Hispanic/Latinx participants, with no significant trend in improvement of enrollment in these racial/ethnic minority groups over this time period [9]. Another analysis examined RCTs that collectively evaluated 24 drugs involving 7 CV conditions and found that the RCTs only included 2.9% Black adults [45]. In these trials, Black adults had a participation-prevalence ratio of 0.29, indicating that they were poorly represented relative to their disease burden in the general population [45]. In another study of ACS

patients, only 15% of participants were other than White patients including 4% Black patients, 10% Asian patients, and 8% Hispanic/Latinx patients [11]. Perhaps even more discouraging, over 75% of these trials did not even report race/ethnic data [11].

Although American Indian/Alaskan Native (AI/AN) populations have high rates of cardiometabolic and CV diseases, they are poorly represented in almost all major CV outcomes trials, affected by a history of mistrust and unethical practices [46,47]. Especially, certain AI/AN populations have higher rates of hypertension than members of other major race/ethnic populations, and rates of diabetes were almost twice as high as the general U.S. population [47]. It is not only important to include AI/AN in clinical trials, but to recognize the heterogeneity in risk factors, especially for conditions in which they are disproportionately represented such as diabetes and CVD, particularly CHD and stroke [46].

*Defining race/ethnicity*

Race as defined by Merriam-Webster dictionary is "any one of the groups that humans are often divided into based on physical traits regarded as common among people of shared ancestry" and reflect social definitions that do not define race biologically, anthropologically or genetically [48]. In addition, ethnicity is defined as "the fact or state of belonging to a social group that has a common national or cultural tradition." As race/ethnicity terms are based on social constructs and are evolving with time, these terms should be used in adjectival forms (i.e. Black patients, White participants, Hispanic/Latinx adults) as this follows the preferred American Medical Association (AMA) style [49]. Being socially constructed, the use of race as a proxy for genetic admixture or biological differences is problematic because it can obscure root social and structural causes of health inequities. On the other hand, using the social-classification of race is important for identifying groups that experience health disparities, and of which these social determinants impact the effectiveness of CV interventions.

In view of the lack of easily accessible information on participants, the FDA's Center for Drug Evaluation and Research (CDER) developed the Drug Trials Snapshots initiative to report on the diversity of participants in clinical trials stratified by demographic factors [50]. Racial and ethnic minority groups currently account for 36% of the population of the U.S. [51]. The proportion of the U.S. population self-identified as a member of a racial/ethnic minority group is projected to increase, with the most rapid growth of individuals defined as Hispanic/Latinx and Asian American. The Hispanic/Latinx population itself is very diverse, representing individuals' whose countries of origin stem from Central America, South American, and the Caribbean, which in turn leads to cultural, ethnic, linguistic, and biological differences. This makes it even more critical to collect additional demographic information to help stratify within this population. Similarly, there are marked differences between individuals of South Asian vs. East Asian descent. Different Hispanic/Latinx and Asian subgroups exhibit a wide range of CVD risk factors; thus disaggregation, not simply inclusion, in clinical trials can provide insight into prevention and personalized treatment [52]. Furthermore, South Asian, Filipino, and Black individuals have more ASCVD compared with non-Hispanic White individuals, requiring ongoing diversification of trial cohorts. Despite this, individuals self-identifying with racial and ethnic minority groups remain under-represented in CV clinical trials [9,11]. Therefore, it is critical to review the impact of racial/ethnic diversity and inclusion across CVD subtypes and CV risk factors as discussed further below.

*Race/ethnicity inclusion in hypertension CV trials*

Notwithstanding the recent decrease in overall CVD, there has been an increase in U.S. adults with hypertension from 116.4 to 121.5 million, based on 2015 to 2018 data, and 47.3% of U.S. adults had hypertension (defined as a blood pressure ≥130/80) [1]. During this same time frame, 58.8% of non-Hispanic (NH)-Black females and 60.1% of NH-Black males had some form of CVD [1]. NH-Black adults had significantly higher rates of hypertension compared to NH-White adults, while Hispanic/Latinx and NH-Asian individuals had lower rates than both groups [53]. Furthermore, National Health and Nutrition Examination Survey (NHANES) data revealed that hypertension control rates among NH-White adults (55.7%) was significantly higher than NH-Black (48.5%), NH-Asian (43.5%), and Hispanic/Latinx (47.4%) adults [54].

A prior 2016 systematic review by Brewster et al identified 35 trials with 7 classes of antihypertensive drugs that collectively enrolled 25,540 African ethnicity patients; the report did not give the overall number of participants to determine the proportion of total participants whom were Black adults [55]. However, this review found that calcium channel blockers and diuretics, as first step, were effective in lowering blood pressure in Black adults with lesser effect for angiotensin-converting enzyme (ACE) inhibitor and beta-blockers. On the other hand, treatment with an ACE inhibitors and angiotensin receptor blockers, as first step therapy, was associated with an increased risk of adverse cardiovascular outcomes among patients of African ethnicity. This same review identified 16 RCTs with blood pressure outcomes for 1719 South Asian patients with hypertension. In contrast to the aforementioned studies of African ethnicity patients, there were no significant differences in the efficacy of blood pressure lowering between drug classes, and no trials available in this population with mortality outcomes [55].

The pivotal Systolic Blood Pressure Intervention Trial (SPRINT), which shaped the 2017ACC/American Heart Association (AHA) blood pressure guideline, did successfully recruit 30% NH-Black participants into the trial and importantly found no interaction of the efficacy of intensive blood pressure lowering by race [56]. Nonetheless, there is a lack of clinical trials designed to test interventions that address and account for impactful societal inequities, as well as the different antihypertensive responses specific to Black individuals [57]. A recent review of hypertension trials indexed in ClinicalTrials.gov between 2009–2018 found 5.4% of trials were Black race-specific, with the majority of trials not specific to race [57].

*Race/ethnicity inclusion in lipid-lowering trials*

Disparities exist in diagnosing and treating dyslipidemia in diverse groups despite clinical trial and observational data that lipid-lowering medications have a significant benefit in persons from diverse racial/ethnic backgrounds [51]. The majority of clinical trial data regarding lipid-lowering medications were derived from largely White populations, with the notable exception of the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial, which enrolled a significant proportion of Asian (49%) and Hispanic/Latinx (28%) participants, although Black participants were still <4% [58]. Several of the pivotal statin studies did not report participant data by ethnicity and list race only as White or other than White, if included at all (i.e., Scandinavian Simvastatin Survival Study (4S), West of Scotland Coronary Prevention Study (WOSCOPS), Heart Protection Study (HPS), Treat to New Targets (TNT), and Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE-IT)). One prominent exception was Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which due to mandated diversity by the National Heart, Lung and Blood Institute (NHLBI) included 35% Black and 19% Hispanic/Latinx patients. Although pravastatin compared to usual care overall at the time did not demonstrate significant benefit in CV outcomes, the pravastatin group fared better in NH-Black adults. However, the reduction in CHD events in Black individuals was partly due to the undertreatment of Black patients in the usual care group [59].

Over time, both the reporting, and more importantly, the inclusion of greater numbers of racial and ethnic groups in statin trials have occurred [51]. More recent RCTs have examined newer LDL-C lowering therapies. Data from the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor trials included only ~2.5% Black individuals, but 8-

16% Hispanic individuals and 10-13% Asian individuals. On the other hand, Black individuals represented ~8% of the bempedoic acid trial participants and ~13% of the inclisiran trial participants. For all populations, levels of lipoprotein (a) [Lp(a)] are predictive of increased ASCVD risk. In consideration of reported higher Lp(a) median levels in persons of African and South Asian descent [60], ongoing and future clinical outcome trials should ensure inclusion of diverse populations and researchers in order to effectively establish therapeutic impacts on various racial/ethnic populations.

*Race/ethnicity in obesity trials*

As with other disease states, the demographics of U.S.-based obesity clinical trials differ from international studies. Lorcaserin is a serotonin 2C receptor agonist that was previously approved as an anti-obesity drug. In one of the few obesity CV outcomes trials, the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients – Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) demonstrated that in a population of approximately 12,000 patients, consisting of ~89% White participants (primarily from North America/Europe) with overweight or obesity at high CVD risk, lorcaserin facilitated sustained weight loss without a higher rate of major CV events than placebo [61]. On the other hand, in an earlier U.S.-based study (N = 3182) of lorcaserin, the trial population consisted of 67% NH-White, 18% NH-Black, and approximately 12% Hispanic/Latinx participants [62]. Unfortunately, the drug was subsequently withdrawn due to a safety signal regarding cancer.

More recently, semaglutide, a glucagon-like receptor agonist approved for treatment of type 2 diabetes (T2D), is being developed as an anti-obesity agent. In a large recent RCT evaluating semaglutide for weight loss (the STEP 1 trial) involving predominantly European sites, the final cohort enrolled approximately 6% Black, 12% Hispanic/Latinx, and 13% Asian participants [63]. This trial was encouraging in that among adults with overweight or obesity, semaglutide (2.4 mg/weekly) in addition to lifestyle interventions conferred sustained reduction in body weight. However, further study in more diverse populations is warranted.

Therefore, as with other clinical trials of metabolic drug treatments, the demographics in obesity studies should represent the populations with underlying disease burden available for enrollment, and also should reflect the countries of the clinical sites involved in the research. Hence, for non-obesity metabolic clinical trials (e.g., drug treatments for diabetes mellitus and dyslipidemia), it is common to find that studies with increasing percent of European research sites. These study population demographics will often report a lower body mass index, higher rates of smoking, and decreased percent of Black and Hispanic/Latinx participants.

Therefore, when investigators recruit from their indigenous patient populations, for example in Europe, it may not reflect the heterogeneity of U.S. cohorts. Thus, when international clinical trials serve as the basis for guidelines that apply to all populations, it is important, especially in obesity, which is disproportionately prevalent in certain racial/ethnic populations, to include a more diverse cohort for which the drug will eventually be applied. Unfortunately, there remains a relative scarcity of investigators from Sub-Saharan African and Central/South American countries. Nevertheless, with obesity, which disproportionately affects NH-Black and Hispanic/Latinx populations in the U.S., it is important that clinical trials, which are the basis for treatment guidelines, increase cohort diversity.

*Race/ethnicity in studies of smoking*

Although Black Americans usually smoke fewer cigarettes and start smoking cigarettes at an older age, they are more likely to die from smoking-related diseases than their White counterparts [64] and Black children are more likely to be exposed to secondhand smoke [65]. Despite these data, the tobacco industry has continuously aimed its campaigns at this population. The strategies used have disproportionately promoted menthol cigarettes, such that nearly 90% of Black smokers use them. This makes Black smokers 11 times more likely than White smokers to use menthol cigarettes, with the highest rates among Black youth aged 12–17 years [66]. The overuse of menthol cigarettes, which are easier to smoke and harder to quit as per the FDA [67], is one reason why despite Black Americans having more attempts at smoking cessation, they are less successful at quitting than White and Hispanic/Latinx smokers. For the AI/AN population, the prevalence of cigarette smoking is the highest of any group in the US, but most surveys of tobacco use do not account for traditional tobacco that is used for ceremonial or medical purposes [68]. The tobacco industry has also targeted their product promotion towards these communities [69].

With these clear racial/ethnic differences in smoking habits. predominantly due to the tobacco industry's predatorial behaviors coupled with socioeconomic factors and stressors, more research is necessary to expand the availability and promotion of smoking cessation services. For example, one large RCT based in the United Kingdom (UK) evaluated electronic cigarette use vs nicotine replacement therapies for smoking cessation, but did not report proportion of enrollment or outcomes by race/ethnicity in their published paper [70]. Smoking cessation trials need to include diverse populations to understand socially and culturally-sensitive ways to facilitate cessation. Data have shown that there is a lower utilization of cessation treatments such as counseling and medication in Black communities [64,71]. One nationally representative study found a significantly lower use of prescription smoking cessation medications, compared to White adults [Black adults, OR, 0.51 [95% CI, 0.38–0.69]; Asian adults: 0.31 [0.10–0.93]; Hispanic/Latinx adults: 0.53 [0.36–0.78]), even after adjustment for other socioeconomic factors such as health insurance [71]. Thus, ensuring barrier-free access to and promotion of all proven cessation therapies to medically underserved communities and the promotion of culturally-competent national campaigns are ways to help mitigate the troubling disparities in health we see.

Adherence to varenicline and combination nicotine replacement therapy benefits those who are low in dependence and have a positive history of quitting. However, these therapies may be less available to at-risk smokers and individuals of racial/ethnic backgrounds [72]. Quit rates for Black (37.5%) and Hispanic/Latinx (42.9%) individuals were significantly lower compared with NH-White (50.4%) individuals [73]. Due to the underrepresentation of Black adults and other underrepresented racial/ethnic groups in smoking cessation research, there is limited information on the effectiveness of cessation treatment and thus, critical to investigate best practices to treat smokers from diverse backgrounds [74].

*Race/ethnicity in CV trials among persons with diabetes*

Approximately 34.2 million Americans have been diagnosed with diabetes, along with another 88 million individuals diagnosed with prediabetes [75]. Patients with diabetes often have other comorbidities, such as obesity, hypertension, hypercholesterolemia and physical inactivity, contributing to an increased risk of CVD and its complications, therefore indicating a need for research on mitigation efforts [75]. Moreover, in patients with diabetes, the most prominent cause of mortality is CVD, along with HF and increased healthcare spending [1,75–77]. Thus, the prevention of CVD onset especially in persons with diabetes is necessary to mitigate disease morbidity and mortality.

Overall, diabetes, obesity, and associated CVD indicates the need for intensive risk reduction, especially in Black and Hispanics/Latinx individuals [78,79]. Recently, Cai and colleagues analyzed racial/ethnic patterns in the results of CV outcome trials of anti-diabetes medica-

tions in people with T2D in a systematic review [80]. In this meta-analysis, trials investigating anti-diabetes medications included 68.1% White, 17.9% Asian, 4.4% Black, and 9.7% Other (Hispanic/Latinx, Pacific Islander, Hawaiian, AI, AN) adults. Compared to placebo or control, treatment with anti-diabetes medications reduced the risk of composite CV outcome among White, Asian, and the "Other" adult populations comprised mostly of Hispanic/Latinx and Pacific Islander adults; while a similar trend for reduction was seen among Black participants, this was not statistically significantly likely due to the small sample size. Trials need to enroll more Black and other racial/ethnic participants to confirm CV benefits with these drugs in these populations. The suboptimal representation of Black participants and other high-risk groups in the populations enrolled in CV outcome trials left the unresolved question as to whether the benefits demonstrated for White individuals in these studies may be generalized to the other racial groups.

*Race/ethnicity in HF prevention and treatment*

HF is an increasingly prevalent CV condition, as the population ages, along with poorer control of hypertension, increasing obesity and T2D. These HF risk factors are also influenced by diet, environment and other social determinants of health [81–83]. The racial differences of incident HF are often dependent on the differential burden and impact of risk factors between groups. A recent analysis totaling 38,028 individuals determined the population attributable fraction (PAF) of different racial groups' incident HF [82]. The cohort consisted of 8,407 (22%) Black adults and 27,611 (78%) White adults. Of the risk factors evaluated, hypertension was associated with the greatest PAF in Black men and women. The PAFs of HF in patients presenting with three or more risk factors were significantly higher in Black men and women. Therefore, the most potent and prevalent risk factor must be identified early, treated intensively and controlled in all populations, especially non-Hispanic Black populations [84,85]. Other studies suggest non-Hispanic Black and Hispanic/Latinx patients are more likely to have more preventable HF hospitalizations when compared with White patients due to the risk and social factors [86,87]. The FDA approval of isosorbide and hydralazine in a fixed-dose combination (Bidil) marketed for a single racial group (Black adults) for the treatment of HF raised much controversy [88]; as mentioned above, race is problematic when considered a surrogate for genetic or biological processes.

In one prominent example of absent racial/ethnic cohort diversity, ivabradine was FDA approved in 2015 to induce slow heart rate in patients who are intolerant of beta blockers, based on a $N = 19{,}102$ non-U.S. cohort, did not include any significant African American/Black populations, with reporting 13.2% Asians and 5.2% other [89]. Moreover, a recent trial ($N = 5050$) studying the effect of vericiguat (FDA approved in 2021), a novel oral soluble guanylate cyclase stimulator, in patients with HF and reduced ejection fraction who had recently been hospitalized or had received intravenous diuretic therapy enrolled 64.1% White patients, 22.6% Asian patients, and only 4.9% Black patients [90]. Presently considered a class 1 A guideline-directed medical therapy, sacubritil-valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), was initially FDA approved in 2015, despite limited diversity in the first major trial, including only 5.1% of Black patients [91]. Moreover, a more recent study expanding FDA approval for demonstrating the benefits of sacubitril/valsartan to reduce risk of CV mortality and hospitalization in patients with HF, included 81.8% White patients and only 9.1% Asian and 1.5% Black patients [92]. On the other hand, another trial studying sacubritil-valsartan therapy initiated in the inpatient setting enrolled a larger percentage of Black individuals (35.9%) and demonstrated benefit [93]. In view of the high and increasing burden or HF related morbidity and mortality in Black and other diverse racial/ethnic populations, ongoing and future research must include adequate representation of diverse study participants.

*Community-based interventions for cardiovascular risk reduction*

These aforementioned pre-existing disparities in ASCVD risk factors and outcomes are projected to significantly increase given the disproportionate impact of the COVID-19 pandemic on communities of color from both health outcomes and socioeconomic standpoints [94–97]. A concerted effort to address upstream negative social determinants of health (SDOH) such as inadequate access to quality health care is critical towards the achievement of CV health equity as these factors are inextricably linked to CV risk [98]. Prioritizing the SDOH has also been outlined as a guideline-based component of comprehensive, patient-centered approaches to CVD prevention [99]. Thus, integration of innovative, community-based strategies and interventions are warranted to meet the needs of socioeconomically disadvantaged populations while promoting their overall CV health.

Community-based interventions have demonstrated effectiveness in addressing a myriad of CV risk factors for CVD prevention [100]. Several successful efforts have integrated academic-community partnerships with key community stakeholders including faith-based organizations [101,102], barbershops [103] and public libraries [104] as a means to simultaneously address the complexity of the SDOH and CV risk reduction [105]. Engagement of community leaders is one way to promote diverse trial enrollment. One demonstrated efficacy of a barbershop-based, health promotion strategy in improving hypertension control among Black men through a barber-pharmacist-led medication management intervention [103,106]. In addition, culturally tailored, lifestyle interventions targeting multiple CV risk factors (behavioral and biometric) in partnership with Black churches have shown improvements in CV health metrics in Black individuals [107–110]. Other evidence-based approaches, including integration of mobile technologies [111–113] and community health workers [114,115], can expand the reach of community-based interventions while enhancing adoption of healthy behaviors and efficacy of proven CVD prevention recommendations. Widespread adoption of community-based interventions beyond the clinical setting to reduce the burden of CV risk factors among diverse racial and ethnic groups has the potential to ultimately eliminate CVD disparities. Further, these interventions can also serve as avenues to build sustainable trust and capacity in under-resourced and underserved communities, and facilitate their enrollement in future research.

The Hispanic/ Latinx community, the largest minority group in the U.S., suffers from higher rates of certain chronic diseases compared with non-Hispanic/Latinx White individuals. Hispanic/Latinx individuals are particularly susceptible to disparate care as they may lack language and culturally appropriate health care services which may lead to lower quality of care. Community health workers or 'Promotores' may be used to circumvent this problem as they are often perceived as having similar values and experiences as their community [116] and thus improve chronic disease management.

*Diversity in clinical trial leadership*

A lack of cultural competency of trial investigators has been cited as a barrier to enrollement of individuals from diverse backgrounds into clinical trials [117]. Clinicians and researchers who BIPOC remain underrepresented as clinical trial investigators and as trial leaders [118]. In an on-line survey of active physicians, 31% of White physicians vs. 26% of physicians from minority populations reported being involved in clinical research as a principal investigator or subinvestigator. The disparity was even worse when it came to FDA-regulated clinical trials, where only 3.7% of minority physicians reported being active PIs compared to 9.3% of White physicians [30]. There needs to be greater efforts by academic institutions to diversify the pipeline with more diverse physicians entering medicine and cardiology, and to mentor and develop the leadership skills of their diverse faculty to prepare them for careers in clinical trial research. More diversity among research teams will encourage new approaches to framing research questions that are

relevant to under-served communities [119]. Diversity of trial investigators can improve the diversity of trial participants by being able to better connect with the language, customs and beliefs of the target recruitment population and foster community engagement and involvement of underserved populations in research planning [31,119]. Funding agencies need to be deliberate and intention when choosing overall and site-based principal investigators for their trials with an eye towards diversity

*Potential interventions to increase diversity in clinical trials*

There are multiple factors that interplay in the underrepresentation from a lack of access to centers performing trials, financial issues, or mistrust and fear of exploitation [118]. A detailed investigative review regarding barriers to enrolling participants from diverse racial and ethnic backgrounds identified the following 5 factors: [1] mistrust or fear; [2] lack of comfort with clinical trial process; [3] lack of information about the process of clinical trials; [4] time and resource contracts; [4] lack of awareness about ongoing trials [117]. Addressing each one of these barriers will be required to improve the current status of trial enrollment.

Increasing diversity in clinical trials involves implementation of both micro- and macro- systems (Fig. 1). On the micro level, cultural sensitivity, compassion, and community engagement are needed to build trust. Some specific measures can be taken to promote inclusion of previously underrepresented groups. Site selection processes should incorporate race and ethnicity data of potential trial enrollees into feasibility assessments to ensure diversity. Research outreach efforts should target communities of color to promote engagement in clinical studies. Incorporating the participant perspective by including patient advisors in the study design process, who can also review and provide feedback on prospective participant-facing materials can help increase interest in study enrollment for a broad patient population. Ensuring that participant-facing forms are available in Spanish and that adequate translation services are available to sites to improve enrollment of Hispanic/Latinx persons. Race and ethnicity data should be collected and reported in every study and monitored to identify under-enrolled groups and allow targeted interventions during the enrollment phase. Data on ethnicity in Hispanic/Latinx persons should go beyond Hispanic/non-Hispanic and include specific origin and race information to increase the knowledge base regarding the heterogeneity of risk and response to therapies in this broad population.

On the macro level, although clinical trials in the U.S. are often inclusive of racial/ethnic populations, many national and international guidelines are based on RCTs conducted world-wide. Compared to Sub-Saharan African and Central/South American countries, many world-wide clinical outcomes trials are often weighted towards a European population. A potential solution, if achievable, is to increase the number of clinical research sites from Sub-Saharan African and Central/South American countries. Facilitating such a transition would require investment in initial and ongoing training to applicable Investigators, as well as support from stakeholders interested in improving minority health, and expanding diverse racial/ethnic representation in clinical trials.

## Conclusions

Both women and racially/ethnically diverse populations are underrepresented in CV clinical trials (**Central Illustration**). Multiple factors have been identified as barriers to participation of individuals which include fear, mistrust, unawareness about on-going trials, not being approached for participation, overly restrictive eligibility criteria, lack of comfort with participating in trials, impacts of SDOH on participation, and logistical challenges to participation stemming from time, financial and other resource constraints. These barriers can be overcome with patient and community engagement to help build trust, education about the benefits and importance of clinical trials, and the diversification of study team investigators

Underrepresentation compromises the generalizability of CV drugs, especially in ASCVD risk conditions, where the burden is disproportionate across demographic groups. Equitable representation by sex and by race/ethnicity in clinical trials of CV drugs is essential so that clinicians and researchers can be assured that data reflect the diverse U.S. population [45].

Going forward, NIH- and industry- funded trials need to increase efforts to reach out to multiple communities and diverse communities and this effort will be needed to overcome the history of mistrust. Augmenting diversity in clinical trials will yield results that better reflect patient populations and be especially important in studying diseases that disproportionately affect different patient populations.

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## Ethical review

As this article was a literature review of published papers and did not involve enrollment of study participants, no ethical review board approval was required.

## Authorship Roles

The concept and design for paper was by EDM, TKR, and KCF. EDM drafted the first draft. TKR, MG, LCB, RMB, GPV, ALB, MRE, SAN, HEB, AMN, and KCF all provided critical input to the manuscript draft for intellectual content and approved final document.

## Declaration of Competing Interests

Erin D Michos - Advisory Boards for Novartis, Amarin, AstraZeneca, and Esperion. Given her role as an Editor, Erin Michos had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

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