Heart, Lung and Circulation (2022) **31**, 1263–1268
1443-9506/22/$36.00
https://doi.org/10.1016/j.hlc.2022.06.668

ORIGINAL ARTICLE

# Inclusion of Under-Represented Racial and Ethnic Groups in Cardiovascular Clinical Trials

**Viliane Vilcant, DO [a], Carlos Ceron, MD [a], Gagan Verma, DO, MPH [b], Roman Zeltser, MD, FACC [a,b], Amgad N. Makaryus, MD, FACC [a,b,*]**

[a]Nassau University Medical Center, East Meadow, NY, USA
[b]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, Hempstead, NY, USA

*Received 27 January 2022; received in revised form 2 June 2022; accepted 4 June 2022; online published-ahead-of-print 16 July 2022*

**Introduction** Non-White racial and ethnic groups have been traditionally under-represented for decades in the field of cardiology, specifically in cardiovascular research studies. This underrepresentation has occurred despite the fact that these racial and ethnic groups have been shown to be at increased risk of cardiovascular disease (CVD).

**Methods** To assess the trend of representation in mainstream landmark cardiovascular trials, we performed a review of major cardiovascular trials published between 1986 and 2019. Mainstream landmark trials were selected as classified by established cardiology standards. The reported numbers of racial and ethnic participants were assessed within these categorised cardiovascular trials over a continuous time period.

**Results** A total of 1,138,683 patients were assessed from 153 randomised clinical trials. Of these trials, only 56% (n=86) reported information about race. Of note, 99% (n=152) of these trials reported gender. About three-quarters of the trials (77%) were undertaken at least partly in the United States (US). Our results show that the percentage of non-White participants in clinical trials was not significantly different over time (p=0.85), suggesting no significant improvement in non-White racial/ethnic representation. Further analysis of only the US inclusive trials (n=20) also showed no significant improvement in representation (p=0.38).

**Conclusion** Only about half of all major cardiovascular landmark trials reported any racial or ethnic information, despite more recent calls over the last 5–10 years for diversity and representation in cardiovascular research studies. Additionally, no significant improvement in inclusion of traditionally under-represented racial and ethnic groups (UREGs) in these trials has occurred over time. Our analysis shows that there is still major work to be done to foster better representation and evaluation of the UREG population in cardiovascular trials.

**Keywords** Racial minorities • Ethnic minorities • Underrepresentation • Race • Ethnicity • Cardiology • Trials

## Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the United States (US), responsible for 868,662 deaths in the US in 2017. According to the latest heart disease statistics from the American Heart Association (AHA), approximately every 39 seconds, an American will have a myocardial infarction (MI), with the average age being 65.6 years for males and 72.0 years for females. This cardiovascular burden is one of the continually increasing costs contributing to health care expenditures [1]. It has been documented in numerous studies that under-represented

*Corresponding author at: Professor, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Chairman, Department of Cardiology, NuHealth, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, USA; Email: amakaryu@numc.edu; Twitter: @AmgadMakaryus

racial and ethnic groups (UREGs) in the United States are at increased risk of developing cardiovascular diseases; furthermore, this specific population is also more likely to experience adverse outcomes and receive suboptimal treatment [2].

Current guidelines used in the prevention and treatment of CVD are supported by clinical trials which form the "evidence-base". These guidelines recommend preventative strategies with acknowledgement of certain factors that play a role in individuals' health care such as physical barriers to care, limited health literacy, cultural influences and socioeconomic risk factors. Assessment of atherosclerotic CVD (ASCVD), consuming a plant-based diet high in vegetables, fruits, nuts, whole grains, lean vegetable or animal protein and moderate physical activity for at least 150 minutes per week are just a few of the recommendations in the latest prevention guidelines from the American College of Cardiology (ACC), which ultimately guides our clinical decision making [1,2]. As such, cardiovascular trials should reflect a reliable representation of the patient population, including UREGs, given the disparities that exist that inevitably increase both inpatient and outpatient costs of health care.

Few studies have assessed the trend in UREG inclusion over a period of time, but none have focussed on the trend over this last decade. In our analysis, we reviewed mainstream landmark cardiovascular clinical trials. Landmark clinical trials can be defined as those trials which mark an important stage of development or a turning point in medical diagnosis and therapeutics and create important historical change that impacts clinical practice [2]. The mainstream landmark trials in our analysis have paved the way for inclusion in evidence based clinical practice guidelines; thus, it is vital to understand the study population evaluated in these trials. We sought to assess the trend of UREG inclusion in mainstream landmark cardiovascular trials with the hypothesised hope that representation has improved over the past several decades.

# Methods

## Study Selection

We performed a literature review of major cardiovascular trials published between 1986 and 2019 in five major journals publishing cardiovascular trials: *Circulation, Journal of the American College of Cardiology, Journal of the American Medical Association, Lancet* and *The New England Journal of Medicine.* These journals were selected because they have the greatest impact on clinical practice and wide dissemination based on their impact factors. To select which trials to include, an internet search using the term "landmark cardiology trials" was performed on each of the following website sources: Cardiology Trials [3], Healio Review of Cardiology Trials, [4] and Wiki Journal Club [5]. *Evidence Based Cardiology* was an additional source used to select landmark trials [6]. We prespecified a trial as "landmark" if it was cited in at least two of the above noted journal sources, was a randomised controlled trial, and included 100 or more patients, since those with less than 100 were often preclinical studies that generally may not lead to a change in clinical practice. Due to lack of recent updates on these chosen online websites, trials from 2015–2019 were abstracted from the ACC Top Ten Cardiology Trials website [7]. Literature search and abstraction was performed by two of the authors (V.V. and G.V.) who are well-versed in literature review, analysis, and abstraction. Data compiled from the two researchers was gathered to produce the complete study list (Appendix) for analysis.

## Data Collection and Analysis

The reported number of UREGs was assessed within the categorised cardiovascular trials. UREGs were defined as non-Whites, and divided into Blacks, Hispanics, Asians and "other". Reported data for each included landmark trial was obtained from the primary study publication source and data gathered included patient demographics (race, gender, and age) and characteristics of the trials (year of publication, journal of publication, study size, study population including country, and internet source used to support a study being considered as "landmark"). Trials were further characterised by the disciplines within cardiology as follows: cardiac arrhythmia, coronary artery disease, heart failure, hypertension and prevention [8].

A total of 153 trials were categorised according to year of publication ranging from 1986 to 2019. The reported country where the study was performed was also noted. Summary statistics, including average number of participants and age were calculated for the aggregate data. Trials were categorised by whether they published information about participants' race. This was analysed by stratifying race into White versus non-White. The average percentage of non-White participants was analysed using a Spearman Rank Correlation and the correlation was performed on a decade basis for comparison over time. All analyses were performed using standard Statistical Analysis Software (SAS® version 9.4, SAS Institute Inc., Cary, NC, USA). P-values $<0.05$ were considered statistically significant.

# Results

A total of 1,138,683 patients were evaluated in 153 randomised clinical trials (Appendix). The average number of participants per trial was 7,442. There was a total of 25 studies in the 1986–1999 study period with 45% of these trials with UREGs reporting, 54 studies in the 2000–2009 time period with 65% of these trials with UREGs reporting, and 74 studies in the 2010–2019 time period with 60% of these trials with UREGs reporting. Overall, racial information was reported in 56% (n=86) of trials (Table 1). Among these trials, 13.1% (20 trials) took place in the US alone, 64.1% (98 trials) took place in multiple countries including the US, 13.1% (20 trials) took place in multiple non-US countries and 9.8% (15 trials) took place in another single non-US country. Coronary

**Table 1** Percentage of Race/Ethnicity Reported.

| | N (Total=153) | Percentage |
|---|---|---|
| **Not reported** | 67 | 43.8 |
| **Reported** | 86 | 56.2 |

artery disease trials were the most represented discipline with the greatest number of trials (coronary artery disease [CAD]: 66 trials [43.1%]; arrhythmia: 15 trials [9.8%]; heart failure: 33 [21.57%]; hypertension: 19 trials [12.4%]; prevention: 20 trials [13.1%]). Heart failure and hypertension trials had the highest reporting rates of racial information. The racial reporting rates per discipline were 46.7% for arrhythmia, 43.9% for coronary artery disease, 69.7% for heart failure, 73.7% for hypertension and 65% for prevention trials (Table 2).

Overall, the average percentage of non-White representation was 19.96%. The percentage of non-White participants in clinical trials was not significantly different over time (p=0.85), suggesting no significant improvement in UREG inclusion as we transcend several decades with more studies evolving to show the increased risk of cardiovascular disease in the UREG population (Figure 1). The percentage of non-White participants per trial type shows that there is a slight increase with heart failure and prevention trials; but overall, we found that UREGs were under-represented in all disciplines within cardiology (Figure 2) with a mean of 11.3% for arrhythmia, 16.5% for coronary artery disease, 22.2% for heart failure, 20.8% for hypertension and 26.9% for prevention trials (Table 3).

# Discussion

While some attention has been focussed on the trend in UREG inclusion over a period of time, no major studies have focussed on the trend over this last decade. Zhang et al. [9] evaluated trials from 1997–2010 and found that only about half of all major cardiovascular trials reported racial information and that ethnic minority groups were under-represented. Another report by Berger et al. [10], evaluated randomised controlled trials cited in the 2007 AHA guidelines and found that there was an increase in reporting of race over time, but that two-thirds of these trials still did not provide information on race. Our investigation focusses on the trend over this last decade in order to provide an update for future research.

According to the latest Census Bureau's Population Estimation Program, in 2018 the United States racial composition was 60.4% Whites, 13.4% Blacks, 18.3% Hispanics and the rest being accounted for by American Indian, Asian, Native American and other Pacific Islanders [11]. Although mortality rates for acute myocardial infarction (MI) and cerebrovascular disease (CVD) have declined in the United

**Table 2** Reporting of Race/Ethnicity per Trial Type.

| Trial Type | Reported (N, % of total trials) | Not Reported (N, % of total trials) | Total (N, % of total trials) |
|---|---|---|---|
| **Arrhythmia** | 7 | 8 | 15 |
| | 4.6 | 5.2 | 9.8 |
| **Coronary** | 29 | 37 | 66 |
| **artery disease** | 18.9 | 24.2 | 43.1 |
| **(CAD)** | | | |
| **Heart failure** | 23 | 10 | 33 |
| | 15.0 | 6.5 | 21.6 |
| **Hypertension** | 14 | 5 | 19 |
| | 9.2 | 3.3 | 12.4 |
| **Prevention** | 13 | 7 | 20 |
| | 8.5 | 4.6 | 13.1 |
| **Total** | 86 | 67 | 153 |
| | 56.2 | 43.8 | 100.0 |

States since the 1970s, there is data to suggest that there is a steeper decline for Whites than for Blacks [12]. According to one study, Black men and Black women had twice the fatal rates of CVD compared to White men and White women. This increased risk was associated with racial differences in risk factors including smoking, hypertension, and diabetes; which were more prevalent among the minority population [13]. About 60% of non-Hispanic Blacks will have some form of cardiovascular disease; therefore, the appropriate non-pharmacologic as well as pharmacologic interventions needed to prevent CVD can be sought, only if we study this specific population.

Our findings show that there is no significant improvement in the representation UREGs in cardiovascular clinical trials over time. Despite the decline in cardiovascular mortality over the last several decades, cardiovascular mortality at all ages tends to remain highest in Blacks [14]. Many population subgroups characterised by race, gender, socioeconomic status and educational level show striking disparities in cardiovascular health. Such disparities inevitably lead to adverse clinical outcomes and suboptimal quality of life [15]. Some potential reasons for lack of representation may include lack of awareness of clinical trial availability, mistrust for medical professionals and those involved in clinical research, lack of diversity among the research and clinical professionals, and location of conducted research, including lack of means to participate and concern over unexpected costs [16]. Additionally, UREG populations tend to overall have less access to medical care, so this likely translates to less access to CVD trial participation opportunities.

In an attempt to decrease under-representation, the National Institutes of Health (NIH) mandated the inclusion of women and under-represented racial and ethnic groups with the passage of the Revitalization Act of 1993. The Act was intended to increase the number of women and individuals from disadvantaged backgrounds, including UREGs, in the

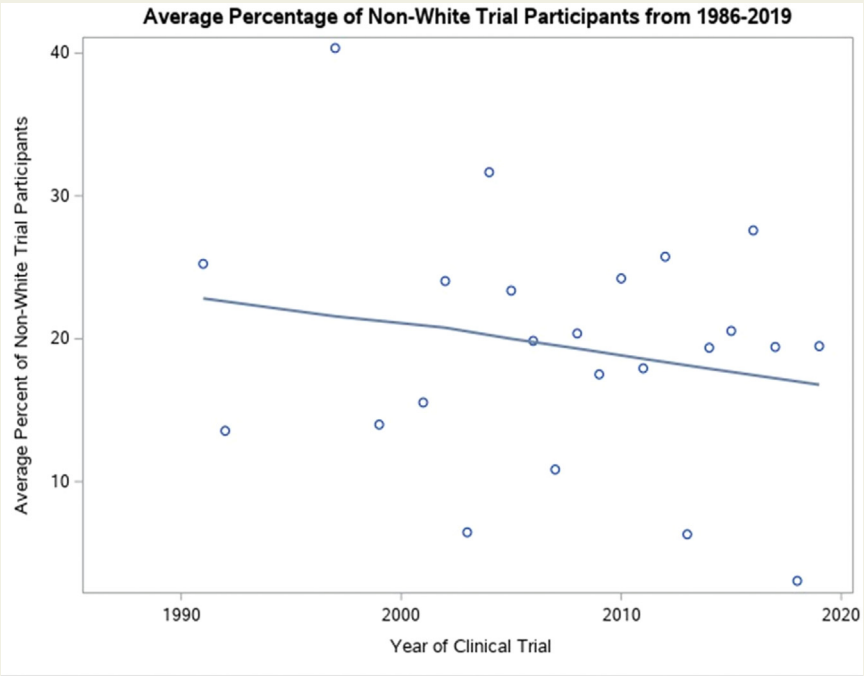


**Figure 1** Non-White Representation for All Trials as Compared Over Time by Trial Time Periods.
Data points represent average non-white trial representation per trial year noted and the graphical line represents the running average used to make the time period comparisons for the analysis.

field of research [17]. In addition, the Food and Drug Administration (FDA) as well as the American College of Cardiology has been pushing forward initiatives for greater inclusion in patient participation. According to the FDA, "a wide range of people should have the opportunity to participate in trials, both for access to new therapies and to have the chance to contribute to better treatment of everyone" [16]. This is especially important when race-based

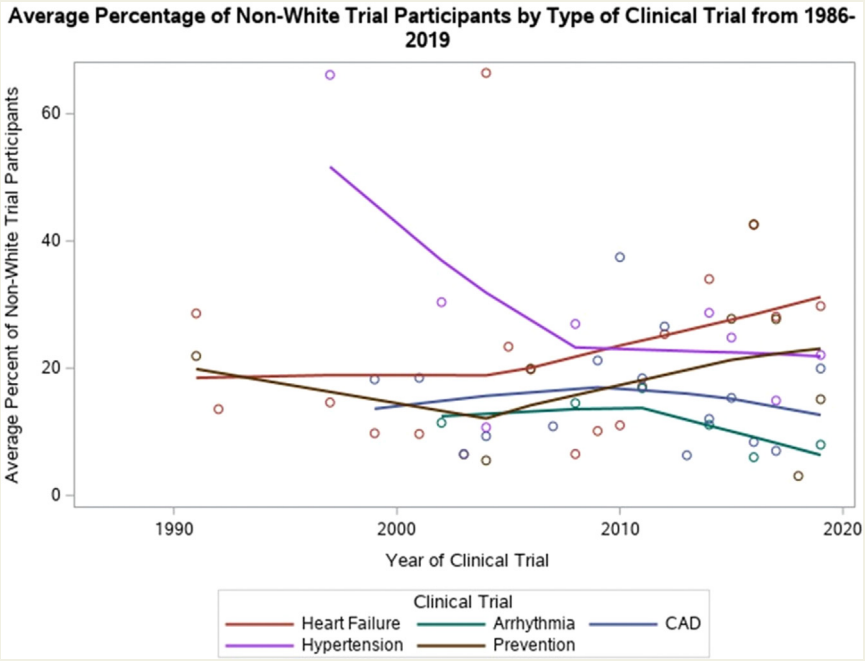


**Figure 2** Representation of Non-White Participants by Type of CVD Trial Over Time by Trial Time Periods.
Data points represent average non-White trial representation per trial year noted and the graphical line represents the running average used to make the time period comparisons for the analysis.
Abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease.

**Table 3 Average Percentage of Non-White Participants per Trial Type.**

| Type of Trial | N | Mean % ± SD |
|---|---|---|
| Arrhythmia | 7 | 11.3±3.8 |
| Coronary artery disease (CAD) | 29 | 16.5±9.8 |
| Heart failure | 23 | 22.2±20.2 |
| Hypertension | 13 | 20.8±20.3 |
| Prevention | 14 | 26.9±17.7 |

differences exist in the diagnosis and treatment of cardiovascular disease.

Our study showed that UREGs continue to be underrepresented in all disciplines within cardiology with prevention trials having the third lowest mean percentage of under-represented ethnic participants. While it is known that prevention is key in CVD outcomes, only 65% of prevention trials reported race. There are multiple efforts by the FDA that are promising. These efforts include guidance documents that have been published to encourage increased diversity in clinical trials. Such documents encourage close examination of exclusion criteria to avoid unnecessary limitations to study populations and to consider various trial designs to hopefully enrol a broader population. According to the FDA, "broadening eligibility criteria, when appropriate, maximises the generalisability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice, without jeopardising patient safety" [18].

More efforts should be undertaken to increase clinical trial awareness and opportunity to participate; thereby hopefully leading to better recruitment outcomes [19]. More forums for advertising of trials and education should be available for specific targeted populations. Financial incentives such as transportation vouchers could be distributed to those UREGs outside of the local community where the research study is taking place. Furthermore, more initiatives for medical school diversity will lead to more diverse medical professionals and often, UREG populations feel more comfortable when researchers and medical professionals are from their own racial background [20]. In addition to improving UREG inclusion, study investigators should be more aware of the need to report racial and ethnic information, which is reflected in the data collection process. While recent publications have documented positive efforts in representation [21], and recognition of the under-representation [22], additional studies are needed to aid in understanding the discrepancy in UREG enrolment.

As with any study that compares analyses from diverse multiple investigators, we are limited by sample size variations, availability of data points reported, and possibly varied data quality across the varied disciplines within cardiology that were evaluated. Finally, our review included studies from the US and non-US countries, which involves different study protocols and differences in how UREGs are characterised, recorded, and recruited.

## Conclusion

In the recent decades evaluated, almost half of cardiovascular trials still do not report racial and ethnic information and there has been no significant improvement in the inclusion of UREGs over time. We were hopeful that there would be a positive upward trend in inclusion of the underrepresented racial and ethnic subgroups; however, our study highlights the progress that is still needed moving forward, and should serve as a call to action for not only the CVD community, but the medical community as a whole.

## Appendices

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2022.06.668

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