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Underrepresentation of Women in Reduced Ejection Heart Failure Clinical Trials With Improved Mortality or Hospitalization

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Abstract

BACKGROUND—There are established sex-specific differences in heart failure with reduced ejection fraction (HFrEF) outcomes. Randomized clinical trials (RCTs) based on cardiovascular outcome benefits, typically either reduced cardiovascular mortality or hospitalization for heart failure (HHF), influence current guidelines for therapy.

OBJECTIVES—The authors evaluate the representation of women in HFrEF RCTs that observed reduced all-cause or cardiovascular mortality or HHF.

METHODS—We queried Cumulative Index to Nursing and Allied Health Literature, Excerpta Medica dataBASE, Medical Literature Analysis and Retrieval System Online, and PubMed for HFrEF RCTs that reported a statistically significant benefit of intervention resulting in improved mortality or HHF published from 1980 to 2021. We estimated representation using the participation-to-prevalence ratio (PPR). A PPR of 0.8 to 1.2 was considered representative.

RESULTS—The final analysis included 33 RCTs. Women represented only 23.2% of all enrolled participants (n = 24,366/104,972), ranging from 11.4% to 40.1% per trial. Overall PPR was 0.58, with per-trial PPR estimates ranging from 0.29 to 1.00. Only 5 trials (15.2%) had a PPR of women representative of the disease population. Representation did not change significantly over time. The proportion of women in North American trials was significantly greater than trials

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conducted in Europe ($P = 0.03$). The proportion of women was greater in industry trials compared to government-funded trials ($P = 0.05$).

CONCLUSIONS—Women are underrepresented in HFrEF RCTs that have demonstrated mortality or HHF benefits and influence current guidelines. Representation is key to further delineation of sex-specific differences in major trial results. Sustained efforts are warranted to ensure equitable and appropriate inclusion of women in HFrEF trials.

Keywords

heart failure; heart failure reduced ejection fraction; representation; women

Clinical trials have played a pivotal role in advancing the treatment of heart failure and improving patient outcomes. Randomized clinical trials (RCTs) of new therapies in heart failure with reduced ejection fraction (HFrEF) typically evaluate cardiovascular (CV) outcome benefits through the key endpoints of CV mortality or hospitalization for heart failure (HHF).[1] HFrEF RCTs that observe a significant benefit in CV mortality or HHF are likely to influence the HFrEF practice landscape.[2]

The lifetime risk of HFrEF for men and women is 1 in 5, and the incidence increases disproportionately with age for women compared to men.[3,4] There are established sex differences in CV physiology, drugs' pharmacokinetics, pharmacodynamics, effectiveness, safety, and outcomes.[5–7] For example, women with HFrEF have more symptoms and signs, poorer health-related quality of life, and greater functional and psychological impairment than men.[7] Certain traditional risk factors such as diabetes portend a worse prognosis in women with HFrEF compared to men, and sex-specific risks such as peripartum cardiomyopathy, breast cancer therapy, and stress cardiomyopathy make HFrEF in women a unique disease process.[6] CV trials have also suggested modification of treatment effect based on sex, with women experiencing differential outcomes compared with men in prior RCTs evaluating guideline-directed medical therapy.[8,9] Therefore, adequate representation of women is crucial in HFrEF trials.

Prior work has reported that trials with statistically significant results had a significantly lower representation of women than those that did not.[10] Given that underrepresentation of women in CV trials has been documented, we extended prior work by only analyzing HFrEF trials that reduced mortality or heart failure hospitalizations and explored factors that may influence lower trial representation in this subgroup. Additionally, these trials are more likely to be practice-changing and incorporated into clinical guidelines.[11] To our knowledge, this will be the first study analyzing trials in the same time frame as the recent 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) guidelines for the management of heart failure.

METHODS

STUDY SELECTION.

We utilized the online electronic databases Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica dataBASE (Embase), Medical Literature Analysis

and Retrieval System Online (MEDLINE), and PubMed to query RCTs that reported a statistically significant benefit of intervention resulting in improved mortality or HHF using prespecified search terms (Figure 1). We limited our search to studies published in English. Books, dissertations, and pediatric trials were eliminated. Duplicate results, post hoc analyses, negative trials, and trials that focused primarily on diastolic dysfunction, ischemia, or arrhythmias were also eliminated to stay consistent with prior work reporting representation in heart failure trials separate from coronary artery disease and arrhythmias. The abstracts of the remaining articles were evaluated for interventions with a primary or secondary endpoint that showed a statistically significant reduction in HHF or improved all-cause or CV mortality. Only full-length articles were included.

We mirrored the timeline used by the 2022 AHA/ACC/HFSA guidelines for the Management of Heart Failure, which included studies after their initial review that were published through September 2021.[12] The data from this study are available from the corresponding author upon reasonable request. Institutional Review Board approval was not obtained because public articles were reviewed.

DATA EXTRACTION.

We extracted data from each full-length manuscript and supplementary data. Funding sources were categorized based on ClinicalTrials.gov classifications: industry, government, or university/nonprofit/nonfederal organizations. Trials were grouped by decade based on the publication year. Sex-specific outcomes were evaluated from primary manuscripts, post hoc analyses, and secondary publications using ClinicalTrials.gov. We reviewed primary manuscripts and identified the first author/principal investigator/study chair and then reviewed their profiles for gender data.

STATISTICAL ANALYSIS.

Similar to previous studies assessing the representation of women in clinical trials, we used participation-to-prevalence ratio (PPR).[10,13] The PPR was calculated by dividing the proportion of women in the trial by the estimated proportion of women in the population with heart failure. For the prevalence of women among HFrEF patients, we used estimates from the Framingham cohort,[4] similar to prior work.[13] The Framingham cohort is the longest running CV study and spans 3 generations mirroring our study time frame. A PPR of 0.8 to 1.2 was considered representative of the study population.[14] A PPR of <0.8 indicated that women were underrepresented relative to the disease population, and a PPR >1.2 indicated that women were overrepresented. PPR assesses if trial cohorts are reflective of the disease population under study. The Food and Drug Administration uses PPR to evaluate if trials are inclusive or if there are sex-specific biases in trial enrollment. Unpaired *t*-tests and Tukey's Honest Significant Difference were used to analyze the difference in the representation of women in RCTs based on intervention, enrollment region, and funding source. Trials that received both government and industry funding were categorized as government-funded during statistical analysis. A linear model for trend was used to examine the change in the representation of women in RCTs over time. A meta-analysis was not performed due to the heterogeneity in the study designs. PPR was not used to assess

sex-specific outcomes but only representation. We reviewed trial manuscripts and collected their sex-specific outcomes if they were reported.

RESULTS

A total of 33 trials were in the final analysis (Figure 1). The trials were published between 1980 and 2021 in 4 journals, and the sample sizes ranged from 253 to 10,917 participants. All except for 2 trials (CIBIS and ELITE II) were discussed in the 2022 ACC/AHA/HFSA guidelines for the manage-ment of heart failure.[12] Trial characteristics including the year of publication, publication journal, trial intervention, number of participants, percentage of women, region of enrollment, funding source, and sex-specific outcomes are presented in Table 1. Of 104,972 total trial enrolled participants, women represented 23.2% (n = 24,366) with pertrial representation ranging from 11.4% to 40.1% across studies. Five trials included a patient population of <20% women, twenty trials included between 20% and 30% women, and 8 trials included >30% women. The per-trial PPR estimates of all trials ranged from 0.29 to 1.00, with an overall PPR of 0.58 (Figure 2). Only 5 trials (15.2%) had a PPR of women representative of the disease population. On reviewing trial manuscripts/subsequent publications, 22 of them described sex-specific outcomes. Two of the 33 trials were led by women.

The proportion of women enrolled in randomized clinical heart failure trials did not change significantly over time ($P = 0.22$). There was no significant difference in the proportion of women in pharmacologic trials (PPR 0.61) vs device trials (PPR 0.59) ($P = 0.85$) (Table 2). The representation of women was greater in trials conducted in North America (PPR 0.75) compared to Europe (PPR 0.51) but not multiregional enrollment regions (PPR 0.60) ($P = 0.03$ and $P = 0.16$, respectively). The representation of women was greater in industry-funded trials (PPR 0.62) compared to government-funded trials (PPR 0.45) ($P = 0.05$).

DISCUSSION

In our review of HFrEF trials that observed mortality or HHF reduction, only 23.2% of trial participants were women, with an overall participation prevalence ratio of 0.58 indicating significant underrepresentation. There was no change in representation over time and underrepresentation was observed across all geographic regions of enrollment and trial funding type, though government-funded trials were significantly less representative than industry-funded trials.

Ninety-four percent of trials included in our study are referenced in the 2022 ACC/AHA/HFSA heart failure guidelines and guide care for women with heart failure, yet women are significantly underrepresented in most of these trials.[12] The importance of trial representation is evidenced by prior work suggesting important sex-specific considerations for guideline-directed medical therapy for HFrEF.[54] Santema et al showed that the lowest risk of hospitalization and mortality occurred in men at guideline recommended target doses of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers. However, women showed this at only 50% of the target recommended doses, with no further benefit from the up-titration of these agents.[54] In the DIG trial, women had a

higher mortality rate with digoxin treatment than with placebo.[22] Appropriate representation is needed to delineate and further address these existing sex-specific differences in HFrEF.[6]

In 1977, women were excluded from clinical trials.[55] The Food and Drug Administration was aiming to protect women of reproductive age groups.[55] A decade later, appropriate representation in clinical trials began to be recognized, a National Institutes of Health Memorandum on Inclusion was established, encouraging adequate recruitment of women and ethnic minorities. In 1993, the United States Congress reinforced this by implementing the National Institutes of Health Revitalization Act, requiring phase II clinical trials to include an adequate number of women and minorities to conduct subgroup analyses.[56,57] Despite potentially more specific requirements surrounding representation for government-funded trials, they were significantly worse than industry-funded trials at representing women.[56]

In a review by Jin et al,[13] examining the representation of women between 2010 and 2017 including all registered CV trials, noted participation prevalence ratios of women for HFrEF were low but notably showed significant increases in participation in the latter half of the decade. In a review by Gong et al,[10] they included trials from only 3 major CV journals, not limited to heart failure reduced ejection fraction and also found an improvement in representation over time for their study period 1986 to 2015. Interestingly, they noted women were significantly more underrepresented in trials showing statistically significant results compared to those that did not. In our review, we included trials over a longer time frame from 1980 to 2021, evaluating only statistically significant clinical trials of HFrEF and found that participation prevalence ratios were low and did not improve significantly over time. Women represented 23% of the study population in 1987 in the CONSENSUS trial and in 2019 in the DAPA-HF trial.[15,51]

Contemporary clinical trials in HFrEF have yielded remarkably significant reductions in morbidity and mortality across therapies.[58] Yet, when comparing representation among heart failure trials, reduced EF trials had the lowest weighted proportions of women, with women representing only 24% of participants in HFrEF trials.[59] Our findings are consistent with prior work in the field highlighting this gross sex-based underrepresentation.[14,59–61]

Barriers to equitable participation should be studied systematically to increase the representation of women. Several factors influence this, ranging from trial design to recruitment practices.[62] For example, in our cohort, the most recently published trial did not stratify total consented or screen failure participants by sex. Publishing pretrial participation screening data may aid in understanding factors influencing the likelihood of women being recruited and retained. All our included trials were published in 4 major CV journals. Journals and reviewers should encourage publication of data relevant to gender. Additionally, improving the representation of women in trial leadership positions has been shown to lead to improved recruitment of women.[62] Notably, only 2 of our included 33 trials, 6% of the cohort, were led by women.

STUDY LIMITATIONS.

Our study has certain limitations that should be considered when interpreting the results. By design, our review is limited to trials that reduced all-cause mortality or CV mortality or HHF. Our search terms, although comprehensive, may not have captured the entirety of relevant literature. We included published trials and complete manuscripts and did not include preprints or abstract data. Our search was limited to studies published in English and may have missed relevant studies published in other languages. Studies in representation routinely use PPR and guided our study, but by using the Framingham cohort as our reference population, we may be underestimating the representation of women given that other diverse cohorts have reported a higher prevalence of heart failure in women.[63] Additionally, it is important for trials to be statistically powered to detect sex-specific outcomes. While underrepresentation assessed by PPR implies a lack of power, in trials with representative PPR, power calculations are still needed to evaluate sex-specific differences in outcomes. Lastly, our study question was focused on sex at birth and not gender identity, and this is an important distinction that should be delineated in future work.

CONCLUSIONS

In summary, women with HFrEF remain underrepresented in RCTs that influence their guideline-directed therapy, and there has been no significant change in representation over the last 3 decades (Central Illustration). Regulatory mandates and further studies are needed to understand and address system- and patient-level barriers to representation and improve representation.

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ABBREVIATIONS AND ACRONYMS

ACC	American College of Cardiology
AHA	American Heart Association
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CV	cardiovascular
Embase	Excerpta Medica database
HFF	hospitalization for heart failure
HFrEF	heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America

MEDLINE	Medical Literature Analysis and Retrieval System Online
PPR	participation-to-prevalence ratio
RCT	randomized clinical trial

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PERSPECTIVES

COMPETENCY IN SYSTEM-BASED PRACTICE:

Women and men have similar prevalence rates of HFrEF, yet women remain underrepresented in clinical trials that are incorporated into clinical guidelines. It is important in clinical practice to be aware of these limitations in the guidelines and advocate for better representation of our patients to reduce sex-specific disparities in care. Our work ties into the following clinical competencies: Medical Knowledge, Patient Care, and Systems-Based Practice.

TRANSLATIONAL OUTLOOK:

Over the decades, there has been no significant change in representation of women in HFrEF clinical trials. Improving enrollment and representation of women is a significant undertaking that will need investment from investigators, research coordinators, data monitoring and oversight committees, and funding sources. The underrepresentation of women needs to be continually highlighted and recognized by guideline writing committees to create system-level changes in RCT designs and execution to further delineate gender differences in heart failure management and ensure appropriate care of women with HFrEF.

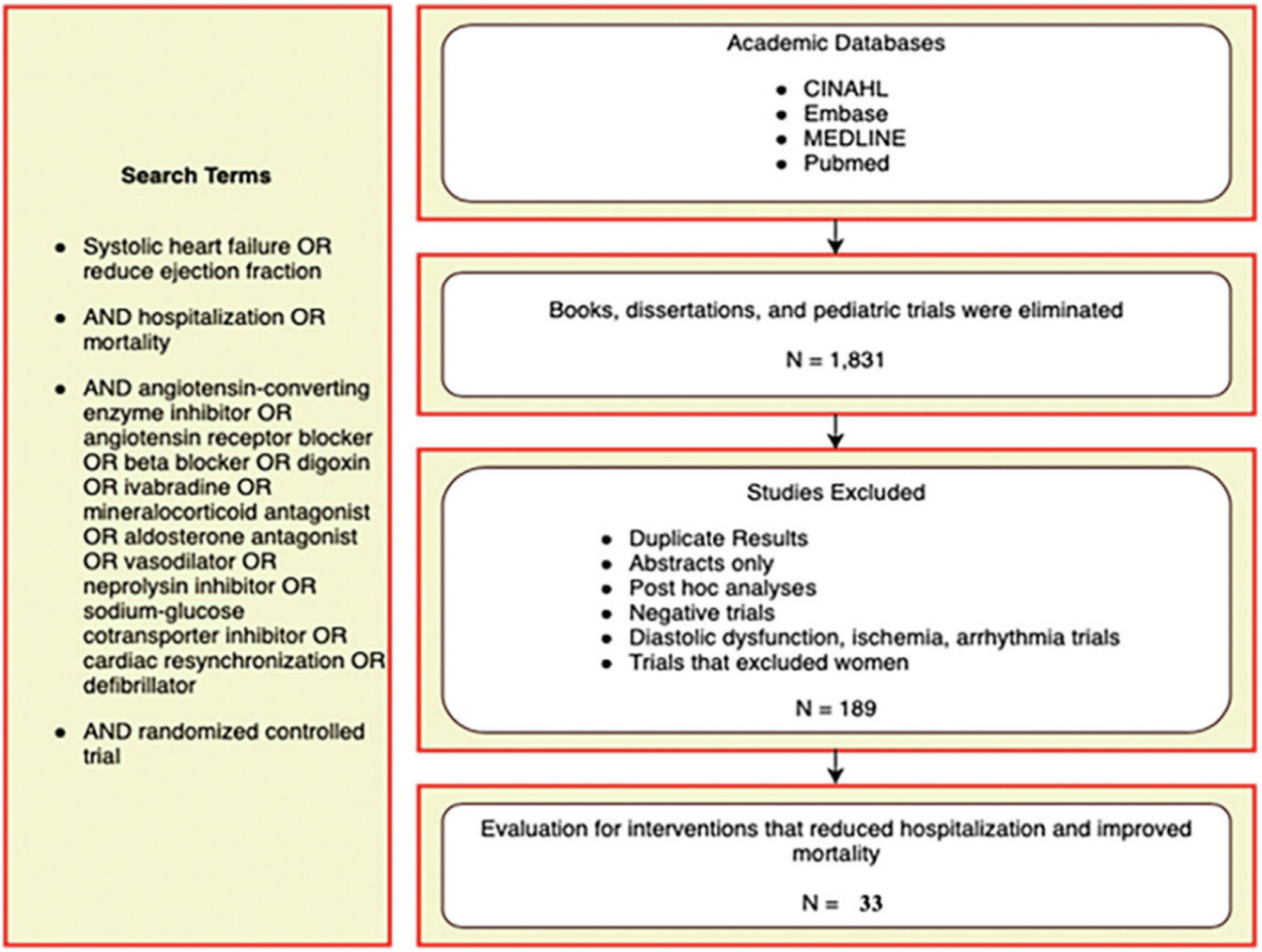
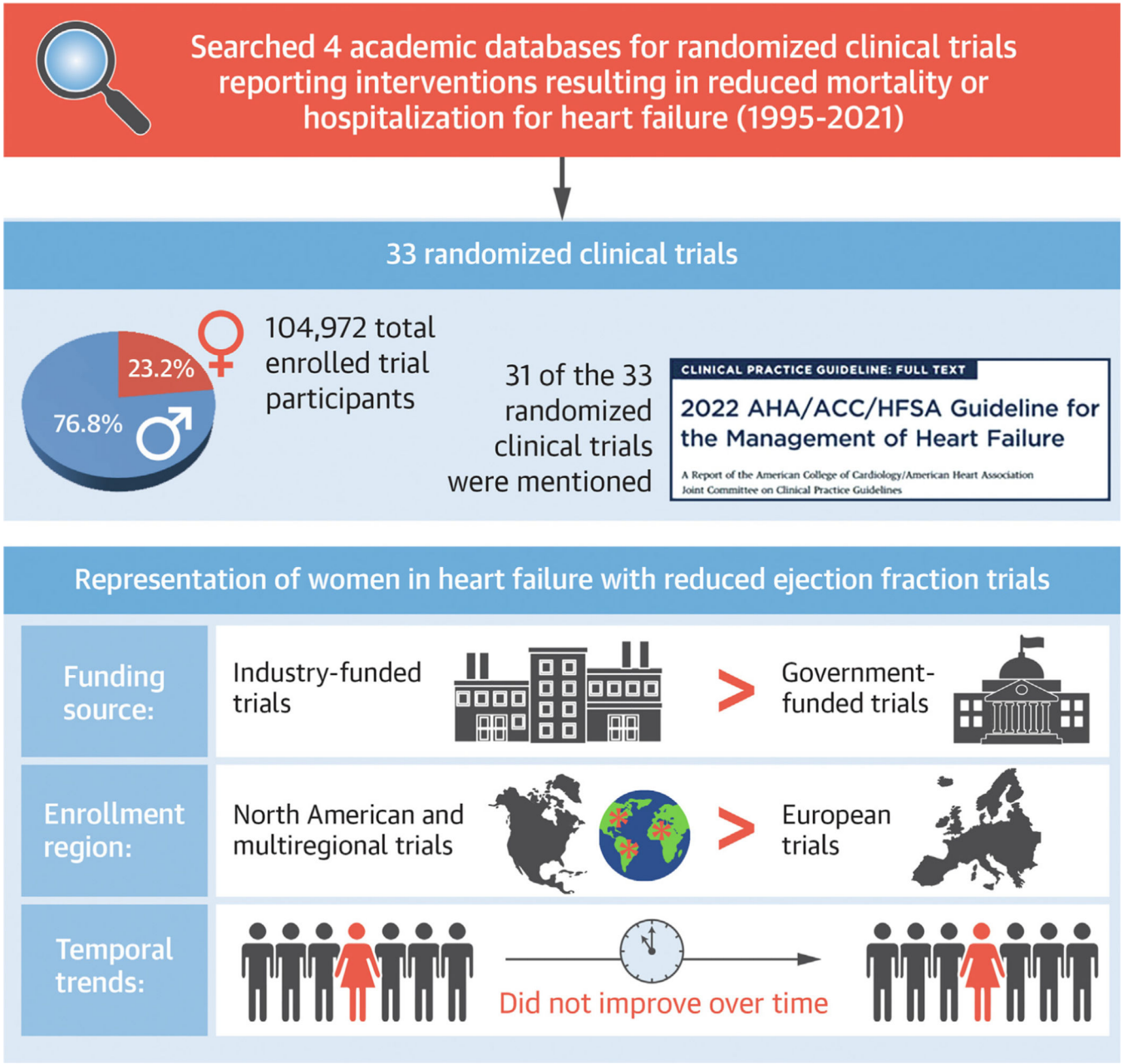


FIGURE 1. Search Criteria for Literature Review on HFrEF Trials
HFrEF = heart failure with reduced ejection fraction.

FIGURE 2. PPR for Major Randomized Clinical Trials of Heart Failure With Reduced Ejection Fraction in Order of Publication Year

Blue dots represent PPR based on the prevalence of all women with heart failure with reduced ejection fraction in the Framingham cohort.



CENTRAL ILLUSTRATION.
Underrepresentation of Women in Randomized Clinical Trials of Heart Failure With Reduced Ejection Fraction
Ekpo E, et al. JACC Adv. 2024;3(1):100743.

TABLE 1

Representation of Women in Randomized Clinical Trials of Heart Failure With Reduced Ejection Fraction

Trial (Year) *Journal*	Intervention	N	Percentage of Women Enrolled	Sex-Specific Outcomes, Risk of Mortality, or Hospitalization	Funding Source	Enrollment Region	Sex of First Author/ Principal Investigator
CONSENSUS (1987)[15] *NEJM*	Enalapril vs placebo	253	23.3%	Mortality at 6 mo overall 40% reduction. Subgroup analysis did not show a statistically significant reduction in mortality in women.[16]	Industry	Europe	Male
SOLVD Treatment (1991)[17] *NEJM*	Enalapril vs placebo	2,569	19.6%	Mortality RR overall 16% (95% CI: 5%−26%). A 12-y follow-up study found a nonsignificant survival benefit for women who were randomized to enalapril.[18]	Government and industry	Multiregional	Male
SOLVD-P (1992)[19] *NEJM*	Enalapril vs placebo	4,228	11.4%	*a*	Government and industry	Multiregional	Male
CIBIS (1994)[20] *Circulation*	Bisoprolol vs placebo	641	15.5%	*a*	Industry	Europe	Male
US Carvedilol (1996)[21] *NEJM*	Carvedilol vs placebo	1,094	23.4%	Mortality reduction in risk overall 65% (95% CI: 39% −80%). Men vs women HR 0.41 (95% CI: 0.22–0.80) vs 0.23 (95% CI: 0.07–0.69).	Industry	Multiregional	Male
DIG (1997)[22] *NEJM*	Digoxin vs placebo	6,800	22.4%	Mortality risk ratio overall 0.99 (95% CI: 0.91–1.07). Women with HFrEF had a higher rate of death with digoxin treatment than placebo.[9]	Industry	North America	
ELITE (1997)[23] *The Lancet*	Losartan vs captopril	722	33.2%	*a*	Industry	Multiregional	Male
ATLAS (1999)[24] *Circulation*	Low-dose lisinopril vs high-dose lisinopril	3,164	20.5%	*a*	Industry	Multiregional	Male
MERIT-HF (1999)[25] *The Lancet*	Metoprolol CR/XL vs placebo	3,991	22.5%	Mortality RR overall 0.66 (95% CI: 0.53–0.81). Men vs women RR represented in figure without exact numbers. Mortality RR females to males 0.63 (95% CI: 0.43–0.91) metoprolol CR/XL reduced HF hospitalization by 42% (P = 0.021).[8]	Industry	Multiregional	Male
RALES (1999)[26] *NEJM*	Spironolactone vs placebo	1,663	26.8%	*a*	Industry	Multiregional	Male
CIBIS-II (1999)[27] *The Lancet*	Bisoprolol vs placebo	2,467	20.9%	*a*	Industry	Europe	Male
ELITE II (2000)[28] *The Lancet*	Losartan vs captopril	3,152	30.6%	Mortality HR overall 1.13 (95% CI: 0.95–1.35). Men vs women HR 1.12 vs 1.14.	Industry	Multiregional	Male
Val-HeFT (2001)[29] *NEJM*	Valsartan vs placebo	5,010	29.9%	HF hospitalizations HR represented in figure without exact numbers. Valsartan did not significantly reduce mortality in women. Valsartan reduced hospital stays.[30]	Industry	Multiregional	Male

Trial (Year) *Journal*	Intervention	N	Percentage of Women Enrolled	Sex-Specific Outcomes, Risk of Mortality, or Hospitalization	Funding Source	Enrollment Region	Sex of First Author/ Principal Investigator
MADIT-II (2002)[31] *NEJM*	ICD vs conventional medical therapy	1,232	15.6%	Mortality HR 0.57 (95% CI: 0.28–1.16). There was a nonsignificant trend toward lower mortality in women with an ICD.[32]	Industry	Multiregional	Male
COPERNICUS (2002)[33] *Circulation*	Carvedilol vs placebo	2,289	20.5%	CV mortality or hospitalization overall risk reduction of 27%. Men vs women HR represented in figure without exact numbers.	Industry	Multiregional	Male
EPHESUS (2003)[34] *NEJM*	Eplerenone vs placebo	6,632	28.9%	*a*	Industry	Multiregional	Male
COMET (2003)[35] *The Lancet*	Carvedilol vs metoprolol tartrate	3,029	20.2%	Mortality HR overall 0.83 (95% CI: 0.74 0.93). Men vs women HR 0.80 (95% CI: 0.70–0.91) vs 0.97 (95% CI: 0.73–1.27).	Industry	Europe	Male
CHARM-Alternative (2003)[36] *The Lancet*	Candesartan vs placebo	2,028	31.9%	*a*	Industry	Multiregional	Male
CHARM-Added (2003)[37] *The Lancet*	Candesartan vs placebo	2,548	21.3%	*a*	Industry	Multiregional	Male
A-HeFT (2004)[38] *NEJM*	ISDN/Hydralazine vs placebo	1,050	40.1%	Mortality or HF hospitalization Men HR (0.67 (95% CI: 0.49–0.92) Women HR 0.58 (95% CI: −0.39 to 0.86).[39]	Industry	North America	Female
COMPANION (2004)[40] *NEJM*	CRT vs optimal medical therapy	1,520	32.6%	*a*	Industry	North America	Male
SCD-HeFT(2005)[41] *NEJM*	ICD only vs amiodarone vs placebo	2,521	23.3%	Mortality in ICD vs placebo: Overall HR 0.77 (95% CI: 0.62–0.96) Men vs women HR 0.73 (95% CI: 0.57–0.93) vs 0.96 (95% CI: 0.58–1.61). Mortality in amiodarone vs placebo: Overall HR 1.06 (95% CI: 0.86–1.30). Men vs women HR 1.04 (0.83–1.30) vs 1.17 (95% CI: 0.72–1.90).	Government	Multiregional	Male
REVERSE (2008)[42] *JACC*	CRT turned on vs CRT turned off	610	21.5%	HF worsened OR overall 0.70 (95% CI: 0.45–1.07). Men vs women OR 0.69 (95% CI: 0.43–1.11) vs 0.75 (95% CI: 0.26–2.19).	Industry	Multiregional	Female
BEAUTIFUL (2008)[43] *The Lancet*	Ivabradine vs placebo	10,917	17.1%	*a*	Industry	Europe	Male
HEAAL (2009)[44] *The Lancet*	High-dose losartan vs low-dose losartan	3,834	29.9%	CV mortality or HF hospitalization HR overall 0.90 (95% CI: 0.82–0.99). Men vs women HR 0.86 (95% CI: 0.77–0.96) vs 1.02 (95% CI: 0.85–1.23), $P = 0.10$.	Industry	Multiregional	Male
MADIT-CRT (2009)[45] *NEJM*	ICD only vs ICD-CRT	1,820	24.9%	Mortality or nonfatal HF HR overall 0.66 (0.52–0.84) Men vs women $P = 0.01$ (HR represented in figure without exact numbers). Exploratory analyses suggested that women but not men had a benefit from CRT-ICS therapy independent of QRS duration.	Industry	North America	Male

Trial (Year) *Journal*	Intervention	N	Percentage of Women Enrolled	Sex-Specific Outcomes, Risk of Mortality, or Hospitalization	Funding Source	Enrollment Region	Sex of First Author/ Principal Investigator
SHIFT (2010)[46] *The Lancet*	Ivabradine vs placebo	6,558	24.2%	CV mortality or HF hospitalization HR overall 0.82 (95% CI: 0.75–0.90). Men vs women HR 0.84 (95% CI: 0.76–0.94) vs 0.74 (95% CI: 0.60–0.91).	Industry	Europe	Male
RAFT (2010)[47] *NEJM*	ICD-CRT vs ICD only	1,798	17.1%	Mortality or HF hospitalization HR overall 0.75 (95% CI: 0.64–0.87) Men vs women P = 0.09 (HR represented in figure without exact numbers). The rate of hospitalizations was lower in women with CRT-D compared with men (8.8% vs 21.4%; P = 0.022).[48]	Government and industry	Multiregional	Male
EMPHASIS-HF (2011)[49] *NEJM*	Eplerenone vs placebo	2,737	22.3%	CV mortality or HF hospitalization adjusted HR overall 0.63 (95% CI: 0.54–0.74). Men vs women P = 0.36 (HR represented in figure without exact numbers).	Industry	Multiregional	Male
PARADIGM-HF (2014)[50] *NEJM*	ARNI vs enalapril	8,399	21.8%	CV mortality or HF hospitalization HR overall 0.80 (95% CI: 0.73–0.87). Men vs women P = 0.63 (HR represented in figure without exact numbers).	Industry	Multiregional	Male
DAPA-HF (2019)[51] *NEJM*	Dapagliflozin vs placebo	4,744	23.4%	CV mortality or HF hospitalization overall HR 0.74 (95% CI: 0.65–0.85). Men vs women HR 0.73 (95% CI: 0.63–0.85) vs 0.79 (95% CI: 0.59–1.06).	Industry	Multiregional	Male
EMPEROR-Reduced(2020)[52] *NEJM*	Empagliflozin vs placebo	3,730	23.9%	CV mortality or HF hospitalization overall HR 0.75 (95% CI: 0.65–0.86). Men vs women HR 0.80 (95% CI: 0.68–0.87) vs 0.59 (95% CI: 0.44–0.80).	Industry	Multiregional	Male
SOLOIST-WHF (2021)[53] *NEJM*	Sotagliflozin vs placebo	1,222	33.7%	CV mortality or HF hospitalization overall HR 0.67 (95% CI: 0.52–0.85). Men vs women HR 0.62 (95% CI: 0.47–0.82) vs 0.80 (95% CI: 0.51–1.25).	Industry	Multiregional	Male

[a] Exact values not found.

CV = cardiovascular; HFrEF = heart failure with reduced ejection fraction.

TABLE 2

Representation of Women in Randomized Clinical Heart Failure Trials Based on Intervention, Enrollment Region, and Source of Funding

	Number of Trials	Average Participation-to-Prevalence Ratio	*P* Value
Intervention			
Pharmacologic	28	0.61	0.85
Devices	5	0.59	
Enrollment region			
North America	4	0.75	0.03[a]
Europe	6	0.51	
Multiregional	23	0.60	
Funding			
Government	4	0.45	0.05
Industry	29	0.62	

P = 0.03 comparing North America and Europe, *P* = 0.16 comparing multiregional and North America, *P* = 0.32 comparing multiregional and Europe.