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EDITORIAL COMMENT

# Importance of Sex Disaggregated Data in Heart Failure Clinical Trials

## Where Are We in 2022?*

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Well-designed randomized controlled trials (RCTs) are the gold standard for informing clinical practice in various diseases, including heart failure (HF). However, even the most well-designed clinical trials are of limited value if the results are not generalizable to the patient population we treat. Many RCTs are often underpowered for sex-specific analyses, and when present, subgroup analyses often do not include testing for sex-treatment interactions.[1,2] Females have been underrepresented in HF RCTs for many years despite having comparable lifetime risk of the disease as males.[3] Whitelaw et al[2] recently examined 317 RCTs including 183,097 participants with HF with reduced ejection fraction and found that only 25.5% of participants were female. Factors associated with underenrollment of females were sex-related eligibility criteria, trial coordination in North America/Europe/Asia, ambulatory recruitment, and gender of trial leaders.[2] Despite underrepresentation of the female sex in RCTs, ongoing investigations of the sex differences in cardiovascular disease have informed us that sex plays a role in the pathophysiology and clinical manifestation of various cardiovascular diseases. Additionally, females have metabolic differences that impact the half-lives and clearance of certain HF medications. This raises the concern that the optimal dosing of drugs and adverse effects may also be different in both sexes. These sex-specific differences in etiology, clinical presentation, and treatment response cannot be determined without a sufficient number of female participants in RCTs. Historical underrepresentation in large clinical trials has led to insufficient sex-specific data and subsequently resulted in clinical guidelines and practice that are based on predominantly male participants' response to HF therapies.

In this issue of the *JACC: Advances*, Au et al[4] sought to examine how frequently modern high-impact HF RCTs report sex-disaggregated trial flow information and primary outcomes. The authors conducted a systematic review of 224 HF RCTs including 228,801 total participants to examine the frequency of sex-specific reporting of enrolled participants, loss to follow-up, treatment efficacy, and adverse effects. They included large HF RCTs published in journals with an impact factor ≥10 from January 2000 to July 2020, those with participants older than 18 years, and those published in English language. Studies with <100 total participants or written in non-English language were excluded. The frequency of sex-disaggregated reporting of trial flow and primary outcome in the HF RCTs was described in percentages, and logistic regression was used to assess the independent association between prespecified covariates (trial size, type of intervention, type of funding, gender of trial leaders) and sex-disaggregated reporting of the primary outcome. The temporal trends in sex-disaggregated reporting were analyzed using the Cochran-Armitage test.

The main findings of the study revealed the current state of sex-specific reporting in high-impact HF RCTs. First, Au et al[4] observed that none of the RCTs reported

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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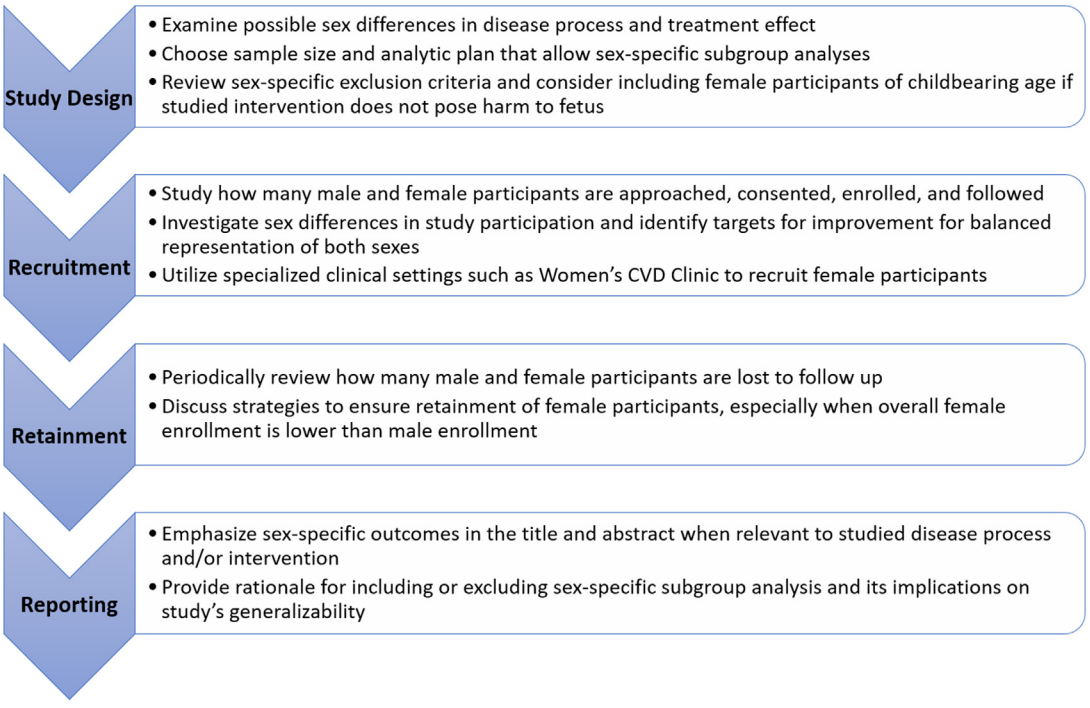
**FIGURE 1 Considerations for Improvement of Sex-Specific Analysis and Reporting in Heart Failure Clinical Trials**




CVD = cardiovascular disease.

information about trial flow and design, such as how many female patients were screened, eligible, and consented for the trials. Only 2 trials (0.9%) reported the number of female participants who were lost to follow-up. Second, sex-specific subgroup analyses of treatment and adverse effects were uncommon in modern HF RCTs, but there was an increase in temporal trends of sex subgroup analysis from year 2000 to 2020. Only one-third of the RCTs (33.4%) reported sex-specific subgroup analysis, and less than one-third (28.3%) examined treatment effect modification by sex. None of the RCTs reported sex-specific adverse effects. They found that HF trials frequently incorporated sex-specific eligibility criteria, but justification for these criteria was not provided. Lastly, the authors found that trials with female first or last authors were associated with more frequent reporting of sex composition of study participants in the abstract than male-led trials ($P < 0.01$). Also, larger trials and device trials (as opposed to drug studies) were independently associated with the performance of a sex subgroup analysis.

The study had important limitations. First, the authors were unable to assess possible interaction between age and representation of female participants in the included RCTs as age of trial participants was not reported by sex. Age is an important factor that can limit inclusion of female participants as many RCTs exclude females who are of childbearing age, pregnant, or breastfeeding. Second, the review only included large RCTs written in English language and might have unintentionally excluded smaller studies looking at a specific disease process or intervention in the female population. Finally, the association between gender of the first/last author of RCT and sex-specific reporting would not lead to a meaningful conclusion as the final publication of a large RCT is usually a product of team effort and peer review rather than the leading author's reporting style or preference.

The findings of this paper help us understand the current state of HF RCTs and identify areas of improvement. First, enrollment in female participants needs to be improved in HF RCTs to match the sex distribution of the disease. When there is underenrollment of female participants, there needs to be an increased effort for retainment and follow-up. Understanding the sex-specific breakdown of patients approached, eligible for intervention,

consented for randomization, and reasons for withdrawal/loss to follow-up will help us identify targets of improvement for better representation of female participants in large clinical trials. Second, investigation of sex-specific treatment response should begin during the initial stage of the RCT design. Whenever applicable, sex differences in the pathophysiology and dose response should be reviewed to determine the need for sex subgroup analysis, and the study should be powered for such analysis. Third, special considerations should be made when designing HF RCTs to incorporate individuals that are often excluded from clinical trials. As mentioned in the review, females of reproductive age, those who are pregnant, or those breastfeeding are often excluded from large clinical trials due to the concern for potential teratogenicity.[5,6] The sex-specific eligibility/exclusion criteria found in the RCTs were all related to potential pregnancy or lactation. While patient safety is our first and foremost concern, sex-specific exclusion criteria should only be used when there is clinical relevance, rather than as a blanket statement. Inclusion of young females should be considered when the studied intervention does not have potential teratogenicity or harm to fetus/breastfed baby. The importance of inclusion, retainment, and reporting of subgroup analysis extends to other underrepresented groups in cardiovascular clinical trials, such as ethnic minorities, those with limited access to health care (eg, non-English speakers), low socioeconomic status, and transgender/nonbinary individuals.

The authors should be applauded for their work investigating the sex-specific reporting of HF RCTs that have impacted the care of many patients over the past 20 years. This is the first study that has examined the sex-specific reporting of trial flow in cardiovascular clinical trials. The results of this study confirmed once again that it is not yet a standard practice in cardiovascular research to consistently report sex-specific findings such as trial flow, treatment efficacy, and adverse effects. In this well-conducted systematic review, the authors not only highlighted the lack of sex-specific reporting but also gave recommendations to improve the same. Additional considerations for improvement are shown in **Figure 1**. Both sexes must be represented in proportion to the sex distribution of the disease so as to improve RCT generalizability. To make sex-specific recommendations in clinical guidelines, sex-specific subgroup analyses need to be incorporated into the sample size and analytic plan of HF trials.

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**KEY WORDS** clinical trials, heart failure, sex differences