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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

A Systematic Review of Sex-Specific Reporting in Heart Failure Clinical Trials

Trial Flow and Results

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ABSTRACT

BACKGROUND Females are historically underenrolled in heart failure (HF) randomized controlled trials (RCTs) relative to disease prevalence. Sex differences in trial flow, including withdrawals and losses to follow up, may further limit the generalizability of results.

OBJECTIVES This study aimed to assess the frequency of sex-specific reporting of trial flow, treatment efficacy, and adverse events in HF RCTs.

METHODS We systematically searched MEDLINE, Embase, and CINAHL for HF RCTs published between 2000 and 2020 in journals with an impact factor ≥10. We assessed whether trial flow, treatment effect, and adverse events were disaggregated by sex. We used multivariable regression to assess associations between trial characteristics and sex subgroup analysis. We analyzed temporal trends in sex-specific reporting.

RESULTS We included 224 RCTs with 228,801 total participants (28.2% female). No RCT reported sex-disaggregated screening, consent, or withdrawal rates; and 2 (0.9%) reported sex-disaggregated losses to follow-up. Seventy-five RCTs (33.4%) presented sex subgroup analysis, and 63 (28.3%) reported sex-treatment interaction. No RCT reported sex-specific adverse events. Large trial size (odds ratio: 13.16, 95% CI: 5.67-30.52; $P < 0.001$) and device/procedure interventions (odds ratio: 5.13, 95% CI: 1.55-16.95; $P < 0.007$) were independently associated with sex subgroup analysis. Over the study period, there was an increase in sex subgroup analysis ($P < 0.001$) and testing for sex-treatment interaction ($P < 0.001$).

CONCLUSIONS HF RCTs rarely reported sex differences in trial flow or adverse events and uncommonly performed sex subgroup analysis. Improved sex-disaggregated reporting could highlight the causes and extent of sex differences in trial participation and facilitate appropriate inferences about treatment effect. (JACC Adv 2022;1:100079)

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ABBREVIATIONS AND ACRONYMS

HF = heart failure

OR = odds ratio

RCT = randomized controlled trial

Heart failure (HF) is a significant cause of morbidity and mortality among females, and the lifetime incidence of HF in females is similar to males.[1] However, there are knowledge gaps in the optimal management of HF in females as randomized controlled trials (RCTs), which inform practice, underenroll females relative to disease distribution. The National Institutes of Health Revitalization Act requires inclusion of people in clinical trials proportionate to the sex-related prevalence of the disease under investigation.[2-4] When trials underenroll females relative to disease prevalence, primary treatment effect and safety of interventions are estimated based on trial data primarily from male participants. Sex differences, if present, are neither detected nor adequately reflected in the overall estimated treatment effect.[5,6] Although there are several factors associated with the underenrollment of females in trials, the reasons for underenrollment are not completely understood.[2]

Sex-disaggregated reporting of trial flow can add important insights into the reasons for and extent of underrepresentation of females in RCTs. For example, the underenrollment of females may be because of disproportionately lower screening for or consent to trial participation. Sex differences in the rate of study adherence to the intervention, study withdrawals, and losses to follow-up may further exacerbate trial imbalance but are not accounted for in intention-to-treat analyses.[7] It is assumed that treatment cessation, study withdrawals, and losses to follow-up are balanced between sexes, but this may not be the case; it is important to understand who remained in the study to contribute to its outcomes.[8]

Clinical trials are statistically powered to assess the effect of an intervention on a primary outcome without considering how the sex composition of the trial population may influence estimated treatment effect. Furthermore, marked imbalance in sex subgroups means that there is often inadequate statistical power to test for sex-treatment interaction.[9] Such treatment effect modification may exist due to sex differences in pathophysiology, hormones, cardiac chamber size, volume of distribution, pharmacokinetics, social determinants of health, and event rates.[10] These differences may influence tolerability, treatment effect, and adverse events following drug, device, and surgical interventions.[11-14] When there is marked underrepresentation of females and no sex-specific analysis in trials, we are left to rely on posttrial surveillance or observational studies to understand sex differences in drug tolerability, ideal dosing, and adverse events[5,6]

In this study, we analyze HF RCTs in high-impact journals to assess the frequency of sex-specific reporting of trial flow (from screening to follow-up), treatment efficacy, and adverse events. We assess temporal trends in reporting of sex subgroup analysis for primary treatment effect and examine the association between trial design factors and inclusion of sex-specific subgroup analysis.

METHODS

STUDY OVERVIEW. This review was registered in the International Prospective Register of Systematic Reviews (CRD42022307619). This study was performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and guidance for methodological studies.[15,16] Data may be available upon request as per the Population Health Research Institute Data Sharing Policy. The Population Health Research Institute will approve the use of the data after a committee review. Interested parties may contact the study principal investigator for a copy.

DATA SOURCES AND SEARCHES. We performed a systematic search of 3 online databases (MEDLINE, Embase, and CINAHL). The initial search strategy in MEDLINE was developed with guidance from the senior author (H.G.C.V.) and a professional information specialist. Our search strategy included Medical Subject Headings and keywords such as “heart failure” and “randomized controlled trials.” The complete search strategy used in MEDLINE can be found in the Supplemental Appendix. We manually searched databases for separately published trial protocols of RCTs included in this study. If the primary publication for an RCT did not include sex subgroup analysis, we searched for secondary publications linked to the trial identifier on clinicaltrials.gov. If there were no linked publications, we performed manual searches of PubMed and Google Scholar using the trial names and keywords such as “sex,” “subgroup,” and “interaction.”

STUDY SELECTION. We independently screened article titles and abstracts against predefined eligibility criteria. We included RCTs published between January 1, 2000, and July 17, 2020, recruiting participants aged >18 years with HF, which were available in the English language. Studies were included in the systematic review if the primary publication for the

RCT was published in a journal with an impact factor ≥10 in 2020 as indexed by Clarivate. This impact factor threshold was selected to capture the RCTs that would be most likely to impact clinical practice. If the primary RCT manuscript was published in a journal with an impact factor ≥10 and the sex subgroup analysis was reported in a secondary publication, the data from the sex subgroup analysis were included in the systematic review regardless of the journal in which the sex subgroup analysis was published. We excluded studies that used methodologies other than RCTs. We also excluded RCTs with sample size <100, as these studies would be unlikely to have adequate power for sex-specific analysis.

DATA EXTRACTION. Data abstraction was completed by 2 independent assessors (M.A. and S.W.) and included review of supplementary materials, separately published trial protocols, and trial registration databases where relevant. Any disagreement in data abstraction was resolved by discussion and if needed, consultation with a third assessor (H.G.C.V.). Adapting the Sex and Gender Equity in Research guidelines,[16] we assessed for sex-specific reporting as follows: abstract (percentage of participants male/female), methods (sex-specific eligibility criteria, justification for sex-specific eligibility criteria), results (sex-specific breakdown of patients screened for eligibility, deemed eligible, consented, randomized, withdrawn, lost to follow-up; reporting of sex-specific treatment effect and adverse events), and discussion (implications of sex differences). We collected information on study authorship, specifically the proportion of woman authors for each trial and whether there was a woman first or last author; gender was determined through manual online search of author names in combination with institutional names. Sources included photographs, pronoun descriptors on institutional and professional websites, and social media profiles. For consistency, we reported "sex" of trial participants and reported "gender" of trial authors.

ANALYSIS. We presented continuous variables as mean ± SD for normally distributed data, and median (IQR) for data that were not normally distributed. We reported categorical variables as numbers and percentages. Descriptive analysis was used to examine reporting of sex differences in trial flow and presented as a percentage of total included trials and percentage of trials with a woman first or last author. We assessed for the association between the presence of a woman first or last author and sex-disaggregated reporting using Fisher exact test.

We examined the association between quantitative assessment of sex differences in a trial and woman authorship using the chi-square test. We used logistic regression to assess for factors independently associated with sex-disaggregated reporting of the primary outcome. The prespecified covariates included trial size, type of intervention, type of funding, and gender of first and last authors. We reported adjusted odds ratios (ORs) and corresponding 95% CIs. We used the Cochran-Armitage test for trend to analyze temporal trends in sex-disaggregated reporting in trial flow and treatment effect. The *P* values were 2-tailed, and the level of significance was alpha = 0.05. Statistical analyses were completed using SPSS (version 28, IBM Corporation) and GraphPad Prism (version 9.3.1, GraphPad Software, LLC).

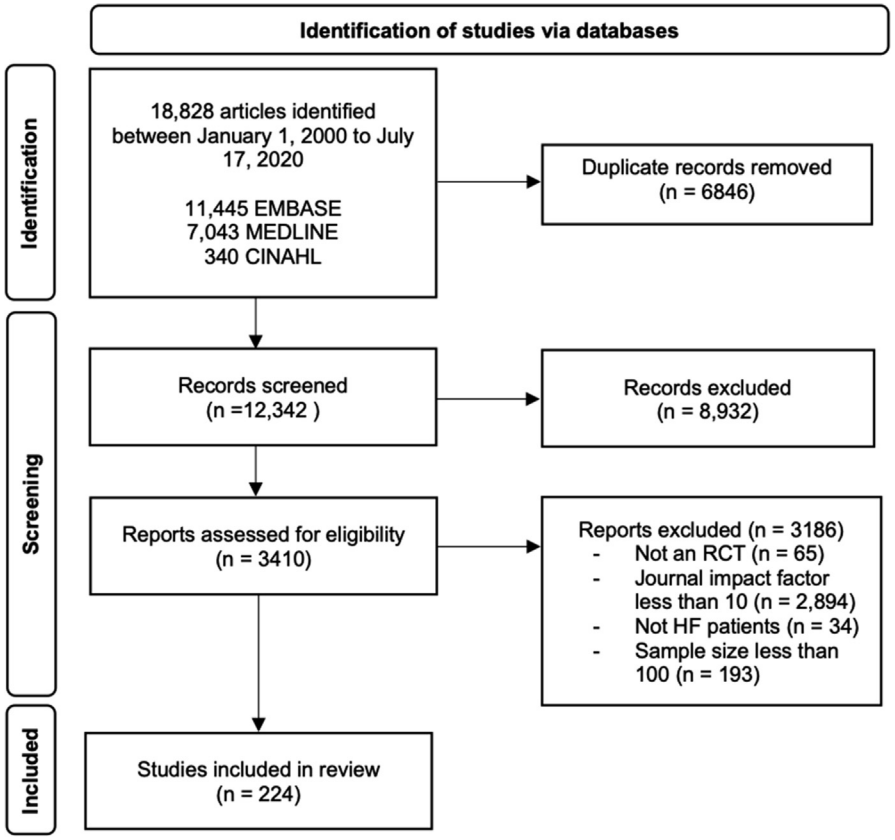
RESULTS

CHARACTERISTICS OF INCLUDED RCTs. A total of 224 RCTs met the inclusion and exclusion criteria (Figure 1) with a total of 228,801 participants, 28.2% of whom were female (Table 1). The mean enrollment of females across the included studies was 29.6%. A majority of the RCTs included participants with HF with reduced ejection fraction (181 trials, 80.8%) were coordinated in Europe or North America (206 trials, 92.0%) and tested drug therapies (144 trials, 64.3%).

SEX-DISAGGREGATED REPORTING OF TRIAL FLOW. The percentage of male and female participants was reported more frequently in the abstract of trials with a woman first or last author (28.8%) compared with trials with a man first and last author (12.8%), $P < 0.010$ (Table 2). A large proportion of trials had sex-specific eligibility criteria (46.9%), but none provided justification for this. HF trials frequently excluded participants who were pregnant (49.5%), not on scientifically accepted contraceptive methods (43.8%), or who were lactating or nursing (30.5%) (Table 3). No RCTs provided a sex-specific breakdown of participants screened for eligibility, deemed eligible, and consented. Of the 224 RCTs, 222 (99.1%) provided sex-specific breakdown of patients randomized. Very few RCTs reported participant flow in the study by sex: 1 RCT provided sex-specific breakdown of treatment cessation (0.4%), no RCT provided sex-specific breakdown of withdrawals, and 2 RCTs provided sex-specific breakdown of losses to follow-up (0.9%).

SEX-DISAGGREGATED REPORTING OF TREATMENT EFFECT AND ADVERSE EVENTS. Of the 224 RCTs, 75 (33.4%) included sex subgroup analysis of the primary outcome, and 63 (28.3%) tested for interaction between sex and the intervention. Of these 63 RCTs, only 4 (6.8%) demonstrated significant sex-treatment interaction. There was no significant difference in

FIGURE 1 PRISMA Diagram of Randomized Controlled Trials Identified and Included in the Analysis



A systematic search was performed using MEDLINE, Embase, and CINAHL databases to identify randomized controlled trials of heart failure in adults with >100 participants and published in medical journals with impact factor ≥10. A total of 224 studies were included in this review. HF = heart failure; RCT = randomized controlled trial.

reporting the primary treatment effect in sex subgroups in trials with a woman first or last author compared with trials led by men (36.5% vs 32.6%; $P = 0.594$). No RCT reported sex-specific occurrence of adverse events.

On multivariable analysis, a large trial size (OR large trial vs small trial: 13.16; 95% CI: 5.67-30.52; $P < 0.001$), and device/procedure interventions (OR device/procedure vs other: 5.13; 95% CI: 1.55-16.95; $P < 0.007$) were independently associated with sex subgroup analysis of the primary outcome. Women in first or last authorship position (OR: 1.11; 95% CI: 0.51-2.41; $P = 0.79$) and type of funding (OR industry vs public: 0.70; 95% CI: 0.32-1.55; $P = 0.38$) were not associated with sex subgroup analysis of the primary outcome (Figure 2).

TEMPORAL ANALYSIS OF SEX-DISAGGREGATED REPORTING IN TRIAL FLOW AND PRIMARY TREATMENT EFFECT. Over the study period, there was a significant increase in sex subgroup analysis ($P < 0.001$) and sex-intervention interaction testing ($P < 0.001$; Figure 3). There was no significant temporal change in sex-disaggregated reporting in study abstracts ($P = 0.906$) and the use of sex-specific eligibility criteria ($P = 0.312$). Temporal trends in sex-disaggregated reporting of trial flow could not be assessed as sex breakdown of trial flow was rarely reported.

DISCUSSION

In this systematic review of 224 studies with 228,801 participants, we found that <1 in 100 of RCTs provided sex-disaggregated data on any aspect of trial flow (screening, eligibility, consent, and withdrawal rates), no RCT reported sex-disaggregated data on adverse events, and <1 in 3 RCTs reported a sex subgroup analysis of the treatment effect on the

TABLE 1 Characteristics of Randomized Controlled Studies (N = 224) Included in the Study

Trial size	
Small (<250)	81 (36.2)
Medium (250-750)	76 (33.9)
Large (>750)	67 (29.9)
Year of study	
2000-2003	55 (24.6)
2004-2007	46 (20.5)
2008-2011	36 (16.1)
2012-2015	27 (12.1)
2016-2020	60 (26.8)
Heart failure with reduced ejection fraction	181 (80.8)
Region of coordinating center	
Europe	94 (42.0)
North America	112 (50.0)
Central and South America	5 (2.2)
Australia	5 (2.2)
Asia	8 (3.6)
Type of intervention	
Drug	144 (64.3)
Device/procedure	25 (11.2)
Health services	49 (21.9)
Exercise/rehabilitation	6 (2.7)
Type of funding	
Public	74 (33.0)
Private	150 (67.0)
Gender of first author	
Man	194 (86.6)
Woman	30 (13.4)
Gender of last author	
Man	193 (86.2)
Woman	31 (13.8)

Values are n (%).

TABLE 2 Sex-Disaggregated Reporting in Trial Flow, Treatment Effect, and Adverse Events (N = 224)

Abstract	
Sex-specific breakdown of trial participants	37 (16.5)
Methods	
Sex-specific eligibility criteria	105 (46.9)
Justification for sex-specific eligibility criteria	0 (0.0)
Description of sex-specific analysis	68 (30.4)
Results	
Sex-specific breakdown of patients approached, eligible, and consented	0 (0.0)
Sex-specific breakdown of participants randomized	222 (99.1)
Sex-specific breakdown of treatment cessation	1 (0.4)
Sex-specific breakdown of withdrawals	0 (0.0)
Sex-specific breakdown of losses to follow-up	2 (0.9)
Subgroup analysis of the primary outcome by sex	75 (33.4)
Interaction between sex and intervention tested	63 (28.3)
Sex-specific breakdown of adverse events	0 (0.0)
Discussion	
Implications of sex mentioned	17 (7.6)
If no sex-specific analysis was performed, a rationale was provided	0 (0.0)

Values are n (%).

primary outcome (with a smaller proportion testing for effect modification of the treatment by sex) (**Central Illustration**). In adjusted analysis, large trials had 12 times the odds and device/procedure interventions had 6 times the odds of sex subgroup analysis. There was an increase in sex subgroup analysis ($P < 0.001$) between the years 2000 and 2020.

The lack of sex-specific reporting of participants who were screened, deemed eligible, or who provided consent limits our ability to assess whether underrepresentation of females in pivotal HF trials[2,3,8] is related to recruitment strategies, eligibility, or consent. The lack of sex-disaggregated reporting of treatment withdrawals or losses to follow-up limits assessment for attrition bias. Although estimates of treatment effect are typically based on intention-to-treat analysis, in trials with sex imbalances in enrollment, disproportionate withdrawals or losses to follow-up in the underrepresented sex may introduce biases in estimated treatment effects that further impair the generalizability of results. Although data on who was screened or declined consent are not typically collected in RCT logs, sex-specific data on trial flow following inclusion should be reported.

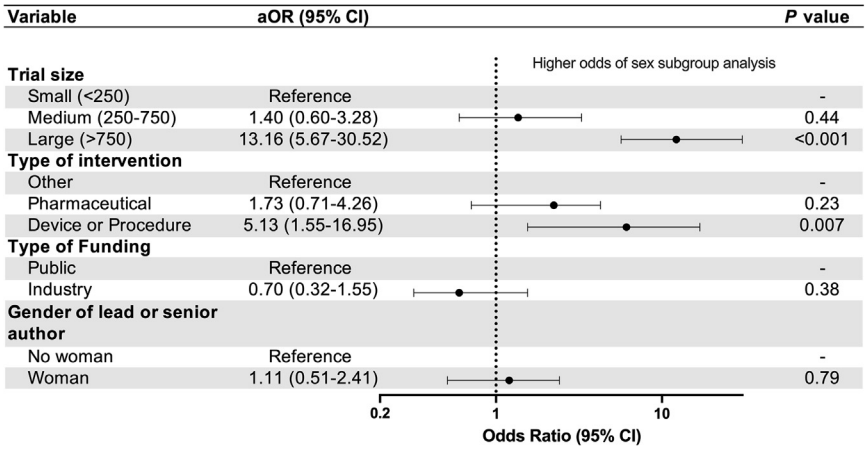
We found that HF trials frequently incorporated sex-specific eligibility criteria, and justification for these criteria was not provided. Historically, females who are pregnant, lactating, or with childbearing potential are commonly excluded from trials due to concern for potential teratogenicity or harm to the fetus; however, there is not always evidence or biological plausibility to support these concerns.[6,17,18] As a consequence, care for females who are pregnant

TABLE 3 Sex-Specific Eligibility Criteria Reported in 105 Heart Failure Trials (N = 105)

Must not be pregnant	52 (49.5)
Must be on scientifically accepted method of contraception	46 (43.8)
Must not be lactating or nursing	32 (30.5)
Must be without childbearing potential based on surgical treatment or confirmed postmenopausal	10 (9.5)
Must not have a desire to become pregnant during the study period	7 (6.7)
Must not be of childbearing age	3 (2.9)

Values are n (%).

FIGURE 2 Multivariable Analysis of Trial Characteristics Associated With Sex Subgroup Analysis

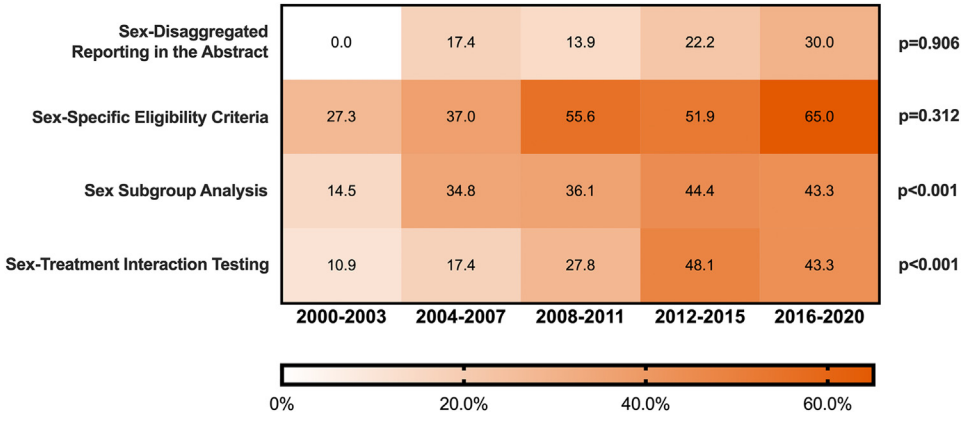


Multivariable logistic regression was performed to assess trial characteristics associated with sex subgroup analysis in randomized controlled trials (N = 224) of heart failure. We reported aORs, 95% CIs, and *P* values. Large trial size (>750 participants) and device/procedure interventions were associated with sex subgroup analysis. aOR = adjusted odds ratio.

or breastfeeding relies on observational data or anecdotal evidence for most drugs and also for simple interventions such as exercise.[6,17,18]. Importantly, the presence of sex-specific eligibility criteria is independently associated with the underenrollment of females in clinical trials.[2] The exclusion of females who are pregnant, lactating, or with childbearing potential should be considered carefully based on each intervention rather than applied as a blanket exclusion and should also be justified in trial protocols.

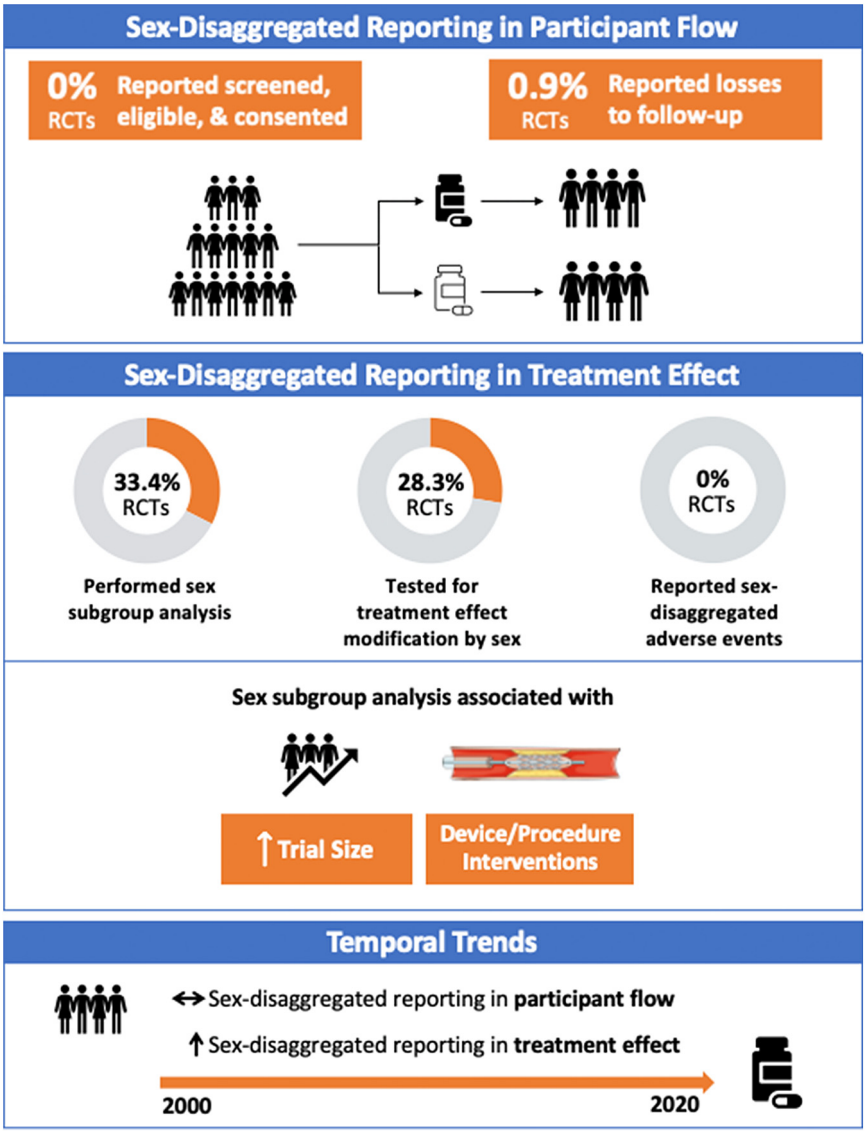
The finding that only one-third of trials report sex-specific treatment effect and even fewer tests for effect modification by sex is a concern, as is the lack of sex-disaggregated reporting of adverse events. This is consistent with a recent systematic review of 253 cohort studies of cardiac resynchronization therapy, which found that outcome data were disaggregated

FIGURE 3 Temporal Trends in Sex-Disaggregated Reporting of Trial Flow and Outcomes



A temporal analysis was conducted to examine trends in sex-disaggregated reporting in randomized controlled trials of heart failure between 2000 and 2020. The heat map displays the percentage (%) of trials published in each year group with sex-disaggregated reporting. The Cochran-Armitage test for trend was used to test for statistical significance and *P* values were reported. Over the study period, there was an increase in sex subgroup analysis and sex-treatment interaction testing.

CENTRAL ILLUSTRATION **Sex-Disaggregated Reporting in Trial Flow and Outcomes in Heart Failure Trials**



Au M, et al. JACC Adv. 2022;1(4):100079.

RCT = randomized controlled trial.

by sex in only 16% of studies.[13] Among 10 prescription drugs withdrawn from the U.S. market between 1997 and 2001, 8 caused greater harm to females than males.[14] Indeed, sex differences in treatment effect are common but often discovered in observational data years after RCTs are published. Observational data have revealed that females benefit from angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and beta blockers at lower doses than those informed by RCTs (with predominantly male participants).[11,12,19] Similarly, females incur higher bleeding risk post percutaneous coronary intervention, experience greater benefit from cardiac resynchronization therapy, and have higher complication rates post-surgical revascularization than males.[19] Sex differences in cardiac chamber and coronary artery size, volume of distribution, and pharmacokinetics are well documented; these may

TABLE 4 Recommendations to Improve Sex-Specific Reporting in Clinical Trial Publications

Title and abstract	If only 1 sex is included in the study or if the results of the study are to be applied to only one sex, the title and the abstract should specify the sex of participants.
Introduction	Authors should report whether sex differences may be expected.
Methods	Authors should describe incorporation of sex into the study design, justify any sex-specific exclusion criteria of males or females, and describe sex-specific analysis.
Results	Reporting should include the sex-specific breakdown of patients approached, eligible, consented, and included. The sex-specific breakdown of withdrawals and losses to follow-up should be included. The sex distribution of study participants and sex-specific results should be reported. Interaction between sex and the intervention should be tested.
Discussion	Discussion should include the implications of sex on the results and the extent to which the results are generalizable to broader populations. If no sex-specific analyses were conducted, the rationale for the absence of analyses and the implications on generalizability should be addressed.
Funding and publication	Funding agencies and journals should consider benchmarks for the enrollment of females based on the sex distribution of diseases to award funding and publish research.

Adapted from Whitelaw S, Sullivan K, Eliya Y, et al. Trial characteristics associated with under-enrolment of females in randomized controlled trials of heart failure with reduced ejection fraction: a systematic review. *Eur J Heart Fail*. 2020;23:15-24.

influence tolerability, treatment effect, and adverse events following drug, device, and surgical interventions.[10-12] It is not uncommon for HF RCTs adequately powered for sex subgroup analysis to demonstrate sex-treatment interaction of some drugs (eg, digoxin, sacubitril-valsartan).[20,21] We found that 6.8% of RCTs that tested for sex-treatment interaction had statistically significant results. The low proportion of studies with statistically significant sex-treatment interaction could be in part due to studies that are underpowered to detect sex differences in treatment effect. To generate the evidence necessary to make generalizable and sex-specific recommendations in clinical guidelines, sex-specific analyses need to be incorporated into the sample size and analytic plan of HF trials.

The independent association between trial size and sex-disaggregated reporting of the primary treatment effect is intuitive. In trials with large sample sizes, sex subgroup analysis may be prioritized and pre-specified; the corollary is that trials with a priori plans to include sex or gender analysis have to incorporate this in the sample size for meaningful analysis. In smaller trials, subgroup analysis may not be relevant or feasible due to inadequate statistical power to show sex differences. The association between surgical or device interventions and sex-disaggregated reporting of the primary outcome is less clear but may relate to perceived relevance. Previous observational studies suggest sex-specific differences in device therapies; for example, compared with males, females receive cardiac resynchronization devices and implantable cardioverter-defibrillators less frequently and potentially derive greater benefit from cardiac resynchronization therapy.[19,22]

We found no association between the gender of trial leaders and reporting of sex subgroup analysis, although women trial leaders were more likely to report the sex composition of trial participants in the abstract. In a recent review of HF trials, having a woman first or last author was associated with higher enrollment of female participants and a greater percentage of women steering committee members.[2,23] In cardiology clinical guideline development, however, the proportion of women authors was not associated with the inclusion of sex and gender content in guidelines.[24] The inclusion of sex and gender analysis in the methodology of HF trials may be constrained by factors beyond influence or there may have been inadequate power to demonstrate a significant difference, given the small proportion of large, adequately powered trials—led by women authors.[25] In guideline development, an additional limitation may include the quality of evidence that is suitable for generating sex-specific recommendations.[26] Although the underrepresentation of women authors in HF trials is an important gap to address, the varying association between woman authorship and the inclusion of sex and gender content suggests a need for broader efforts at the level of funding agencies and publications to promote the inclusion of sex and gender analysis as a standard practice in cardiovascular research.[26-28]

The increase in sex subgroup analysis and testing for effect modification by sex in HF trials over the course of the study period may reflect increased awareness about the integration of sex and gender analysis in research design and reporting, as well as the publication of the Sex and Gender Equity in Research guidelines in 2016 and the CONSORT-Equity 2017 reporting standards.[3,16,24,28] Although this is important particularly for large RCTs that seek to impact HF management for broad populations, representativeness among research participants and sex-specific analysis must also extend to preclinical and early phase trials. Although there was an increase over the study period of sex-disaggregated reporting of treatment effect, reporting of sex-specific adverse events and trial

flow remained rare. Transparent sex-disaggregated reporting can provide insights into the reasons for and the extent of sex differences in trial representativeness and facilitate appropriate inferences about treatment effect. Trial regulatory bodies, funding agencies, and journals should consider implementing strict sex and gender conduct and reporting requirements to facilitate meaningful change (**Table 4**).[2]

The strengths of this systematic review include the novel research question, comprehensive data on 20 years of publications, and adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for the conduct and reporting of our study. To the best of our knowledge, there are no other studies that have analyzed the sex-disaggregated reporting of trial flow in cardiovascular clinical trials. Our study was not without limitations. Our search was limited to the English language and high-impact journals, which may impact the generalizability of our study findings. We excluded RCTs with fewer than 100 participants, as these trials would be unlikely to have adequate power for sex subgroup analysis and interaction testing. Another limitation is that we were not able to account for errors in the primary records used to establish author gender. We were also not able to account for gender nonbinary authors. The age of trial participants was rarely reported by sex, and we were not able to account for possible interactions between age and representation of female participants. There may be secondary sex-specific manuscripts for RCTs included in our systematic review that have not been published yet.

CONCLUSIONS

In this study, we found that HF RCTs in high-impact journals did not frequently report sex-disaggregated data in trial flow, and most trials did not perform sex subgroup analysis or interaction testing. This limits our ability to detect and characterize sex differences in treatment effect and to critically appraise trials in the development of sex-specific treatment guidelines. Transparent, sex-disaggregated reporting may help us narrow the sex gap in research representativeness in clinical trials and to make appropriate inferences about treatment efficacy and safety.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Sex-specific differences in HF risk factors, pathophysiology, and pharmacokinetics are well documented, but we currently lack sufficient data on sex differences in treatment effect of several HF interventions.

TRANSLATIONAL OUTLOOK: To assess for sex imbalances in trial flow and understand sex differences in treatment effect, sex-specific trial flow, treatment efficacy, and adverse events should be reported in RCTs.

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APPENDIX For MEDLINE Search Strategy, please see the online version of this paper.