How to Incorporate Sex and Gender Into the Design of Cardiovascular Clinical Trials

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PERSPECTIVE

How to Incorporate Sex and Gender Into the Design of Cardiovascular Clinical Trials

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Women remain underrepresented in cardiovascular clinical trials. In a systematic assessment of completed cardiovascular clinical trials registered in ClinicalTrials.gov over the past decade, the median ratio of women to men was 1:2 per trial and, relative to the proportion of women in respective disease populations, the representation of women was 67% in coronary heart disease trials and 48% in heart failure trials.[1] Both sex and gender are critical determinants of health and disease—"sex" referring to the biological attributes in humans related to physical and physiologic characteristics of males versus females (such as sex chromosomes and hormones) and "gender" referring to the socially constructed characteristics of women, men, and gender-diverse individuals (such as norms, roles, behaviors, and identities). Sex and gender affect lifestyle and occupational risks, risk-taking behaviors, health-seeking behaviors, access to health care, resource use, and pharmacokinetics and pharmacodynamics of pharmacotherapies. Sex- and gender-related differences in cardiovascular disease prevalence, outcome, and treatment response are well known. However, the design of cardiovascular clinical trials neither traditionally nor routinely includes sex or gender considerations.

To incorporate sex and gender into cardiovascular clinical trial design (Table), considerations range from inclusion and exclusion criteria and intervention dose selection to protocol design, sample size calculations, study execution, leadership, data safety monitoring, and publication of results. There are numerous examples of sex differences in cardiovascular physiology that affect cutoffs defining normality in females versus males. Adult females have lower left ventricular (LV) mass and narrower QRS duration (≈10 ms on average shorter than in males), probably as a result of testosterone-related increases in cardiac mass in postadolescent males. Because the magnitude of the QRS prolongation reflects the magnitude of cardiac dyssynchrony in disease, for any given prolonged QRS duration value, a greater relative prolongation from smaller normal values in female patients means that female patients would be expected to have more cardiac dyssynchrony and thus to benefit more from biventricular pacing than their male counterparts. This was indeed the case in the MADIT-CRT study (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy). The smaller left ventricles and the predisposition to concentric LV remodeling among females (versus eccentric remodeling in male patients) also translate to a higher LV ejection fraction in females than males particularly with older age and hypertension, the population most prone to heart failure. Thus for any given LV ejection fraction value <60%, female patients with heart failure would be expected to have more LV systolic dysfunction than male patients and to benefit from therapies for heart failure with reduced ejection fraction, as seen in the PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction),[2] as well as with other neurohormonal blockers. The use of sex-neutral cutoffs in heart failure trial inclusion/exclusion criteria (eg, excluding those with narrower QRS duration or higher LV ejection fraction) may deprive some women of beneficial therapies.

Key Words: gender identity ■ sex ■ women

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Nonstandard Abbreviations and Acronyms

LV	left ventricular

Sex differences in pharmacokinetics and pharmacodynamics are rarely considered in determination of trial dose selection. The DIG trial (Digitalis Investigation Group) showed an increased risk of death in female patients, but not male patients, raising the possibility of sex differences in the pharmacokinetics of digoxin given the higher serum digoxin levels in female versus male patients postrandomization.[3] Compared with male patients, female patients have been shown to have greater drug exposure and greater pharmacodynamic effects with some drugs (eg, metoprolol). In a large observational multinational study across Europe and Asia, female participants (but not male participants) with heart failure and reduced ejection fraction had the lowest risk of death or heart failure hospitalization if taking β-blockers and either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, all at half the guideline-recommended doses, with no further decrease in risk with taking the full doses.[4] These examples underscore the importance of sex-specific dose-finding and treatment efficacy analyses. Equally important is the recognition of sex differences in adverse effects. The QT interval is longer in adult females than males, presumably owing to differences in sex hormones, making females more prone to torsades de pointes when exposed to QT-prolonging medications. Female patients have a higher bleeding risk with anticoagulation and antiplatelet therapies than male patients, with significant mortality risk associated with these bleeding events. Furthermore, female patients are at higher risk than male patients for adverse events with common invasive cardiac procedures, such as implantable cardioverter defibrillator insertion and revascularization procedures. Data safety monitoring should account for potential sex differences in adverse events, which should be reported in a sex-disaggregated manner.

Table. How to Incorporate Sex/Gender Into Cardiovascular Clinical Trial Design

Variables	Methods
Study population	• Where appropriate, use sex-specific cutoffs for inclusion where known sex differences in biological measures exist (eg, left ventricular ejection fraction, QRS duration) • Carefully consider upper and lower age and body mass index limits in exclusion criteria to account for generally older age and lower body mass index of women (vs men) with cardiovascular disease
Study intervention	• Account for potential sex differences in pharmacokinetics and pharmacodynamics in dose selection
Study assessments	• Arrange childcare and facilitate transportation • Offer flexible hours and at-home follow-up
Statistical considerations	• Consider sex-specific prevalence of the disease and need for prespecified sex-/gender- disaggregated analyses in the target sample size calculations
Study execution	• Target outreach in community settings frequented by women versus men specifically, as appropriate • Involve family members and primary care physicians • Provide gender-centered education and information about the risk and benefits of participation • Educate recruiting personnel on the importance of enrolling women • Share experience of enrolling women
Study leadership	• Target diversity in trial leadership and authorship
Data safety monitoring	• Consider potential sex differences in adverse events during safety monitoring
Study publication	• Report how sex/gender were taken into account in the design of the study • Where appropriate, routinely present results disaggregated by sex/gender, regardless of positive or negative outcome • Report data on adverse effects, withdrawals, and dropouts disaggregated by sex/gender • Discuss potential implications of sex/gender on the study results • If sex-/gender-specific analyses were not conducted, provide justification and consider the implications of the lack of such analyses on the interpretation of the results

Gender differences are important to incorporate in trial execution. Informed consent forms may be designed to account for the greater perception of risk from trial participation; the greater aversion for risk-taking, especially under stress; the longer decision-making process; and the greater propensity to external influence (eg, by family and friends) among women than men. In the WIN-Her Initiative (Women Opt-In for Heart Research), quantitative surveys and qualitative interviews identified that potential barriers to trial participation among women included suboptimal understanding of trial processes, limited information from physicians, and misperceptions regarding the risks versus benefits of participation, suggesting that gender-specific educational materials may enhance women's participation in clinical trials. Options to facilitate time-efficient participation, while continuing family caregiving roles, may be emphasized during consent taking.

Equity in access to trials is crucial. Women are more likely than men to be subject to health disparities that arise from sociocultural and political factors. In many parts of the world, gender discrimination, socioeconomic burden, and constraints on physical mobility limit women's access to optimal health care. Compared with men, women are more likely to be responsible for childcare and to be doing unpaid domestic work. Targeting outreach in settings frequented by women, arranging childcare, providing transportation, and offering flexible hours or at-home follow-up can help address gender inequities and facilitate women's participation in trials. Diversity in clinical trial leadership and authorship also play a significant role, and trials led by women investigators have been shown to recruit a greater proportion of participants who are women.[5]

Sex and gender are critical to the optimal interpretation, validation, and generalizability of cardiovascular clinical trial results. Numerous organizations, including the US National Institutes of Health, Sex and Gender Equity in Research, American Heart Association, Canadian Institutes of Health Research, and European Commission, have called for incorporation of sex and gender considerations in the design of clinical research and trials. It is time to heed that call, not as an exception but as routine practice, with mandatory incorporation of sex and gender considerations into clinical trial design.

ARTICLE INFORMATION

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