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Enrollment of Older Patients, Women, and Racial and Ethnic Minorities in Contemporary Heart Failure Clinical Trials
A Systematic Review

Ayman Samman Tahhan, MD; Muthiah Vaduganathan, MD, MPH; Stephen J. Greene, MD; Gregg C. Fonarow, MD; Mona Fiuzat, PharmD; Mariell Jessup, MD; JoAnn Lindenfeld, MD; Christopher M. O'Connor, MD; Javed Butler, MD, MPH, MBA

IMPORTANCE Despite the importance of age, sex, and race/ethnicity representativeness in clinical trials, limited data exist regarding the enrollment trends of these groups in contemporary heart failure (HF) trials.

OBJECTIVE To characterize the representation of older patients, women, and racial and ethnic minorities in HF trials.

EVIDENCE REVIEW We performed a systematic search of HF trials enrolling more than 400 participants published between January 2001 and December 2016 using PubMed/Medline and ClinicalTrials.gov. A total of 118 trials enrolling a cumulative 215 508 patients were included. Trial findings were compared with large epidemiologic studies indexed to hospitalization status and ejection fraction.

FINDINGS Median number of participants per trial was 994 (interquartile range [IQR], 543-1899), enrolled from a median of 82 (IQR, 28-171) study sites. Overall, 94 trials (80%) enrolled patients with HF with reduced ejection fraction (HFrEF) exclusively. Mean (SD) age of trial participants was 65 (11) years (from 64 years in 2001 to 2004 to 65 years in 2013 to 2016), and 58 873 of 215 508 were women (27%; from 26% in 2001 to 2004 to 29% in 2013 to 2016); no significant temporal trends were observed ($P \geq .60$ for both). Chronic HF with preserved ejection fraction (HFpEF) trials enrolled older participants (mean [SD] age, 71 [7] years compared with 65 [11] years for HFrEF and 66 [12] years for acute HF [AHF] trials; $P = .01$). Corresponding mean ages in US epidemiologic studies were 69 years for HFrEF and 73 years for both patients with HFpEF and patients with AHF. The HFpEF trials had a higher proportion of women (n = 4940 of 8845 [56%]) compared with HFrEF (n = 34 397 of 143 538 [24%]) or AHF (n = 11 013 of 34 633 [32%]) ($P < .001$). Corresponding weighted proportions of women in HFpEF, HFrEF, and AHF trials in epidemiologic studies were 62%, 29%, and 50%, respectively. Distribution of racial/ethnic groups was reported in 55% (47%) of the trials; 22% of the participants were not white (n = 27 463 of 124 980), with significant increase over time from 13% in 2001 to 2004 (n = 5606 of 44 616) to 30% in 2013 to 2016 (8421 of 28073) ($P = .01$).

CONCLUSIONS AND RELEVANCE In contemporary HF trials, older patients and women are consistently underrepresented. Race/ethnicity data are reported in less than half of trials; when reported, such data show that enrollment of nonwhite patients increased over time.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Javed Butler, MD, MPH, MBA, Department of Medicine (L650), University of Mississippi, 2500 N State St, Jackson, MS 39216 (jbutler4@umc.edu).

Older patients, women, and racial and ethnic minorities carry a disproportionate burden of heart failure (HF) in the general population, but their enrollment in clinical trials has been lower than expected based on the prevalence of HF in these groups. These findings have raised specific concerns regarding the generalizability of HF trials.[1] Given important biological differences by age, sex,[2] and race/ethnicity,[3,4] the risks and benefits of tested therapies may be anticipated to differ based on differing demographic profiles. Furthermore, ensuring adequate representation of key demographic subsets concordant with the US HF population may also affect regulatory decision making for drug/device approval.[5]

In response, multiple efforts embedded within federally funded and industry-funded clinical trials have been directed to improve the recruitment of older patients, women, and racial and ethnic minorities.[6] Limited data exist to determine whether these efforts have been successful in improving representation across contemporary HF clinical trials, and to our knowledge, no studies have evaluated the representativeness of trials of HF with preserved ejection fraction (HFpEF).

Accordingly, we performed a systematic review of all published HF clinical trials from 2001 to 2016. Our objective was to determine enrollment patterns by age, sex, and race/ethnicity, to compare this demographic makeup with that of US epidemiologic studies of specific HF types, to examine temporal changes in these demographics, and to assess representation by key trial-level characteristics.

Key Points

Question How representative are contemporary heart failure (HF) trials with respect to age, sex, and race/ethnicity?

Findings In a systematic review of 118 HF clinical trials, the mean age of participants was 65 years, 27% were women, and there were no significant temporal changes in age and sex trends over time. Race/ethnicity distribution was reported in less than half of trials, and in trials with available data, enrollment of nonwhite patients increased steadily from 13% to 30% over time.

Meaning Differences in traditionally underrepresented patient groups between trials and epidemiologic studies persist but are less than previously reported. Enrollment of racial and ethnic minorities has improved over time but may be subject to reporting bias.

Methods

Identification of Clinical Trials

We performed a systematic search using 2 strategies to identify all HF clinical trials published between 2001 and 2016: (1) PubMed/MEDLINE query with the following limits: publication year, "heart failure," "trial*," and "randomized"; and (2) ClinicalTrials.gov query with the following limits: adult (18 years and older), interventional, phase II-IV, and "heart failure." The exclusion criteria included (1) phase I or pilot trials; (2) trials enrolling pediatric populations; (3) trials in which hospitals were the units of randomization; and (4) publications reporting secondary, interim, or post hoc analyses. To identify large trials more likely to inform clinical practice, and making the assumption that smaller trials largely represented single-center early-phase studies, we applied a size threshold to include only trials enrolling more than 400 patients. These selected larger trials represented approximately the top fifth of trials identified by the systematic query and enrolled about 80% of the overall population included in all HF trials. PRISMA guidelines were followed for all procedures and reporting. Two independent reviewers screened 5488 studies and selected studies for inclusion; a third reviewer resolved discordant assessments. A total of 118 published trials met inclusion criteria for this study (eTable 1 and eFigure 1 in the Supplement).

Data Abstraction

The following data were abstracted: (1) journal; (2) year of publication; (3) HF type (based on ejection fraction [EF] and hospitalization status); (4) trial intervention; (5) enrollment duration (estimated from starting and ending dates); (6) total sample size; (7) mean or median age; (8) proportion of women; (9) race and ethnicity (if reported); (10) number of participating centers; (11) number of countries; and (12) funding sources. For incomplete data fields, additional data were extracted from secondary publications identified using ClinicalTrials.gov, if available.

Mean or median age and proportion of enrolled women were extracted from trial publications. Data regarding race and ethnicity were collected (if available/reported) in accordance with the 2012 US Food and Drug Administration position statement.[7] Ethnicity was captured as Hispanic/Latino. Race was identified using 5 mutually exclusive categories: (1) American Indian or Alaskan Native; (2) Asian; (3) black or African American; (4) Native Hawaiian or other Pacific Islander; and (5) white. Nonwhite race refers to all trials reporting any data on race (some reported detailed racial information and others only reported the proportion of white participants).

Trials were divided into HF with reduced ejection fraction (HFrEF), HFpEF, or trials enrolling regardless of EF. Trials were also classified into acute and chronic (stable and ambulatory) subsets. Trials were divided into 3 categories based on primary intervention: (1) medications; (2) invasive therapies (intracoronary gene therapy, ultrafiltration, cardiac electronic implantable devices, left ventricular assist systems, intraaortic balloon pumps, or surgical procedures such as coronary artery bypass graft surgery); or (3) others (exercise training, continuous positive airway pressure, multidisciplinary management program, patient education, and behavioral or lifestyle interventions). Based on the ClinicalTrials.gov designations, funding source was categorized as (1) industry; (2) government; or (3) university or other nonprofit or nonfederal organizations. Government funding was further classified into those funded by National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) and non-US agencies. Regions were divided into (1) exclusively North America; (2) exclusively Western Europe; (3) exclusively outside of North America and Western Europe, ie, rest of the world; and (4) mixed/multiregional. Enrollment rates, expressed as patients per site per month, were estimated based on the reported study duration (completion dates minus start dates).

Comparative Data Sources

We compared our database with historical data from Heiat et al,[8] which included HF trials conducted between 1985 and 1999. We

further contextualized these trial-level patterns with epidemiologic data in the United States. Specifically, to most closely mirror target populations of HF clinical trials, we extracted relevant comparator data (weighted for sample size) from large registries or observational studies of patients hospitalized for HF,[9-11] stable outpatients with HFrEF,[12,13] and stable outpatients with HFpEF.[14-17] We derived weighted mean for age and proportion of women by multiplying the mean of each study by a number (weight) based on the study's relative size to the total studies included in each specific HF phenotype.

Statistical Analysis

Trials were assigned to four 4-year periods based on publication date (2001-2004, 2005-2008, 2009-2012, and 2013-2016). Continuous variables are described as mean and standard deviation or as median and interquartile range (IQR), and categorical variables as No. (%). Mean age and proportion of women and various racial/ethnic groups were calculated indexed to sample size of each trial given varying sample sizes across trials. Spearmen rank correlation coefficients were used to define the associations between trial-level mean age, proportion of women, and nonwhite race/ethnicity. Categorical variables were compared using χ^2 testing. To identify differences in quantitative characteristics across nominal categories, we used the Kruskal-Wallis test and Bonferroni adjusted post hoc pairwise comparisons to maintain the family-wise error at $\alpha = .05$. We determined the association between the proportion of demographic subsets enrolled in each trial and enrollment rate (which was log-transformed given skewed distribution). To test for a trend in demographic characteristics of the patient samples across our study period, we used simple linear regression models using year of publication as the independent variable. The dependent variables were the mean age of participants, the proportion of women, and the proportion of underrepresented minority; each model was adjusted for the sample size per trial. We also determined the correlation between the proportion of demographic subsets (percentage of women or percentage of underrepresented minority) and enrollment rate. Analyses were performed with IBM, version SPSS 23 (IBM Corporation), and a 2-sided *P* value less than .05 was considered statistically significant.

Results

General Characteristics

A total of 118 clinical trials that cumulatively enrolled 215 508 patients were included. Trial-level characteristics of HF trials are shown in **Table 1**. Approximately half of HF trials (51%) were conducted in multiple regions. North America sites were involved in 91% of multiregional trials. The median number of participants per trial was 994 (IQR, 543-1899) from a median of 82 participating sites (IQR, 28-171) per trial. Only 16 trials investigated therapies for acute HF and 4 tested therapies in HFpEF. Trends in age, sex, and race/ethnicity in HF trials over time are summarized in **Figure 1**.

Trends in the Enrollment of Older Patients

The mean (SD) age of trial participants was 65 (11) years. Thus, approximately 16% of enrolled participants were older than 76 years (assuming a normal distribution). Overall, very few trials provided information on age distribution and participation of older patients. There was no significant change in age of participants over time (mean, 64 years in 2001-2004 vs mean, 65 years in 2013-2016; *P* = .60; Figure 1A; eFigure 2A in the Supplement). Chronic HFpEF trials enrolled significantly older participants with mean (SD) age of 71 (7) years compared with HFrEF trials (mean [SD] age, 65 [11] years) and acute HF trials (mean [SD] age, 66 [12] years) (*P* = .01). Corresponding weighted mean ages of patients with chronic HFpEF, patients with chronic HFrEF, and patients with acute HF in US epidemiologic studies were 73 years, 69 years, and 73 years, respectively (**Table 2**). Trials conducted exclusively in North America (mean [SD] age, 63 [12] years) and multiregional trials (mean [SD] age, 65 [11] years) enrolled younger patients than trials conducted in Western Europe (mean [SD] age, 67 [11] years) (*P* = .01) (Table 2). Enrollment rate was not associated with the mean age of the enrolled cohort ($\rho = 0.13$, *P* = .18).

Trends in the Enrollment of Women

All trials reported the proportion of women, which overall represented 27% of enrolled participants (n = 58 873 of 215 508; ranging from 10% to 60%). The proportion of women enrolled in HF clinical trials did not change significantly from 2001 to 2004 (26%; n = 14 792 of 57 024) to 2013 to 2016 (29%; n 13 522 of 46 650) (*P* = .61; eFigure 1B and eFigure 2B in the Supplement). Chronic HFpEF trials had a significantly higher proportion of women (56%; n = 4940 of 8845) compared with HFrEF (24%; n = 34 397 of 143 538) or acute HF (32%; n = 11 013 of 34 633) (*P* < .001 for comparison). Corresponding weighted proportions of women of patients with chronic HFpEF, patients with chronic HFrEF, and patients with acute HF in US epidemiologic studies were 62%, 29%, and 50%, respectively, which were consistently higher than corresponding proportions enrolled in HF trials. Trials conducted in North America enrolled a greater proportion of women (32%; n = 8597 of 26 670) compared with trials conducted in Western Europe (26%; n = 5228 of 20 193) or multiregional trials (27%; n = 39 602 of 149 290) (*P* = .003 for comparison). The proportion of women was significantly higher in NIH/NHLBI-funded trials (n = 12) compared with other funding mechanisms, including non-US government-funded trials (36% vs 27%; *P* = .004). When examining trends in enrollment of women by primary funding mechanisms of trials, the proportion of women appeared to increase in government-sponsored trials over time (eTable 2 in the Supplement). A higher proportion of women was observed in trials testing nondrug, noninvasive therapies (32%; n = 6225 of 19 019) compared with drug (27%; n = 44 950 of 165 612) or invasive therapies (25%; n = 6698 of 27 213), *P* = .05 (Table 2). A higher mean age of participants in HF trials was significantly associated with higher enrollment of women ($\rho = 0.27$, *P* = .004; eFigure 3A in the Supplement). A higher proportion of women enrolled was significantly associated with enrollment rate ($\rho = 0.33$; *P* = .004; **Figure 2**).

Trends in the Enrollment of Racial/Ethnic Minorities

Reporting of race/ethnicity data in HF trials was available in only 55 trials (47%). Among trials reporting race/ethnicity data, only 37% reported primary outcome by race/ethnicity. No significant temporal changes in race/ethnicity reporting were observed during the study period (14 studies in 2001 to 2004 compared with 12 studies in 2013 to 2016; *P* = .13). Race/ethnicity data of any kind were reported in 72% of trials conducted exclusively in NA, 56% of multi-

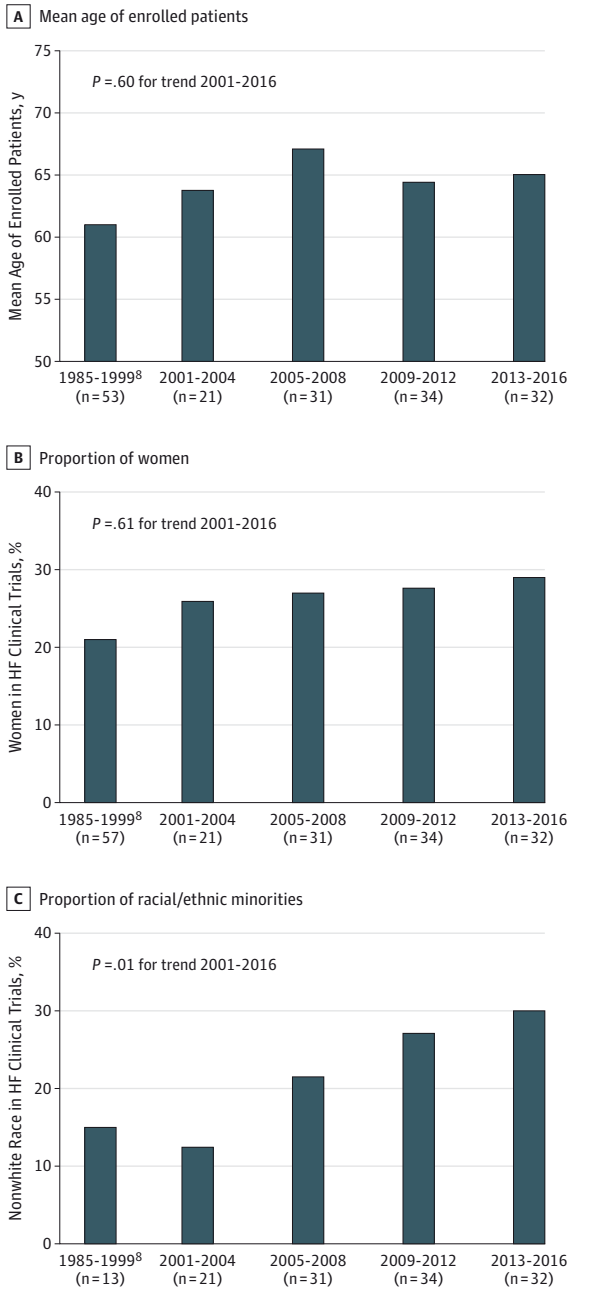
Table 1. Trends in Age, Sex, and Race/Ethnicity of Contemporary Clinical Trials of Heart Failure Over the Last 16 Years

Characteristic	% Median (Range)					*P* Value
	2001-2004	2005-2008	2009-2012	2013-2016	2001-2016	
Trials, No.	21	31	34	32	118	NA
Total participants, No.	57 024	59 902	51 932	46 650	215 508	NA
Participants per trial, median (IQR)	1141 (469-4515)	1023 (610-2426)	941 (550-1820)	920 (561-1336)	994 (543-1899)	.05
Weighted age, mean (SD)	64 (12)	67 (10)	64 (11)	65 (11)	65 (11)	.60
Weighted women	26 (16-49)	27 (16-60)	28 (15-53)	29 (10-52)	27 (10-60)	.61
Reporting nonwhite race, No.	14	12	17	12	55	NA
Nonwhite, all trials	12.5 (1-100)	22 (6-85)	28 (0.2-61)	30 (6-100)	22 (0.2-100)	.01
Nonwhite, trials without race-based selection	10 (1-33)	22 (6-85)	28 (0.2-61)	29 (6-46)	21 (1-85)	.005
Reporting black, No.	10	8	14	8	40	
Black, all trials	9 (1-100)	13 (6-46)	13 (0-39)	6 (0-25)	10 (0-100)	.33
Black, trials without race-based selection	6 (1-33)	13 (6-46)	13 (0-39)	6 (0-25)	9 (0-46)	.79
Reporting Asian, No.	4	0	4	5	13	
Asian, all trials	0.9 (0-2)	NA	17.2 (8-25)	22.4 (14-100)	14.1 (0-100)	.03
Asian, trials without race-based selection	0.9 (0-2)	NA	17.2 (8-25)	20.2 (14-25)	14.1 (0-25)	.04
Reporting Native Hawaiian or Pacific Islander, No.	3	0	1	1	5	NA
Native Hawaiian or Other Pacific Islander	0.1 (0-0)	NA	0 (0-0)	0 (0-0)	0.02 (0-0.1)	.76
Reporting American Indian or Alaskan Native, No.	4	0	4	5	13	NA
American Indian or Alaskan Native	3 (0-6)	0 (0-0)	6 (3-16)	9 (0-11)	6 (0-16)	.12
Reporting ethnicity, No.	4	3	7	1	15	
Hispanic, No. (%)	283 (7)	505 (27)	621 (5)	154 (12)	1563 (8)	.93
Location, No. (%)						
Rest of the world	0	1 (3)	0	5 (16)	6 (6)	.09
Multiregional	9 (47)	14 (48)	16 (52)	18 (56)	57 (51)	
North America	8 (42)	9 (31)	8 (26)	4 (13)	29 (26)	
Western Europe	2 (11)	5 (17)	7 (23)	5 (16)	19 (17)	
Funding, No. (%)						
Government	3 (16)	4 (13)	10 (29)	6 (19)	23 (20)	.25
University/organization	1 (5)	6 (19)	8 (24)	4 (13)	19 (16)	
Industry	15 (79)	21 (68)	16 (47)	22 (69)	74 (64)	
HF setting						
Chronic HF	16 (76)	28 (90)	31 (91)	27 (84)	102 (86)	.38
Acute HF	5 (24)	3 (10)	3 (9)	5 (16)	16 (14)	
Chronic HF type, No. (%)						
HF with reduced EF	15 (71)	24 (77)	31 (91)	24 (75)	94 (80)	.28
HF with preserved EF	0	2 (6)	0	2 (6)	4 (3)	
HF regardless of EF	6 (29)	5 (16)	3 (9)	6 (19)	20 (17)	
Intervention, No. (%)						
Invasive	5 (24)	6 (19)	10 (29)	8 (25)	29 (25)	.74
Drug	13 (62)	18 (58)	14 (41)	18 (56)	63 (53)	
Nondrug, noninvasive	3 (14)	7 (23)	10 (29)	6 (19)	26 (22)	

Abbreviations: EF, ejection fraction; HF, heart failure; IQR, interquartile range.

regional trials, 16.7% in trials conducted in rest of the world, and 0% in trials conducted exclusively in Western Europe or rest of the world. Overall, North American sites were involved in 93% of trials reporting race/ethnicity data. Regional variation in reporting detailed race/ethnicity data is illustrated in eTable 3 in the Supplement. In trials with reported race/ethnicity information, nonwhite race/ethnicity constituted 21% of enrolled participants (n = 27 463 of 124 980). In trials with reported data and that did not apply race-specific inclusion criteria, black and Hispanic patients represented 9% of all patients (n = 9421 of 106 721) and 8% of all patients (n = 1563 of 18 890), respectively, during the study period. Proportion of enrolled nonwhite patients in HF trials increased steadily from 13% in

Figure 1. Patients Enrolled in Heart Failure (HF) Clinical Trials Over Time



A, Mean age of patients enrolled in heart failure clinical trials over time. B, Proportion of women enrolled in HF clinical trials over time. C, Proportion of racial/ethnic minorities enrolled in HF clinical trials over time.

2001 to 2004 to 30% in 2013 to 2016 (*P* = .01) (Figure 1C). Trends in race/ethnicity over time are displayed in Table 1. The proportion of nonwhite race enrollment was similarly low across all HF types (Table 2). Trials funded by universities or independent organizations enrolled the highest proportion of nonwhite race/ethnicity (61% [n = 2245 of 3681]) compared with 27% (n = 5831 of 21 919) in government-sponsored and 20% (n = 19 386 of 99 380) in industry-sponsored trials (*P* = .003 for comparison). Overall, the number of NIH trials increased from 3 trials in 2001 to 2008 to 9 trials in 2009 to 2016. The proportion of nonwhite race was higher in NIH/NHLBI-funded trials compared with other funding mechanisms (31% vs 20%; *P* = .02). However, over time, enrollment of patients of nonwhite race only increased in industry-sponsored trials (from 11% [n = 4568 of 41 026] in 2001-2004 to 31% [n = 6844 of 22 155] in 2013-2016), with unchanged trends in trials with other primary funding mechanisms (eTable 2 in the Supplement). However, the increase in nonwhite race/ethnicity enrollment was mainly driven by increased Asian enrollment (1% [n = 148 of 16 112] in 2001-2004 to 20% [n = 3676 of 18 149] in 2013-2016) and to a lesser extent enrollment of American Indian or Alaskan Native (increased from 3% [416 of 16 112] in 2001-2004 to 9% [1677 of 18 149] in 2013-2016); black race/ethnicity decreased from 8% (n = 2804 of 36 902) in 2001 to 2004 to 5% (n = 989 of 20 388) in 2013 to 2016.

Trials investigating nondrug, noninvasive therapies had higher enrollment of nonwhite race/ethnicity compared with drug or invasive therapies. Trials conducted exclusively in North America enrolled 39% nonwhite race/ethnicity (n = 7020 of 18 196) compared with 19% in multiregional trials (n = 19 566 of 104 685) (*P* = .001) (Table 2). Trials that enrolled greater proportions of nonwhite race tended to enroll younger patients (eFigure 3B in the Supplement) and higher proportions of women (eFigure 3C in the Supplement). Although enrollment rate was not associated with the proportion of nonwhite race/ethnicity enrolled in each trial (ρ= 0.12; *P* = .36), it did appear to associate with the proportion of enrolled black patients (ρ= 0.39; *P* = .01; n = 39 trials) and nonsignificantly with the proportion of Hispanic patients (ρ= 0.48; *P* = .07; n = 15 trials).

Trends in Enrollment of Older Patients, Women, and Racial/Ethnic Minorities in North American HF Trials

Among 29 trials exclusively conducted in North America, no significant changes over time for mean age of enrolled cohorts were observed (eTable 4 in the Supplement). Compared with epidemiologic studies in the United States, mean (SD) age was lower in HFrEF trials (62 [12] years vs 69 years), HFpEF trials (71 [7] years vs 78 years), and acute HF trials (62 [14] years vs 73 years) (**Table 3**).[14-22] The proportion of women increased slightly from 31% in 2001 to 2004 to 37% in 2013 to 2016, although this trend was not statistically significant (*P* = .09 for trend; eTable 4 in the Supplement). The proportion of women enrolled in HF clinical trials was similar to the estimated proportion of women in US epidemiologic studies in chronic HFrEF and HFpEF; women were underrepresented in acute HF (31% in clinical trials vs estimated 50% in epidemiologic data from the United States). The proportion of nonwhite race in North American trials remained unchanged during the study period (eTable 3 in the Supplement; Table 3). Representation of key demographic subsets in any HF trials recruited exclusively or partially from North America is provided in eTable 5 in the Supplement.

Discussion

This systematic review highlights important patterns and trends in representation of traditionally underrepresented demographic subsets in contemporary HF clinical trials and highlights discrepancies in the demographics of populations included in clinical trial cohorts

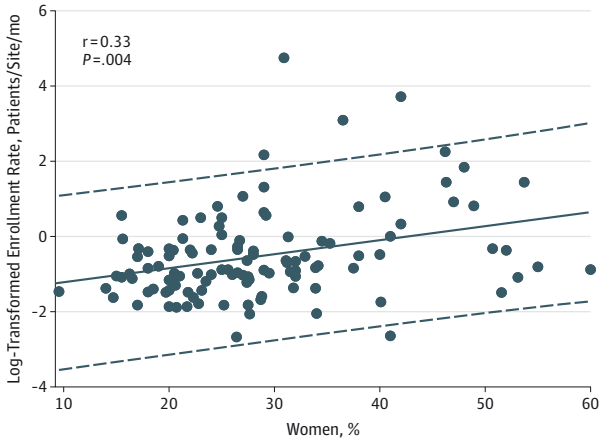
Table 2. Representation in Clinical Trials of Heart Failure Based on Key Trial-Level Characteristics

Characteristic	Age, Mean (SD) [range]	*P* Value[a]	Women, No. (%); Range	*P* Value[a]	URM, No. (%); Range	*P* Value[a]
HF type						
Chronic HFrEF	65 (11) [57-77]	.01	34 397 (24); 10-54	<.001	18 420 (24); 0-100	.59
Chronic HFpEF	71 (7) [67-76]		4940 (56); 52-60		382 (11); 11-11	
Acute	66 (12) [55-72]		11 013 (32); 23-42		5916 (18); 5-44	
Funding						
Government	62 (11) [55-72]	.09	9375 (32); 15-52	.17	5831 (27); 9-51	.003
Universities/organization	67 (11) [57-76]		4695 (31); 16-54		2245 (61); 15-100	
Industry	65 (11) [57-76]		44 520 (26); 10-60		19 386 (20); 0-100	
NIH/NHLBI						
Non-NIH/NHLBI	65 (11) [55-76]	.14	50 873 (27); 14-60	.004	19 997 (20); 0-100	.02
NIH/NHLBI	64 (12) [56-73]		6297 (36); 20-52		5354 (31); 11-61	
Intervention						
Invasive	64 (11) [56-73]	.31	6698 (25); 14-35	.05	1340 (19); 9-40	.02
Drug	65 (11) [55-76]		44 950 (27); 15-60		21 797 (20); 0-100	
Nondrug, noninvasive	66 (12) [57-76]		6225 (32); 10-54		4326 (42); 11-85	
Primary region of enrollment						
Rest of the world	60 (12) [55-66]	.01	2610 (37); 25-51	.003	NA	.001
Multiregional	65 (11) [58-76]		39 602 (27); 10-60		19 566 (19); 0-44	
North America	63 (12) [56-73]		8597 (32); 16-54		7020 (39); 10-100	
Western Europe	67 (11) [57-76]		5228 (26); 15-52		NA	

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; NIH, National Institutions of Health; NHLBI, National Heart, Lung, and Blood Institute; URM, underrepresented minorities.

[a] *P* values compare age, proportion of women, and underrepresented minorities across key trial-level subgroups (HF type, funding, intervention, and region).

Figure 2. Association Between Proportion of Enrolled Women and Log-Transformed Enrollment Rate



Enrollment rates, expressed as patients per site per month, were estimated based on the reported study duration (completion dates minus start dates). Enrollment rate was log-transformed given skewed distribution.

vs registry and community-based studies. In our analysis, older patients and women were consistently underrepresented across the spectrum of different HF clinical trial types over the last 16 years. Overall race/ethnicity reporting was poor (<50% of trials reporting any data) and variably complete. Among trials reporting race/ethnicity data, significant increases in the enrollment of nonwhite participants were observed over time. Representation in race/ethnicity varied significantly by primary region of enrollment, trial funding mechanism, and therapy tested. Notably, increased relative enrollment of women and certain racial/ethnic minorities was associated with improved trial enrollment rate.

Snapshot of Registry and Community-based HF Studies in the United States

Based on data from large-scale inpatient registries and epidemiologic surveys conducted in the United States,[8,9,18,23] mean age of patients with HF is 72 to 74 years, while 47% to 52% are women, and 26% to 34% identify as races/ethnicities other than white (18%-20% overall as black). Prior studies[1,8,19-21] exploring the representativeness of HF trial populations did not include appropriate comparators by EF enrollment criteria or exclusively assessed trials of HFrEF. Indeed, data generated from inpatient registries suggest that patients with HFpEF have an especially distinct demographic profile, characterized by older age (mean age, 74-78 years), higher proportion of women (62%-68%), and lower proportion of patients identifying as black (15%-17%).[9-11] Additionally, some epidemiologic studies excluded patients with prevalent HF; therefore, our estimates may not accurately represent the actual population with HF. These epidemiologic studies may also face similar enrollment challenges as trials (eg, eligibility criteria and requiring informed consent), oversample select populations, and be restricted to specific communities, and thus may not be ideal population-level comparators. Demographic estimates from community-based studies of stable outpatients with HFrEF and stable outpatients with HFpEF[14-17] may be less reliable because many of these observational studies included patients with incident (rather than prevalent) HF. With these

Table 3. Representation of Key Demographic Subsets in Heart Failure Trials Exclusively Conducted in North America[a]

Trial Characteristic	Age, Mean (SD), y	US Registry/ Community-based Comparator, years	No. (%)					
			Proportion of Women	US Registry/ Community-based Comparator	Nonwhite Race/ Ethnicity	Black Race/ Ethnicity	Asian Race/ Ethnicity, %	Other Race/ Ethnicity, %[b]
Chronic HFrEF	62 (12)	69	5632 (30)	29	4373 (41)	3394 (33)	0.6	2
Chronic HFpEF	71 (7)	73	4940 (56)	62	NA	NA	0.6	2
Chronic HF regardless of EF	67 (11)	NA	2377 (39)	NA	2022 (36)	969 (28)	0.6	2
Acute HF	62 (14)	73	588 (31)	50	625 (34)	432 (30)	0.6	2

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

[a] We extracted relevant real-world US comparator data (weighted for sample size) from large registries or observational studies of patients hospitalized for HF,[14-16] stable outpatients with HFrEF,[17] stable outpatients with HFpEF,[18-21] and stable outpatients with HF (without specific criteria for EF).[22] Given significant variability across selected epidemiological studies, real-world estimates of percentage of underrepresented minorities were not provided.

[b] Includes American Indian, Alaskan Native, Native Hawaiian, or Pacific Islander.

caveats in mind, our findings support the presence of discrepancies in key demographics between trials and EF-specific data sources from registries and community-based studies but suggest these differences are more modest than previously reported.

Potential Barriers to Enrollment of Older Participants

Trial-specific factors are also associated with lower rates of enrollment of older patients in clinical trials owing to strict inclusion/exclusion criteria, trial duration, or intensity of follow-up and testing.[22] For instance, older patients are more likely to have comorbidities that make them ineligible for HF clinical trials or unable to participate with follow-up requirements. The lack of financial and social support for the participation of older patients may limit their participation in clinical trials. Characterizing and addressing limitations to enrollment are vital to strategically improving the design and representation of all age groups in HF clinical trials.

Finding Sex Balance in Contemporary HF Trials

Only 28% of the participants were women, with marked variation based on type of HF. These proportions were lower than the estimated proportions of women in studies of corresponding HF types in community and registry settings. Our trial-level data are consistent with a previous study that showed that the representation of women in 14 HF clinical trials was the lowest (29%) among the data used to build American Heart Association guidelines compared with representation in other cardiovascular trials published between 1970 and 2006.[24] We found that enrollment of women differed based on funding source, clinical indication, and trial location. Specific NIH guidelines targeting this issue may have influenced the inclusion of women in HF clinical trials, especially after the approval of the Revitalization Act by NIH in 1993 that required the inclusion of women in every clinical trial supported by federal funding.[25] Although federal agencies have conducted large cardiovascular clinical trials restricted to women, to our knowledge, none yet have been conducted in patients with HF.

Reporting and Representation of Race and Ethnicity

Race/ethnicity was poorly documented in published reports from even HF clinical trial experiences published after 2013. Less than 50% of trials reported data regarding the distribution of race/ethnicity categories. As such, trials with available information may be subject to important reporting bias. Therefore, our estimates may overestimate the actual proportion of nonwhite race participants. Additionally, specific race/ethnicity enrollment in multiregional trials stratified by geographic location per trial is not typically published. A 2013 study by Zhang et al[26] of cardiovascular clinical trials selected from 3 major journals between 1997 and 2010 showed that among trials reporting race/ethnicity information, enrolled proportions were 7% for black individuals and 4% for Asian individuals, compared with 10% and 14% in our analysis. Another 2017 study[20] of 25 HFrEF clinical trials found that only 6% of participants were black. The inclusion of industry-sponsored trials with increasing global sites (many of which are located in Asia) may explain the relative increase in Asian enrollment over time while representation of black individuals remains poor. The pattern of rapid globalization in contemporary HF clinical trials coupled with the increase in selection of sites in regions outside of the United States may have influenced the trends seen in nonwhite race representation.[27,28]

Our data suggest that dedicated efforts to increase enrollment of racial/ethnic minority participants in HF clinical trials funded by the NIH/NHLBI have been successful.[6] Although guidelines and many journals support the publication of subgroup analyses by key demographic factors, more than 60% of reviewed studies failed to report the primary outcome by race/ethnicty. While most trials are not adequately powered to assess racial/ethnic differences in outcomes, differential treatment effects by race/ethnicity have been observed in prior HF trials, and subgroup analyses have the potential to generate hypotheses for future study.

Improving Representation in Contemporary HF Trials: A Path Forward

First, future studies should be required to provide adequate description of age, sex, and race/ethnicity. Reporting of race/ethnicity distribution should be complete and in accordance with the 2012 US Food and Drug Administraton position statement.[7] Second, renewed efforts to improve representative patient participation, with incentives to accomplish this goal, are needed for North American sites in global HF clinical trials. The observed patterns in globalization of contemporary trials serve as a variable that intersects with many important factors, such as race/ethnicity, diet, socioeconomic status, lifestyle patterns, and medical care delivery. Parallel studies evaluating emerging therapies confined to individual regions may be required to more clearly establish generalizability.

Third, improved site-based enrollment of underrepresented minorities may require concerted, multilevel interventions. Site selection in areas with high proportions of underrepresented minority patients may enhance racial and ethnic representativeness. Goals of specific enrollment targets at each step of trial progress have been successful in certain trial experiences (such as the Systolic Blood Pressure Intervention Trial)[29] to improve representation. Perhaps contrary to belief, HF trials in our experience that enrolled higher proportions of women and certain race/ethnic minorities had higher relative enrollment rates. Collaboration between investigators, funding agents, and community members are necessary to ensure broad access to trials and sufficient applicability of their results.

Limitations

There are several limitations to this work. Primarily, we relied only on published trials, which may introduce publication bias. Additionally, in many trials, the information regarding race/ethnicity was inadequate, which may overestimate the proportion of nonwhite participants. Furthermore, while most trials are not adequately powered to assess racial/ethnic differences in outcomes, differential treatment effects by race/ethnicity have been observed in prior HF trials, and subgroup analyses have the potential to generate hypotheses for future study.

Conclusions

This systematic review of published HF clinical trials describes contemporary patterns of enrollment of key demographic subsets. We demonstrate that discrepancies in traditionally underrepresented patient groups between trials and EF-specific registry/community studies data sources persist but appear more modest than previously reported. Targeted efforts to enroll representative proportions of these cohorts are important now more than ever. Although improvements in enrollment of racial and ethnic minorities potentially reflect successful federal and industry-based initiatives, overall, race/ethnicity reporting remains poor and incomplete. This compromises the ability to identify drivers of low enrollment of minorities and assess trial generalizability. Continued efforts to improve reporting of age, sex, and race/ethnicity data within HF clinical trials and enhance the representativeness of trial populations are needed.

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Author Affiliations: Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine, Atlanta, Georgia (Tahhan); Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, Massachusetts (Vaduganathan); Duke Clinical Research Institute and Division of Cardiology, Duke University Medical Center, Durham, North Carolina (Greene, Fiuzat); Ahmanson-University of California, Los Angeles Cardiomyopathy Center, University of California, Los Angeles (Fonarow); Section Editor, *JAMA Cardiology* (Fonarow); Fondation Leducq, Paris, France (Jessup); Vanderbilt Heart and Vascular Institute, Nashville, Tennessee (Lindenfeld); Inova Heart and Vascular Institute, Falls Church, Virginia (O'Connor); Department of Medicine, University of Mississippi, Jackson (Butler).

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Concept and design: Samman Tahhan, Vaduganathan, Greene, Fonarrow, O'Connor, Butler.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Samman Tahhan, Vaduganathan, Butler.
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