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FACTORS ASSOCIATED WITH RACIAL AND ETHNIC DIVERSITY AMONG HEART FAILURE TRIAL PARTICIPANTS: A SYSTEMATIC BIBLIOMETRIC REVIEW

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ABSTRACT

Background – Heart Failure (HF) has a disproportionate burden on patients who are Black, Indigenous, and People of Colour (BIPOC), but not much is known about representation of these groups in randomized controlled trials (RCTs). We explored temporal trends and RCT factors independently associated with the reporting of race/ethnicity data and the enrollment of BIPOC in HF RCTs.

Methods – We searched MEDLINE, EMBASE, and CINAHL for HF RCTs published in journals with an impact factor ≥ 10 between January 1, 2000 and June 17, 2020. We used the Cochran-Armitage and Jonckheere-Terpstra tests to examine temporal trends, and multivariable regression to assess the association between trial characteristics and outcomes.

Results – Of 414 RCTs meeting inclusion criteria, only 157 (37.9%; 95% CI 33.2-42.8%) reported race/ethnicity data. Among 158,200 participants in these 157 RCTs, 29,512 (18.7%; 95% CI 18.5-18.9%) were BIPOC. There was a temporal increase in reporting of race/ethnicity data (29.5% in 2000-2003 to 54.7% in 2016-2020, $p < 0.001$), and in enrollment of BIPOC (14.4% in 2000-2003 to 22.2% in 2016-2020, $p = 0.038$). Trial leadership by a woman was independently associated with twice the odds of reporting race/ethnicity data (odds ratio 2.0; 95% CI 1.1-3.8; $p = 0.028$) and an 8.4% increase (95% CI 1.9-15.0%; $p = 0.013$) in BIPOC enrollment.

Conclusions – A minority of HF RCTs reported race/ethnicity data and among these, BIPOC were under-enrolled relative to disease distribution. Both reporting of race/ethnicity and enrollment of BIPOC increased between 2000 and 2020. After multivariable adjustment, trials led by women had greater odds of reporting race/ethnicity and enrolling BIPOC.

Registration - PROSPERO registration number CRD42021237497

NON-STANDARD ABBREVIATIONS AND ACRONYMS

Abbreviations: BIPOC, Black, Indigenous and People of Colour; HF, heart failure; NIH, National Institutes of Health.

CLINICAL PERSPECTIVE

1) What is New?

- Less than 38% of heart failure (HF) randomized controlled trials (RCTs) reported race or ethnicity data and among these, <19% of participants were Black, Indigenous and People of Colour (BIPOC).
- <20% of RCTs indicated how race or ethnicity was determined in trial participants.
- Between 2000 and 2020, there was an increase in reporting of race and ethnicity data and in enrollment of BIPOC in HF RCTs.
- Trial leadership by a woman was independently associated with twice the odds of reporting race or ethnicity data and an 8.4% increase in the enrollment of BIPOC.

2) What are the clinical implications?

- RCTs should transparently report race/ethnicity data, including method of ascertainment.
- Researchers, institutions, and sponsors should make targeted efforts to enroll diverse RCT participants proportionate to disease distribution to increase generalizability of results.
- Multi-level interventions should address systemic barriers to enrollment in underrepresented groups, and develop capacity for clinical trial leadership among women and BIPOC.

INTRODUCTION

Heart failure (HF) affects more than 64 million people worldwide and is a leading cause of mortality, morbidity, and healthcare expenditure.¹⁻³ Data from HF randomized controlled trials (RCTs) guide practice and policy, and also inform clinical practice guidelines that are implemented across the world. To ensure that RCT evidence is broadly applicable to clinical practice, the demographics of trial participants should be reported transparently and should reflect the diversity of those living with HF. Trial populations, however, tend to be much more homogeneous in demographics and comorbidities than patients in clinical settings.⁴⁻⁷

There are concerns that race and ethnicity data may be inadequately reported in RCTs, but reporting is essential to understanding the interplay between race or ethnicity and treatment outcomes both in clinical and research settings.⁷ Race and ethnicity are heterogeneous social constructs that may influence the estimated treatment effect in RCTs due to variations in healthcare system engagement, quality of care, and socioeconomic factors. There may also be differences in metabolism and response to prescribed medications related to ancestry.⁶⁻⁸ For example, ACE inhibitors appear to be less effective in blood pressure reduction in Black than in White adults.^{9, 10} Likewise, the combination of hydralazine and isosorbide dinitrate reduces mortality in Black patients with HF with reduced ejection fraction, though the same effect is not seen in other subgroups.¹¹⁻¹³ The etiology of these differences in clinical responses may be partly explained by genetic polymorphisms.¹⁴ The FDA encourages diverse representation in clinical trials, but like Health Canada, does not mandate this for cardiovascular pharmaceutical and device approval.^{15, 16}

In this systematic review, we examined temporal trends in 1) the reporting of race or ethnicity data and 2) the recruitment of Black, Indigenous, and People of Colour (BIPOC) in HF RCTs that were published in high-impact factor journals between 2000-2020. We sought to examine the independent association between trial factors and these two outcomes. Our prior work demonstrated an independent association between RCT leadership by women and enrollment of women in RCTs.⁴ Therefore, we hypothesized that RCTs led by women would be associated with increased enrollment of BIPOC as the way that patients are recruited and consented in women-led trials may be tailored to the needs of participants traditionally underrepresented in cardiovascular research.

METHODS

Identification of Clinical Trials

The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42021237497). This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁷ A systematic search of published data in MEDLINE, EMBASE and CINAHL was conducted with the following criteria (Supplemental Methods): 1) search terms “heart failure” and “randomized controlled trials;” 2) English-language publications; 3) Publication dates between January 1, 2000 and June 17, 2020; 4) Recruitment of adults (≥ 18 years of age) with HF; 5) Journal Impact factor ≥ 10 in 2019; 6) fulltext manuscripts reporting primary outcomes. We excluded publications describing post-hoc, interim, or secondary analyses. Two authors independently screened all abstracts from the search against these pre-defined criteria and selected studies for inclusion, with a third reviewer resolving discordant assessments. The data

that support the findings of this study may be shared as per Population Health Research Institute Data Sharing policy, which requires approval of the proposed use of the data by a review committee.

Data Extraction

The following data fields were independently extracted in duplicate: year of publication, journal impact factor, journal name, type of intervention, primary outcome, characteristics of the study population, funding source, location of trial coordination center, number and location of recruitment centers, and setting of recruitment.

When available, we extracted data specific to race or ethnicity, including related eligibility criteria, enrollment, and subgroup analyses. Data regarding race were collected in accordance with the 2012 US Food and Drug Administration position statement.¹⁵ Race was identified using 5 mutually exclusive categories: 1) American Indian, Alaskan Native, or Indigenous; 2) Asian; 3) Black or African American; 4) Native Hawaiian or other Pacific Islander; 5) White. Ethnicity was captured as Hispanic if applicable. Hispanic ethnicity was ascertained prior to designation of race. The category of BIPOC was used in lieu of the first 4 categories in trials that solely reported the proportion of White vs non-White participants or to classify participants not captured in the pre-specified race or ethnicity categories.

We extracted data on the gender of trial leaders, defined as authors in first and last position. We only included authors listed in the author section of the publication, and if applicable, accounted for shared authorship roles in first or last author positions. We excluded

individuals in trial consortia and investigator groups in the analysis. Gender was determined via online searches of author names, with sources of information including photographs and pronoun descriptors on professional, institutional and social media accounts.

Outcomes

The outcomes were: 1) reporting of race or ethnicity data in any section of the publication or supplemental file; and 2) the proportion of BIPOC enrolled in the RCT.

Data Analysis

We used published trial data for all analyses. We performed a descriptive analysis with mean and standard deviation for continuous normally distributed variables, and median and interquartile range for non-normally distributed variables. We used numbers and proportions for categorical variables. For participant level analyses, we computed weighted means and square root of combined variance. Multivariable logistic and linear regression models were used to explore the independent association between woman trial leadership and the outcomes. Models were adjusted for continent of coordinating centre (Europe, Central and South America, Asia or Australia and Africa versus North America), type of intervention (health care service [e.g., home visits, palliative care], exercise, surgery or device, versus pharmaceutical), scope of trial (multicentre versus single centre), type of funding (industry versus public), trial size (<100, 100-500, >500 participants), and year of publication.

Results were reported as odds ratios with corresponding 95% confidence intervals and associated p-values. Temporal trends for the two primary outcomes were analysed using the Cochran-Armitage trend test and the Jonckheere-Terpstra trend test respectively. Data were

analysed using R studio (version 1.1.456) and a 2-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of RCTs and Participants

Our systematic search produced 12,342 unique manuscripts, of which 414 met eligibility criteria and were included in the review and analysis (Figure 1). Informed consent was obtained in all RCTs. Of the 414 RCTs, 101 (24.4%; 95% CI 20.3-28.8%) were led by women (either first or last authorship position). Most RCTs tested pharmaceutical interventions (65.5%; 95% CI 60.7-70.0%) and recruited participants from an ambulatory setting (76.3%; 95% CI 71.9-80.3%). More than half (52.7%; 95% CI 47.7-57.6%) received some industry funding, while the remainder (47.3%; 95% CI 42.5-52.2%) received only public funding. The median number of participants per trial was 120 (interquartile range 40-389) (Table 1).

A total of 234,287 participants were represented in the 414 RCTs. Mean (SD) age was 66.3 (6.5) years. The majority (71.7%; 95% CI 71.5-71.9%) of participants were male and had a reduced ejection fraction (81.9%; 95% CI 81.7-82.1%), and more than half (59.6%; 95% CI 59.4-59.8%) had an etiology for heart failure that was attributable to ischemic disease.

Race or Ethnicity Data

Of 414 RCTs, 157 (37.9%; 95% CI 33.2-42.8%) reported race/ethnicity data in their publication, either in a table, figure or text. A majority of the 157 trials (71.3%; 95% CI 63.6-78.3%) were led in North America and only 22.3% (95% CI 16.1-29.6%) were led in Europe

(Table 1).

Reporting and analysis of race/ethnicity data was suboptimal in a majority of the 157 trials. The manner of assessing race/ethnicity data was not reported in 120 RCTs (76.4%; 95% CI 69.0-82.8%). Race/ethnicity data was self-reported in 29 RCTs (18.5%; 95% CI 12.7-25.4%), recorded by the investigator in 6 RCTs (3.8%; 95% CI 1.4-8.1%), ascertained through medical records in 1 RCT and determined by multiple methods (investigator, patient, medical record) in 1 RCT (Table 2). Of 157 RCTs, 92 (58.6%; 95% CI 50.5-66.4%) specified race beyond White and non-White categories (Figure 2a). Race/ethnicity subgroup analyses were attempted in 31 RCTs, though less than half (13 RCTs) performed interaction tests to assess for race or ethnicity as treatment effect modifiers; an even smaller fraction (10 RCTs) pre-specified the subgroups. In the other 18 RCTs, the statistical method used was either unspecified or a comparison of proportions between difference race categories (Figure 2b). Two of the 13 RCTs found race as an effect modifier of the intervention; it is unclear whether the remainder of the analyses were adequately powered to detect any race-specific differences.

Journals in which a majority of published RCTs reported race/ethnicity data included:

JAMA (including JAMA cardiology and JAMA internal medicine), the Lancet, and the New England Journal of Medicine. Journals in which <30% of publications reported race/ethnicity data included: the American Journal of Respiratory and Critical Care Medicine, Annals of Internal Medicine, British Medical Journal, European Heart Journal, European Respiratory Journal and European Journal of Heart Failure (Supplemental Table 1).

Enrollment of Black, Indigenous and People of Colour

Among the 158,200 participants in the 157 trials that reported data on race/ethnicity, 29,512 (18.7%; 95% CI 18.5 -18.9%) represented BIPOC groups and 128,688 (81.3%; 95% CI 81.1-81.5%) were White participants. Among the 142 trials coordinated in the United States, 20.1% (95% CI 19.9-20.3%) of 112,597 participants were BIPOC.

Temporal Trends

The proportion of trials reporting race/ethnicity data increased significantly from 2000 to present, rising from 29.5% (95% CI 21.6-38.4%) in 2000-2003 to 54.7% (95% CI 43.6-65.4%) in 2016-2020 ($p<0.001$) (Figure 3a).

Among trials reporting race or ethnicity, the percentage of enrolled BIPOC increased significantly between 2000 and 2020, rising from 14.4% (95% CI 14.1-14.8%) in 2000-2003 to 27.1% (95% CI 26.5-27.7%) in 2012-2015, decreasing slightly to 22.2% (95% CI 21.8-22.6%) in 2016-2020 ($p=0.038$) (Figure 3b).

Trial Characteristics Associated with Reporting of Race or Ethnicity Data

Trial leadership by a woman was independently associated with reporting of race or ethnicity data (OR 2.02; 95% CI 1.08-3.81; $p=0.028$). Other trial characteristics associated with reporting of race or ethnicity data included multicentre (OR 2.45 versus single centre; 95% CI 1.26-4.80; $p=0.008$), enrollment of patients from multiple countries (OR 2.86 versus a single

country; 95% CI 1.42-5.88; $p=0.004$), and year of publication (OR 1.06 per year from 2000-2020; 95% CI 1.02-1.11; $p=0.006$) (Figure 4, Supplemental Table 2). Relative to trials coordinated in North America, those coordinated in other regions had lower odds of reporting race or ethnicity data (OR 0.05 Europe; 95% CI 0.03-0.10; $p<0.001$; OR 0.24 Central and South America; 95% CI 0.06-0.91; $p=0.042$; OR 0.11 Asia; 95% CI 0.03-0.39; $p=0.001$; and OR 0.10 Africa or Australia; 95% CI 0.01-0.58; $p=0.019$). Relative to pharmaceutical interventions, surgery or device interventions were associated with lower odds of reporting race or ethnicity data (OR 0.16; 95% CI 0.07-0.37; $p<0.001$); and exercise or health services had no significant association. Funding source (industry versus publicly funded) had no association with the outcome (Figure 4, Supplemental Table 2).

Trial Characteristics Associated with Enrollment of BIPOC

Among the 414 RCTs, women represented 14.7% (61 out of 414) of first and 11.6% (48 out of 414) of last authors (Table 1). Demographics such as race or ethnicity and age of the RCT leaders could not be reliably obtained from online resources. In multivariable analysis, trial leadership by a woman was independently associated with a mean 8.4% (95% CI: 1.9-15.0%, $p=0.013$) adjusted increase in the enrollment of BIPOC relative to RCTs with men-only leadership teams (Figure 5). There was an average 0.6% (95% CI 0.1-1.1%; $p=0.013$) adjusted increase in enrollment of BIPOC per year between 2000 and 2020. There were no significant associations between funding source, trial size, or number of countries enrolling participants and enrollment of BIPOC.

DISCUSSION

In this systematic review of 414 HF RCTs published in high-impact medical journals between 2000 and 2020, we found that less than 38% of RCTs reported data on race/ethnicity and less than 20% of participants were BIPOC. However, there was a temporal increase in both reporting of race/ethnicity data and enrollment of BIPOC. Trial leadership by a woman was independently associated with twice the adjusted odds of reporting race/ethnicity data and an 8.4% adjusted increase in the enrollment of BIPOC.

A minority of RCTs reported race/ethnicity data and when reported, data collection standards¹⁸⁻²⁰ were frequently not met. While self-reporting is the preferred method of establishing race/ethnicity,¹⁸⁻²⁰ more than 76% of the RCTs did not specify how race/ethnicity data were obtained and less than 19% used self-reported data from patients. Only half the RCTs reporting race or ethnicity data specified racial or ethnic groups beyond White and non-White, indicating a need for both reporting and recognition of all groups. Subgroup analysis was uncommon and testing for effect modification by race or ethnicity, rare. These findings are compatible with a study that found race/ethnicity data to be reported in less than one-third of 280 clinical trials published in general medical journals prior to 1999.²¹ Another study found that less than half of RCTs between 2001-2016 reported data on race/ethnicity.²²

Race, ancestry, and ethnicity may influence a patient's response to medical interventions due to differences in physiologic response, socioeconomic factors, and access to health care, as well as structural biases or racism.^{23, 24} Income inequality is associated with worse health outcomes in HF, at a level comparable to comorbidities such as diabetes, myocardial infarction, age and history of hospitalization for HF.²⁵ The risk of the perfunctory use of race in medical research lies in the propagation of misunderstanding and inequality, where disparate

outcomes due to structural racism in healthcare and research settings are misattributed to genetics, engendering bias on the part of clinicians and distrust on the part of patients.^{24, 26} It is essential to balance the goals of improving the reporting of racial data, with the judicious and appropriate analysis of such data to avoid spurious interpretations.²⁶

We found that trial leadership by at least one woman was independently associated with increased reporting of race/ethnicity data and increased enrollment of BIPOC relative to men-only leadership pairs. Although the underlying reasons for this association are unclear, possible explanations include more diverse study teams, more detailed consent discussions, and more patient-centered follow-up protocols in trials led by women.^{4, 27} Notably, these findings complement prior work demonstrating that trials led by women enroll a greater proportion of women trial participants, who like BIPOC, are under-enrolled in HF trials relative to disease distribution.^{28, 29}

We found that trials coordinated in North America had the greatest odds of reporting data on race or ethnicity. Trials coordinated in Europe - where the population is increasingly diverse and where the largest proportion of high-impact HF trials are led³⁰ - had the lowest odds of reporting race/ethnicity data. Reporting in North America may be related to the mandates from the US national health agenda to increase the proportion of underrepresented groups in RCTs, including the 1993 National Institutes of Health (NIH) Revitalization Act requiring BIPOC groups to be included in RCTs receiving public funding unless a justification is otherwise provided, and the 2017 amendment requiring phase III trials to present subgroup analyses on race/ethnicity.³¹ The influence of this amendment may be reflected in our review as a third of the RCTs that included a subgroup analysis were published after 2017. However,

only 13 RCTs (3.1%) assessed whether race or ethnicity modified treatment effect. While the global burden of HF lies in low and middle income countries,³² only 7.4% of the trials were coordinated in these regions and a small minority of these (2.9%) reported data on race/ethnicity; this may be due to the perception of racial or ethnic homogeneity in these regions or lack of awareness on the importance of reporting this data.

Among those trials that reported data on race or ethnicity, BIPOC were underrepresented relative to disease distribution, comprising 18.6% of global trial participants and 20.1% of participants in trials coordinated in the United States. Whether this proportion applies to RCTs that did not report race/ethnicity data is unclear, but it is conceivable that there may have been even less representation of BIPOC in these trials. More than 2/3 of the world's HF population represents BIPOC individuals who live in South America, Africa, and Asia³²; and 30.6% of the US adult HF population self-identified as BIPOC in the National Health and Nutrition Examination Survey (5.5 million adults with HF).³³ In light of possible differences in treatment response between racial and ethnic groups, the under-representation of BIPOC in RCTs relative to disease distribution limits the generalizability of trial results.⁶⁻⁸ Estimates of treatment effect and safety are based on homogenous trial populations and analyses are often underpowered to reliably detect treatment interactions with race or ethnicity. This issue is poised to become even more relevant as BIPOC in the USA, currently estimated at 38% - will surpass 50% of the population by 2042.³⁴ The underrepresentation of BIPOC groups in RCTs disadvantages them as patients enrolled in RCTs – including those who receive placebo - have better outcomes due to more frequent monitoring, expert consultation and access to state-of-the-art interventions.^{35, 36} Under-enrollment of any demographic group relative to disease

distribution limits the external validity of RCTs, which further jeopardizes safety and health equity.

We could not assess patient-level reasons, including lack of consent, for under enrollment of BIPOC as trial flow is not reported by demographic group. Language barriers, cultural differences, financial burden of research participation, mistrust of the clinical trials enterprise related to structural racism, and the lack of pre-existing relationships with the medical system may have all played a role.^{27, 37} In trial design, enriching racial and ethnic diversity by addressing these barriers broadly is preferable over race-specific trials for several reasons.³⁸ Though race-specific trials may be well powered to answer focused clinical questions, separate trials for each racial/ethnic group are not always practical and have cost implications.³⁸⁻⁴⁰ The adequate inclusion of diverse groups in phase III clinical trials can increase trial costs given the need for multilingual staff with training in culturally safe care,^{39, 40} but this investment ensures that the estimated treatment effect on primary outcomes reflects treatment in patients suffering from the disease and offsets the cost of more expensive trials in specific demographic groups.

Recommendations

Trial methods should describe strategies undertaken to enhance sex/gender, race/ethnicity, and geographic diversity of trial participants.^{6,28-30,41} Trial reporting should include race/ethnicity data, including how the data were obtained, with self-identification being the preferred method. Subgroup analysis should include race/ethnicity subgroups, and when relevant, testing for treatment interaction.

A multistakeholder approach can be adopted to ensure diverse trial enrollment (Figure 6). Trial leaders and sponsors can diversify frontline research staff and train them in culturally safe care. Research teams should provide clear, patient centered information in the patient's native language, addressing concerns around research ethics and patient safety.⁴² Virtual rather than face to face research visits and compensation for participant time may mitigate the burden of trial participation and improve enrollment across socioeconomic groups.⁴³

Community-based recruitment can extend reach to individuals with limited engagement in healthcare systems.⁴⁴ Selective recruitment strategies that focus all efforts on underrepresented groups when a proportion of recruitment has been completed may further enhance trial diversity. Professional societies and academic institutions should institute policies to address systemic racism in healthcare and research and develop capacity for research leadership among women and BIPOC groups in cardiovascular sciences.²⁸

Strengths and Limitations

The strengths of our systematic review include a comprehensive analysis of RCTs published in high-impact journals spanning two decades; the scope of this review, largely exceeding that of previous reviews; and the novelty of our findings. In comparison to previous reviews on race and ethnicity in HF RCTs^{22, 45}, our analysis did not limit trial inclusion by size. Arbitrary size thresholds bias against RCTs testing invasive interventions, which are often logistically limited to smaller sizes. While we employed a journal impact factor threshold of ≥ 10 in 2019 to focus on trials that are likely to be highly cited, this, along with the inclusion of only

English language publications, may limit the generalizability of our findings; it is possible that trends and associations in lower-impact, non-English publications are inconsistent with those identified in our review. We could not account for the race or ethnicity of trial leaders as this information could not be reliably gleaned from on-line resources, as institutions, funding agencies, and industry sponsors do not routinely collect race/ethnicity data of investigators. Finally, the multivariable analysis is exploratory and results should be interpreted with caution.

CONCLUSIONS

Our findings suggest that reporting of data on race/ethnicity in HF RCTs is inconsistent, occurring in less than 40% of HF RCTs of which only half specified subgroups beyond White and non-White and <19% included BIPOC (Figure 7). Over the last 20 years, there has been increased reporting of race/ethnicity data and enrollment of BIPOC. Trial leadership by a woman was associated with twice the odds of reporting race or ethnicity data and an 8.4% increase in the enrollment of BIPOC groups. Other factors associated with reporting of race/ethnicity data included pharmaceutical interventions, and trials that were international, multicentre, or coordinated in North America. RCTs coordinated in Europe, which represented the largest proportion of trials, had the lowest odds of reporting data on race or ethnicity and represent a target for improved reporting.

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DISCLOSURES

The authors have no conflicts of interest to disclose.

SUPPLEMENTAL MATERIALS

Supplemental Methods

Supplemental Tables I-II

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TABLES

Table 1. Baseline Characteristics of Heart Failure Randomized Controlled Trials Published in High Impact Journals between 2000 and 2020 (n=414)

CLINICAL TRIAL CHARACTERISTIC	Total (n=414)	NO. (%) OF TRIALS		p-value
		Not Reporting Race/Ethnicity Data (n=257)	Reporting Race/Ethnicity Data (n=157)	
Continent of Coordinating Centre				
Africa	1 (0.2)	0 (0)	1 (0.6)	0.21
Asia	17 (4.1)	13 (5.1)	4 (2.5)	0.20
Australia	9 (2.2)	8 (3.1)	1 (0.6)	0.09
Central and South America	13 (3.1)	9 (3.5)	4 (2.5)	0.57
Europe	219 (52.9)	184 (71.6)	35 (22.3)	<0.001
North America	155 (37.4)	93 (36.2)	112 (71.3)	<0.001
Country(s) of Participant Recruitment				
Single Country	288 (69.6)	202 (78.6)	86 (54.8)	<0.001
>1 Country	120 (29.0)	51 (19.8)	69 (43.9)	<0.001
Not Specified	6 (1.4)	4 (1.6)	2 (1.3)	0.81
Trial Design Characteristics				
Recruitment				
Inpatient	98 (23.7)	53 (20.6)	45 (28.7)	0.06
Ambulatory	316 (76.3)	204 (79.4)	112 (71.3)	0.06
Type of Intervention				
Health Service & Exercise	87 (21.0)	61 (23.7)	26 (16.6)	0.09
Pharmaceutical	271 (65.5)	152 (59.1)	119 (75.8)	<0.001
Surgery & Device	57 (13.8)	45 (17.5)	12 (7.6)	0.005
Type of Funding				
Public	196 (47.3)	147 (57.2)	49 (31.2)	<0.001
Any Industry Funding	218 (52.7)	110 (42.8)	108 (68.8)	<0.001
Number of Centres				
Single Centre	171 (41.3)	140 (54.5)	31 (19.7)	<0.001
Multicentre	243 (58.7)	117 (45.5)	126 (80.3)	<0.001
Trial Size				
<100 Participants	192 (46.4)	157 (61.1)	35 (22.3)	<0.001
100-500 Participants	143 (34.5)	67 (26.1)	76 (48.4)	<0.001
>500 Participants	79 (19.1)	33 (12.8)	46 (29.3)	<0.001
>1000 Participants	57 (13.8)	17 (6.6)	40 (25.5)	<0.001
Gender of first author				
Man	349 (84.3)	216 (84.0)	133 (84.7)	0.85
Woman	65 (15.7)	41 (16.0)	24 (15.3)	0.85
Gender of last author				
Man	368 (88.9)	235 (91.4)	133 (84.7)	0.036

Woman	46 (11.1)	22 (8.6)	24 (15.3)	0.036
Type of Heart Failure				
Reduced Ejection Fraction	339 (81.9)	212 (82.5)	127 (80.9)	0.68
Preserved Ejection Fraction	46 (11.1)	26 (10.1)	20 (12.7)	0.41
Mixed or Not Specified	29 (7.0)	19 (7.4)	10 (6.4)	0.70
Year of Publication				
2000-2003	122 (29.5)	86 (33.5)	36 (22.9)	0.022
2004-2007	106 (25.6)	75 (29.2)	31 (19.7)	0.032
2008-2011	48 (11.6)	28 (10.9)	20 (12.7)	0.58
2012-2015	52 (12.6)	29 (11.3)	23 (14.6)	0.33
2016-2020	86 (20.8)	38 (14.8)	48 (30.6)	<0.001

Table 2. Racial and Ethnic Representation of Heart Failure Randomized Controlled Trial Participants

	No (%) of 414 RCTs	No. (%) of 234 287 Participants
Race/Ethnicity Data Available [†]	157 (37.9)	158 200 (67.5)
Non-Hispanic White Participants		128 688 (81.3)
Black, Indigenous, and People of Colour		29 512 (18.6)
Race/Ethnicity Data Not Reported	257 (62.1)	76 087 (32.5)
RCTs with >20% Black, Indigenous and People of Colour	81 (19.6)	
RCTs with >10% Black Participants	50 (12.0)	

RCT indicates Randomized Controlled Trial.

[†]Method of determining race and/or ethnicity was not reported in 120 out of 157 RCTs (76.4%), self-reported in 29 RCTs (18.5%), recorded by the investigator in 6 RCTs (3.8%), ascertained through medical records in 1 RCT (0.6%) and determined by multiple methods (investigator, patient, medical record) in 1 RCT (0.6%).

FIGURE LEGENDS

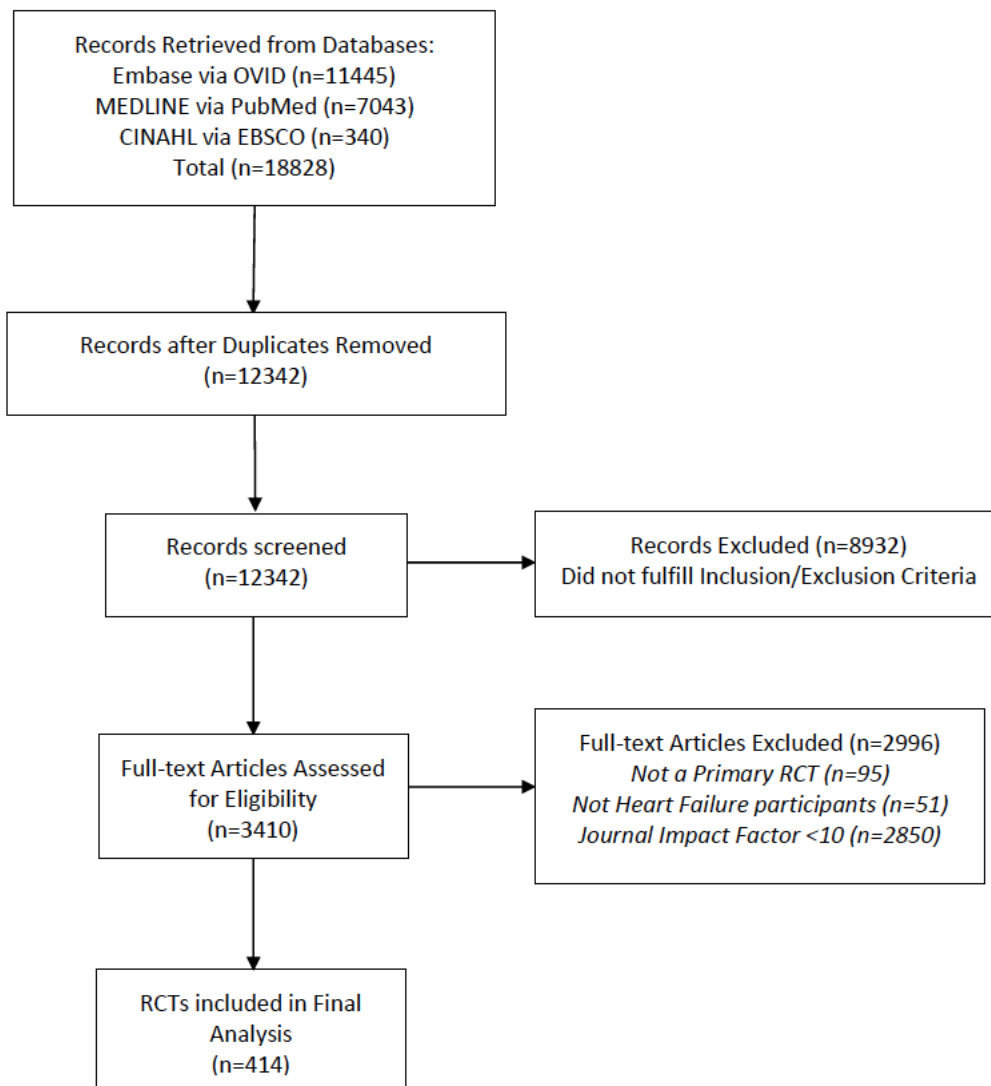


Figure 1. PRISMA Diagram of Systematic Search Strategy. Search conducted in MEDLINE, EMBASE and CINAHL used to Identify all Adult Heart Failure Randomized Controlled Trials with Impact Factor ≥ 10 .

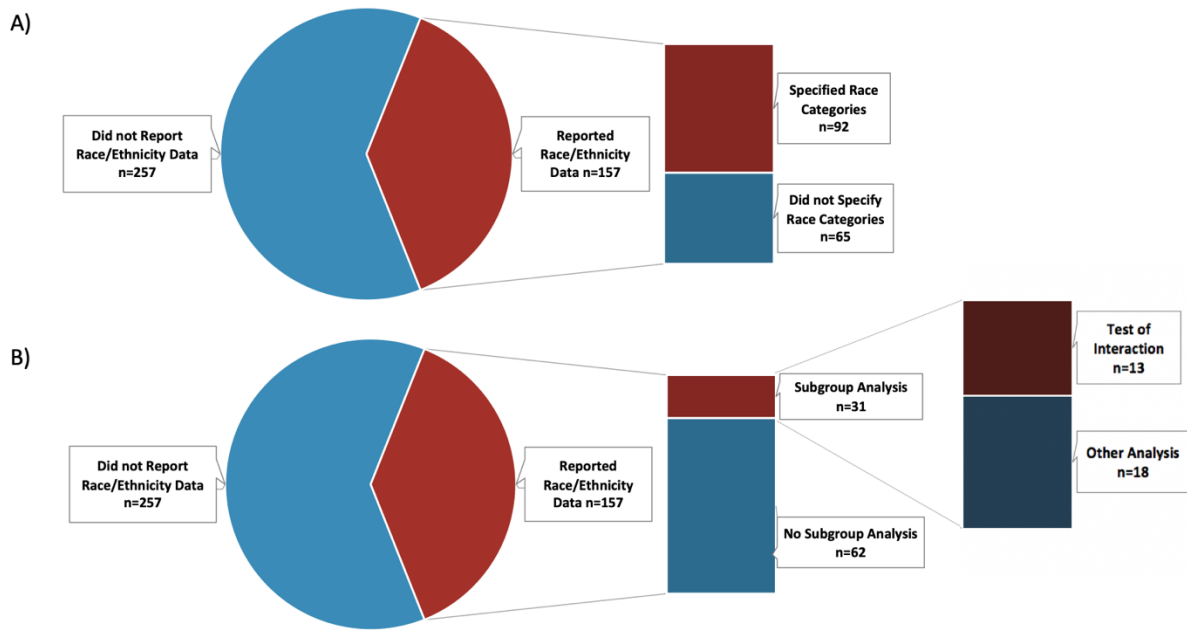


Figure 2. Breakdown of the reporting of race and ethnicity data across 414 RCTs.

Panel A) Reporting of race categories, specifically classification of race or ethnicity beyond White and non-White; B) Reporting of subgroup analyses.

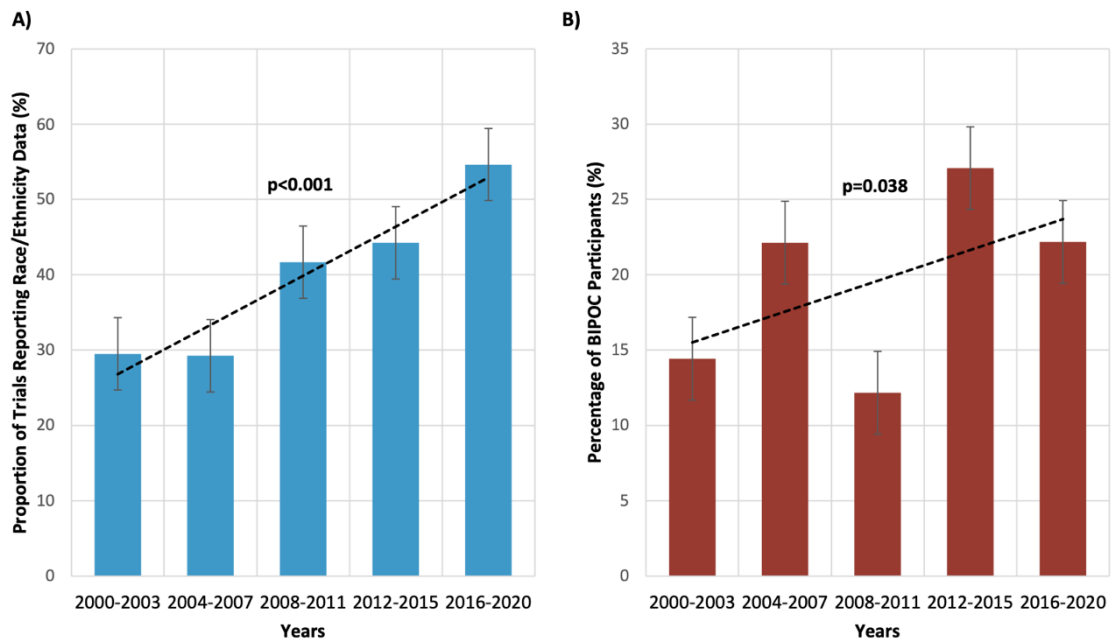


Figure 3. Temporal Trends in the A) reporting of Race/Ethnicity Data and B) enrollment of participants who are Black, Indigenous and People of Colour (BIPOC) in heart failure randomized controlled trials between 2000 and 2020.

Proportion of RCTs reporting Race/Ethnicity data and percent enrollment of BIPOC per trial is shown for each date range, with error bars indicating standard error. Temporal trend testing performed with the Cochran Armitage and Jonckheere Terpstra Trend tests with p-values and trendline shown (2-tailed test, $\alpha = 0.05$).

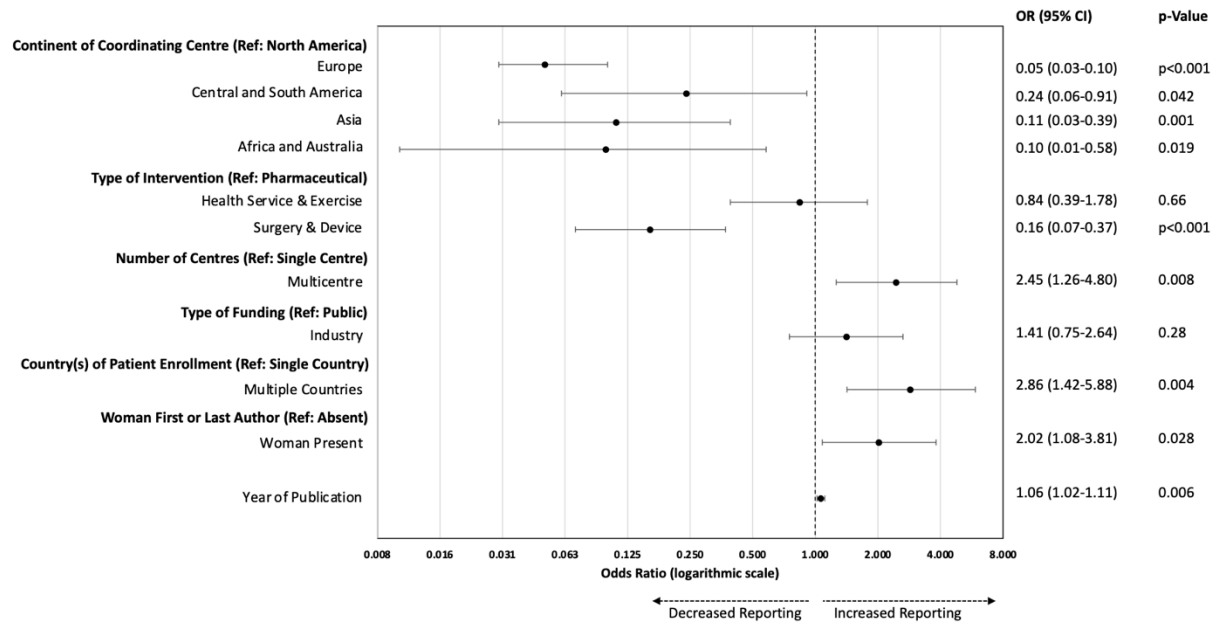


Figure 4. Forest plot of independent trial characteristics associated with the reporting of race and ethnicity data.

Analysis performed in heart failure randomized controlled trials published in high impact journals between 2000 and 2020 (n=414). Odds ratio (OR) with 95% confidence intervals (CI) and p-values are shown for each independent characteristic.

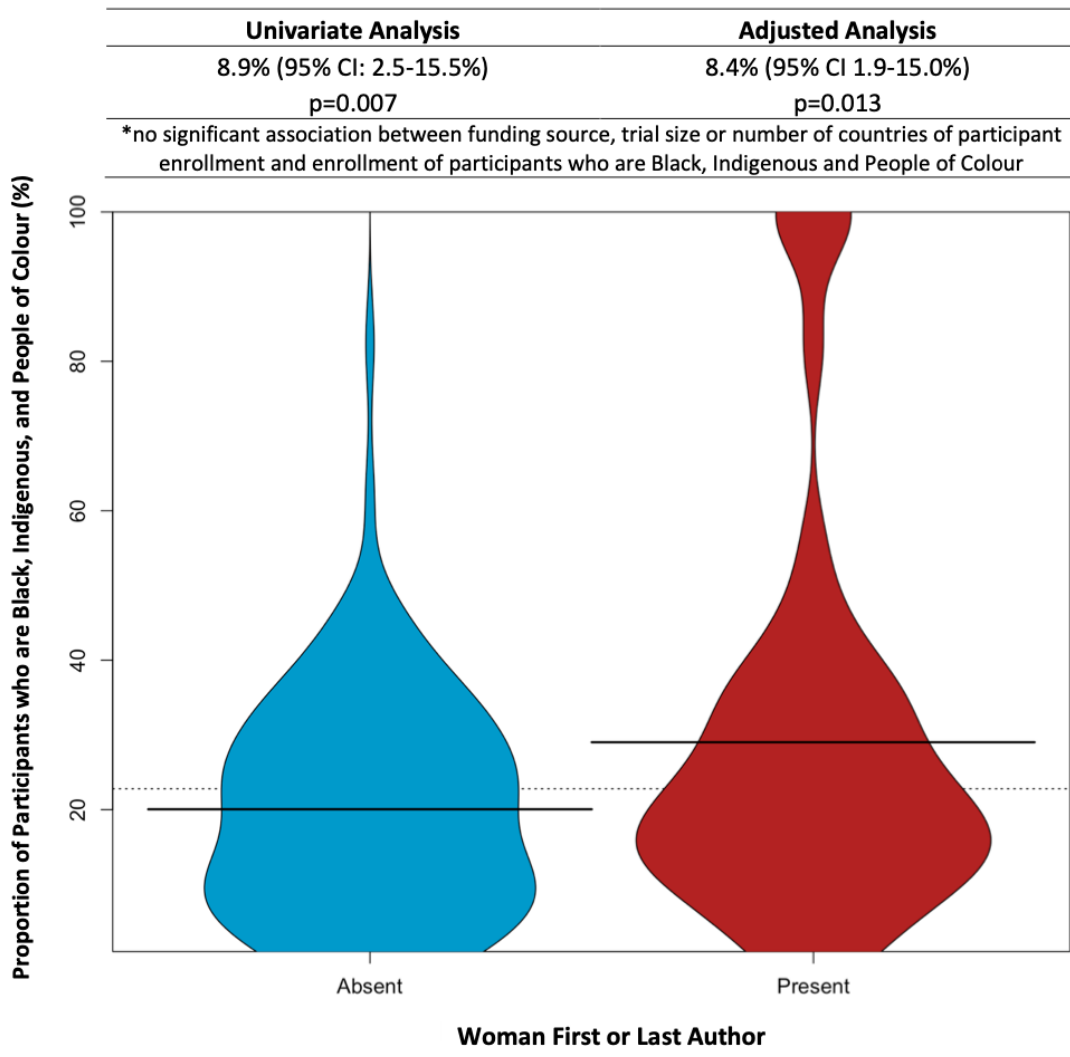
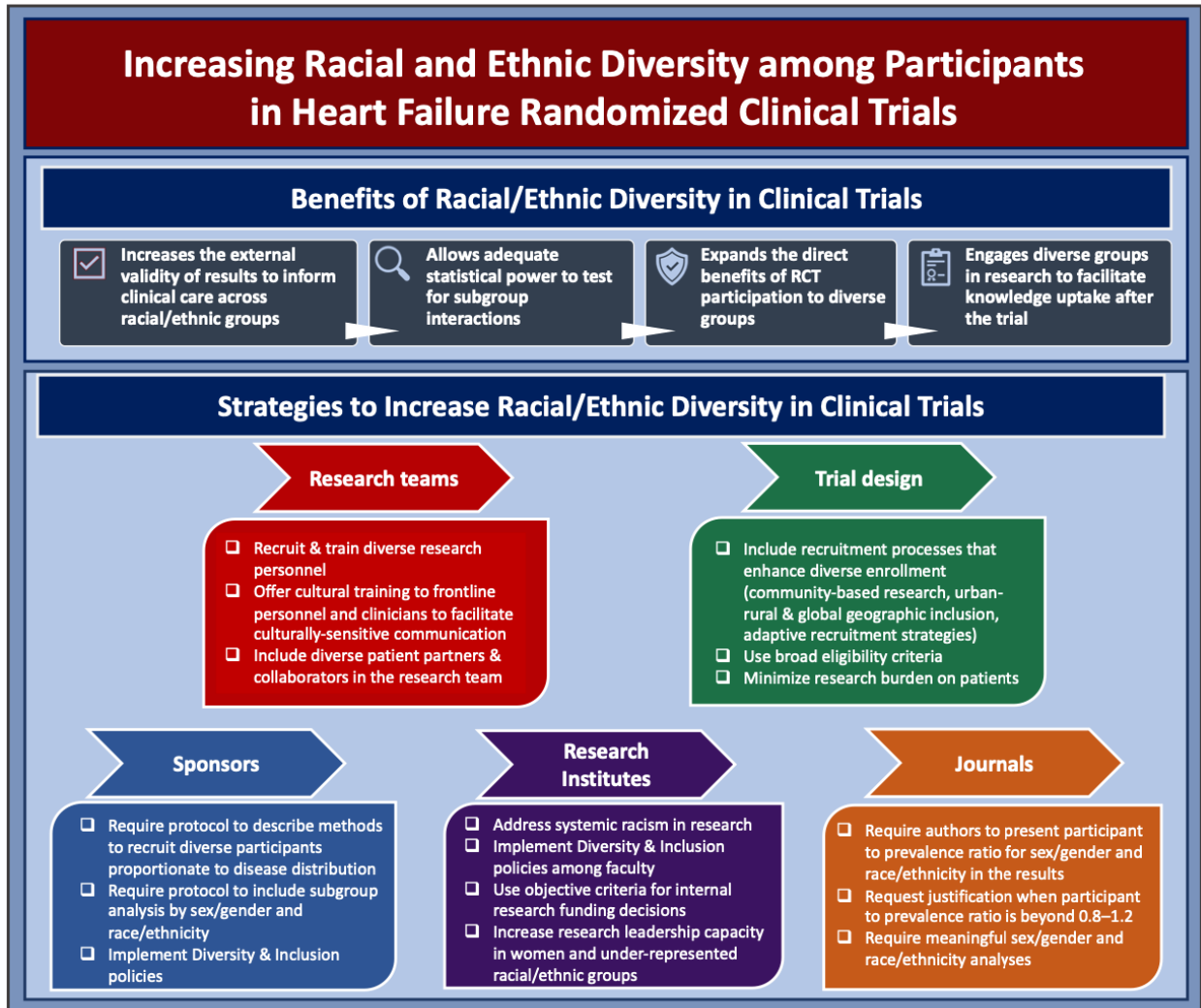


Figure 5. Density plot of the distribution of participants who are Black, Indigenous, and People of Colour (BIPOC).

Analysis performed in randomized controlled trials reporting race data (n=157) and stratified by whether a woman was one of the trial leaders (in first or last author position). Bold lines indicate the mean percentage of BIPOC in both groups and dotted line indicates average percentage of BIPOC across all trials. Univariate analysis estimates an 8.9% increase in proportion of BIPOC when a woman first or last author is present, decreasing to 8.4% when

adjusting for confounders (funding source, trial size, number of countries of participant enrollment, year of publication) CI indicates confidence interval.



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Figure 6. Recommendations to increase reporting of race/ethnicity data and to promote racial and ethnic diversity in heart failure clinical trials.

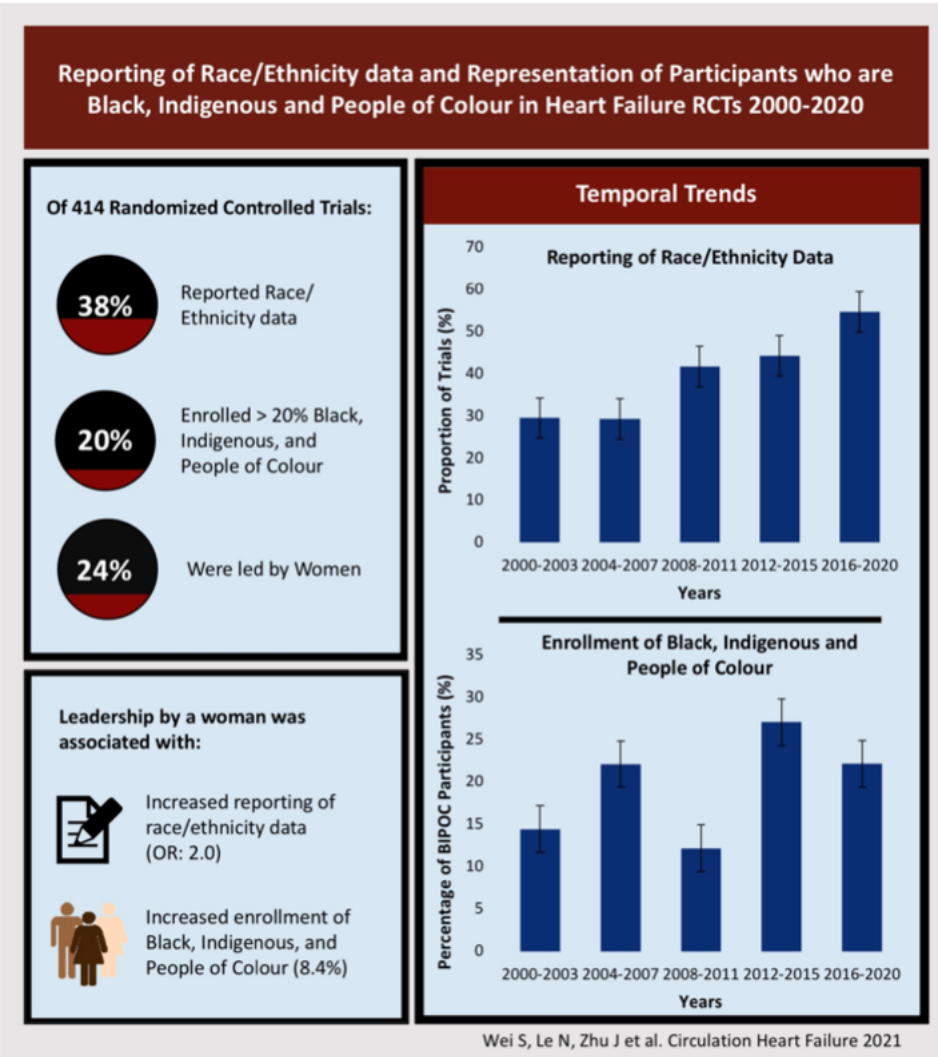


Figure 7. Temporal Trends and Trial Factors associated with Reporting of Race and Ethnicity data and Enrollment of Black, Indigenous and People of Colour in Heart Failure Randomized Controlled Trials Published Between 2000 and 2020. OR indicates odds ratio.

SUPPLEMENTAL MATERIAL

Supplemental Methods. Search Strategy

1. Heart failure.mp or Heart Failure/
2. Limit 1 to (English language or humans)
3. Limit 2 to yr =*2000 – Current*
4. Limit 3 to randomized controlled trial
5. Limit 4 to (meta-analysis or “review” or systematic reviews)
6. 4 not 5

Supplemental Table I. Reporting of Race and Ethnicity Data by RCTs Published in High-Impact Journals (n=414)

Journal	Total RCTs n=414	RCTs Reporting Race/Ethnicity Data n=157
American Journal of Respiratory and Critical Care Medicine	2 (0.5)	0 (0.0)
Annals of Internal Medicine	1 (0.2)	0 (0.0)
British Medical Journal	4 (1.0)	0 (0.0)
Circulation	62 (15.0)	24 (38.7)
Circulation Heart Failure	1 (0.2)	1 (100.0)
Circulation Research	5 (1.2)	2 (40.0)
European Heart Journal	40 (9.7)	6 (15.0)
European Journal of Heart Failure	109 (26.3)	17 (15.6)
European Respiratory Journal	1 (0.2)	0 (0.0)
Journal of the American Medical Association	29 (7.0)	22 (75.9)
Journal of the American Medical Association Cardiology	4 (1.0)	3 (75.0)
Journal of the American Medical Association Internal Medicine	7 (1.7)	7 (100.0)
Journal of the American College of Cardiology	87 (21.0)	32 (36.8)
The Lancet	21 (5.1)	14 (66.7)
The New England Journal of Medicine	41 (9.9)	26 (63.4)

Values are n(%); RCT indicates Randomized Controlled Trial.

Supplemental Table II. Multivariable Analysis of Trial Characteristics Associated with the Reporting of Race/Ethnicity Data in Heart Failure Randomized Controlled Trials (n=414)

	OR (95% CI)	p-VALUE
Continent of Coordinating Center		
North America	1.00 (Reference)	-
Europe	0.05 (0.03-0.10)	p<0.001
Central and South America	0.24 (0.06-0.91)	0.042
Asia	0.11 (0.03-0.39)	0.001
Africa and Australia	0.10 (0.01-0.58)	0.019
Type of Intervention		
Pharmaceutical	1.00 (Reference)	-
Health Service & Exercise	0.84 (0.39-1.78)	0.66
Surgery & Device	0.16 (0.07-0.37)	p<0.001
Number of centers		
Single Center	1.00 (Reference)	-
Multicenter	2.45 (1.26-4.80)	0.008
Type of Funding		
Public	1.00 (Reference)	-
Industry	1.41 (0.75-2.64)	0.28
Country(s) of Patient Enrollment		
Single Country	1.00 (Reference)	-
Multiple Countries	2.86 (1.42-5.88)	0.004

Woman First or Last Author

Absent	1.00 (Reference)	-
Present	2.02 (1.08-3.81)	0.028
Year of Publication	1.06 (1.02-1.11)	0.006

CI indicates confidence interval; OR indicates odds ratio.