

REVIEW

Taking cardiology clinical trials to the next level: A call to action

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Physicians previously perceived heart disease to be a man's disease; yet, since 1984, more women have died of ischemic heart disease. Because women who develop obstructive coronary heart disease and heart failure tend to do so 10 years later than men, cardiology clinical trials that use arbitrary age cutoffs or exclusion criteria based on comorbidities and polypharmacy often limit the pool of potential participants to a greater extent for women. Issues related to trial design and insufficient accounting for female-predominant disease patterns have contributed to low rates of enrollment of women in certain domains of cardiology research. Accordingly, women do not benefit from as rich an evidence base for cardiology as men. Here, we review major sex differences in heart disease and discuss areas of cardiology research in which women have been underrepresented. Considering the widespread sex differences in cardiovascular structure and function, it is important to include balanced numbers of women and men in cardiovascular clinical trials. Beyond inclusion, sex-specific reporting is also essential. Moreover, with ongoing developments of clinical-trial methodology, it is imperative to seek innovative ways to learn as much as possible about how interventions behave in women and men. Adaptive trials are specifically identified as promising opportunities to consider sex-based analyses at interim stages, allowing sex-specific flexibility as these trials unfold. Finally, we emphasize the importance of factoring sex as a biological variable into the design, analysis, and reporting of preclinical research, because this research critically informs the design and execution of clinical trials.

KEYWORDS

Adaptive Design, Cardiovascular, Clinical Trial, Exclusion Criteria, Gender Differences, Heart Failure, Ischemic Heart Disease, Sex as a Biological Variable

1 | INTRODUCTION

Historically, the importance of heart disease in women has been underappreciated. Mortality statistics show that heart disease is the most common cause of death among men and women in the United States.¹ Nevertheless, some physicians continue to perceive lower risks of cardiovascular disease (CVD) for women who have the same quantified risks as men.² Often, women with heart disease have worse outcomes and are less likely to receive beneficial treatments than men. In addition to these healthcare disparities, women have been underrepresented in many mixed-gender cardiovascular (CV) clinical trials.³⁻⁸ Consequently, women do not benefit from

gender-specific cardiologic evidence-based medicine as much as men do. Fortunately, there is increasing awareness of this disparity. It is now clear that more thorough consideration of sex and gender influences on heart disease is warranted during the planning, funding, execution, analysis, and reporting of CV clinical trials, as well as in the preclinical research that informs these trials.

With heart disease, women and men exhibit many similarities in risk factors, pathophysiology, manifestations, and outcomes. However, the recent inclusion of more women in CV clinical research reveals an expanding horizon of sex/gender differences across all domains of CV health and disease, including heart rhythm, valvular disease, ischemic heart disease (IHD), and heart failure (HF).⁹ Within

those domains, research has started to show substantial sex differences in risk factors, epidemiology, disease manifestations, and/or clinical outcomes.

2 | WOMEN AND HEART DISEASE

For both sexes, the overall mortality rate from IHD declined dramatically in the past few decades, but recent advances in CV medicine resulted in much greater declines in case fatality rates for men.¹⁰ Since 1984, more women than men have died annually from IHD in the United States.¹⁰ Traditional risk factors from research emphasizing men underestimate the risk of IHD in women, whereas consideration of novel biomarkers improves risk detection in women.¹¹ Such biomarkers include disrupted ovulatory cycling in premenopausal women and elevated levels of high-sensitivity C-reactive protein.¹²

In many cases, the initial presentation of IHD in women is acute myocardial infarction (MI) or sudden cardiac death (SCD).¹³ Although chest pain is the most common symptom of acute coronary syndromes (including MI and stable angina) in everyone, women with acute coronary syndromes are less likely than men to present with chest pain. Women are more likely to present with upper-back pain; pain in the neck, arm, and/or jaw; difficulty breathing; weakness; and a sense of dread.¹⁴ Compared with men, women have a significantly higher risk of mortality in the first year after an acute MI,¹⁵ especially women age < 55 years.^{16,17} Moreover, women who present with MI are less likely than men to receive fibrinolytic drugs, stents, and related therapies.^{13,18}

Among patients with signs and symptoms of IHD, women have more adverse outcomes than do men, despite having less severe obstructive coronary artery disease (CAD) and better systolic function than men, on average, even after adjusting for age.^{10,13} The female-typical pattern of IHD differs from the male-typical pattern of IHD (also known as coronary heart disease [CHD]), which is characterized by angiographically detectable coronary artery obstructions. In contrast, abnormal coronary reactivity, microvascular dysfunction, and vascular plaque erosion with distal microembolization are primary factors contributing to the IHD pathophysiology typical of women.¹²

Vascular reactivity underlies several disorders that disproportionately affect women, such as migraine headaches, autoimmune arteritis, and Raynaud phenomenon.¹² Thus, it is not surprising that reactivity of the coronary microvasculature plays an important role in the IHD pathophysiology of women.^{11,19} Moreover, plaque erosion (vs plaque rupture) is more common in women (vs men) and is the most common cause of acute coronary thrombosis leading to SCD in women age < 50 years.^{9,13}

The same interventions and therapies for obstructive CAD are generally considered to be optimal for both men and women with this disease, though effectiveness of some treatments may vary between men and women. Consistent with a lingering view that obstructive CAD is primarily a man's disease, women with this condition are less likely to receive several of the indicated medical treatments, such as coronary revascularization, statins, β -blockers, aspirin, and therapeutic lifestyle coaching.^{11,12} Treatment of nonobstructive CAD generally focuses on improving symptoms (eg, angina), vascular

function (eg, coronary microcirculation, endothelial function), and/or lifestyle (eg, exercise).^{11,12} To develop better imaging and treatment paradigms for nonobstructive CAD, robust enrollment of women in clinical studies is essential and will ultimately benefit coronary microvascular health in everyone.

Based on the National Health and Nutrition Examination Surveys (NHANES) from 2011 to 2014, HF was estimated to affect 6.5 million Americans age \geq 20 years.²⁰ Important risk factors for HF include advanced age, CHD, hypertension, diabetes mellitus, obesity, and smoking.^{20,21} The most common cause of HF in elderly women and in men of all ages is IHD, whereas more likely causes of HF in younger women are nonischemic (eg, valvular) heart disease and hypertension.²² The overall incidence of HF is significantly higher in men than in women. Yet, the total number of men and women living with HF in the United States is similar, because women have longer average lifespan and longer survival after HF.^{9,22,23} With the aging of the population, the American Heart Association forecasts a 46% increase in the prevalence of HF from 2012 to 2030, resulting in >8 million people (age \geq 18 years), or 1 in every 33 people, in the United States projected to have HF in 2030.²⁴

HF may be accompanied by reduced or preserved ejection fraction. The 2 forms of HF are nearly equally common,²¹ and both are associated with a high degree of morbidity and mortality.²⁵ Heart failure with preserved ejection fraction (HFpEF) is significantly more prevalent in women.^{9,21,26} When age and other risk factors are adjusted for, however, the risk of HFpEF appears similar in men and women, whereas the adjusted risk of HF with reduced ejection fraction remains greater in men.²⁶

Extensive research has been done on the pathophysiology of HF with reduced ejection fraction, and numerous effective therapies have been developed for this male-prevalent form of HF.^{21,25} In contrast, few treatments have been shown to be beneficial for HFpEF based on randomized clinical trials.^{9,25} In large part, those treatment failures resulted from a lack of consensus on criteria for diagnosing HFpEF and enrolling participants in HFpEF clinical trials,²⁷ as well as underenrollment of women in clinical research on HF, in general.⁹ Recently, however, consensus has increased regarding the evaluation of left ventricular function and the diagnosis of HFpEF,²⁵ which will help identify women and men with similar HFpEF pathophysiology for gender-balanced clinical trials.

Many CVD risk factors are shared between men and women, but their prevalence and the relative risks they confer on various CV conditions vary substantially by gender.^{9,12,28} For instance, systemic autoimmune diseases, which are much more common in women, are associated with accelerated atherosclerosis and increased CHD risk.⁹ Among CVD risk factors, the influences of stress and other sociocultural factors on heart disease exhibit some of the biggest differences between men and women. For example, marital loss through divorce early in life is associated with a significant increase in a woman's risk of CVD later in life, which is likely mediated by the negative effects of divorce on emotional well-being and socioeconomic status.²⁹ By contrast, the relationship between marital loss and CVD in late mid-life appears negligible for men. In addition, emerging data indicate that younger women may be particularly susceptible to mental stress-induced myocardial ischemia.^{30,31}

Stress-related cardiomyopathy (ie, Takotsubo cardiomyopathy or “broken heart syndrome”) is a rapidly reversible form of acute HF characterized by transient apical ballooning,¹⁴ although other ventricular patterns are also described.³² Upon hospital admission, symptoms and electrocardiography of patients with stress-related cardiomyopathy commonly mimic those of MI. Usually triggered by intensely stressful emotional or physical events, Takotsubo cardiomyopathy overwhelmingly affects women,³³ especially postmenopausal women.¹⁴

During pregnancy, the risk of heart disease increases, and certain complications of pregnancy are predictors of heart disease in later life. Pregnancy increases the overall demand placed on the maternal CV system, which is accompanied by increased blood volume and cardiac output, systemic vasodilation, decreased arterial pressure, and remodeling of the heart and vasculature.³⁴ Women have higher risks of cardiac arrhythmias and are at sex-specific risk for MI due to spontaneous coronary-artery dissection during pregnancy or peripartum.⁹ Pregnancy complications such as gestational diabetes substantially increase a woman's risk of later developing diabetes mellitus, which is a strong risk factor for CVD,^{9,28} and preeclampsia doubles a woman's risk of IHD later in life.¹²

3 | INCLUSION OF WOMEN IN CARDIOLOGY CLINICAL TRIALS

Given all that is known about the myriad sex and gender influences on diseases of the heart, clinical trials in cardiology must be designed to answer questions of clinical relevance for both men and women. Unfortunately, women have been underrepresented in many studies from which CVD prevention and treatment guidelines have been drawn. This is particularly true for clinical trials in HF, CAD, hyperlipidemia, and arrhythmia.³⁻⁷ For example, influential trials that investigated the efficacy of implantable cardioverter-defibrillators for primary prevention of SCD in patients with advanced HF enrolled <30% women.⁹ In turn, this underenrollment of women may have contributed to unwarranted gender bias in the use of implantable cardioverter-defibrillator therapy.⁹

Because heart disease generally occurs later in life for women than men, the use of exclusion criteria—such as arbitrary upper age limits and other indirect limits to recruitment of older individuals—contributes to the underrepresentation of women in cardiology research.³⁵ Manifestations of obstructive CHD and HF tend to occur approximately ≥ 10 years later in women, whereas the overall lag for MI and SCD may be as high as 20 years.^{4,10,20,22,25} When an arbitrary age cutoff is applied in a clinical investigation, a common outcome is greater a priori reduction of the pool of potential female participants. Moreover, in terms of age, the eligible women who are enrolled may be less representative of the range of women with the condition in the general population, compared with the situation for men enrolled in the study.

A survey of clinical trials on HF (initiated between 2002 and 2008) found that 1 in 4 trials enforced arbitrary upper age limits during enrollment.³⁵ More than 40% of the trials employed poorly justified exclusion criteria that could limit the enrollment of older

participants.³⁵ Nevertheless, some exclusion criteria are necessary, based on bioethics or study design. In an experimental drug trial, for example, there is good justification for excluding individuals who are taking a pharmacologically similar drug or one that could interact with the experimental drug or confound interpretation of the experimental drug's effects. Variation in number and type of comorbidities among study participants can also confound results of clinical trials. Both the percentage of adults with multiple chronic conditions and the prevalence of polypharmacy increase with age.^{35,36} Given the need to account for those factors and their effects on enrollment, what strategies might help achieve equitable participation of women and men in clinical trials, who are representative of populations bearing the greatest burdens of heart diseases?

The success of a clinical trial depends on the appropriate recruitment of suitable participants as well as the retention of participants (both men and women) until completion of the study. Whenever possible, the use of arbitrary upper age cutoffs should be avoided in clinical research, particularly with diseases that are most prevalent in elderly populations. When justified exclusion criteria preclude age-appropriate women from participating in a study to a greater extent than men, expanded efforts are warranted to engage female participants, including targeted outreach in community settings frequented by women. Such outreach would educate women on the safeguards built into clinical research, the rights of study participants, the potential direct benefits to study participants, and the long-term benefits to women in general, including the participants' daughters and granddaughters. Clinical researchers can also engage an expanded array of community-based healthcare providers to share opportunities to participate in clinical research with appropriate female patients. Other ways to potentially make clinical trials more attractive to women might include female-friendly branding; emphasis on the involvement of female clinician-researchers; selection of sites that fulfill traditional needs of women, such as childcare needs; flexible clinic hours; and the option of at-home follow-up. In certain research topic areas, it might even be possible to create inviting atmospheres that women may find more appealing than traditional clinical settings.³⁷ Surveys of completed clinical trials should be done to examine pitfalls and successes with respect to age-appropriate recruitment and retention of female participants, and this information should be disseminated in addition to the scientific results of clinical research.

As well as varying by gender, CVD incidence varies substantially by race/ethnicity.²⁰ However, some racial/ethnic groups (eg, Hispanic) continue to be underrepresented in clinical research, in general.^{38,39} Accordingly, achieving appropriate representation of minority women in clinical research will benefit from culturally competent strategies for engaging study participants,^{39,40} in addition to the above considerations for enhancing female participation.

4 | BEYOND INCLUSION

Judiciously balanced inclusion of women and men in clinical research, alone, is not enough to elucidate important sex/gender influences on health and disease, nor to inform gender-based clinical guidelines. Appropriate trial designs, innovative methods for sex/gender-based

analyses, and sex/gender-specific reporting are also essential to learning as much as possible about the impact of interventions in both women and men. Differential enrollment of men and women in mixed-gender trials has been commonplace and is inevitable to some extent, especially for certain conditions and contexts. Accordingly, sex-stratified randomization of participants to different arms of a clinical trial should be routine practice in trial design.⁴¹ By not doing so, investigators run the risk of inflating a trial's false-positive error rate. In addition, clinical investigators commonly report that they controlled for the effects of gender in their statistical analyses, without reporting the amount of variance accounted for by gender or whether this factor was a significant covariate in the analysis. Statistically accounting for a gender effect is tantamount to acknowledging its potential importance. We discourage investigators from controlling for gender without reporting the direction and magnitude of this covariate's influence on the results.

Clinical studies are sometimes designed such that individuals receive treatments in groups. When trial participants are unconnected to one another initially but are randomized to groups for treatment (eg, with behavioral interventions), these studies are called individually randomized group treatment trials.⁴² By contrast, group-randomized trials involve existing groups of participants, in which individuals have some connection to one another before and during the trial (eg, trials conducted in communities or schools, or at work-sites).⁴² In mixed-gender individually randomized group treatment trials, investigators should routinely employ constrained randomization to ensure that gender ratios do not vary substantially among groups assigned to different treatment arms. With group-randomized trials, careful attention must be paid to gender ratio variation among the groups (or sites) where the clinical trials are to be carried out, to avoid associated biases.

Adaptive clinical trials, which have flexible design elements and methods that can adjust based on interim assessments, can reduce the costs and increase the efficiency of clinical research. However, dynamically flexible trial designs typically have increased statistical complexity, accompanied by greater necessity to control for hidden biases, and can sometimes result in longer study durations.⁴³ Nevertheless, when adaptive clinical trials are well designed and maintain rigorous masking and appropriate oversight, they promise to generate more information on treatment effectiveness and safety at lower costs than more traditional designs.⁴³ Consequently, the use of adaptive trial designs in clinical research is likely to expand considerably across disciplines in the upcoming years. Researchers using such designs should consider gender-specific analyses at the interim steps of their trials to monitor the risks of toxicity in a gender-specific manner, to differentially adapt drug dosage for men and women based on efficacy considerations, and to reallocate remaining samples between men and women when efficacy is found only in 1 gender.

The need for appropriate representation of women in clinical research applies to all phases of clinical trials.⁴¹ Early-phase trials typically aim to determine the recommended dose (or methodology) and the toxicity profile (or other risks) of an investigational drug (or intervention). It is critically important to have equitable representation in early-phase trials for drugs that are intended for both men and women, because in general, women are more likely than men to

have adverse drug reactions.⁴⁴ Pragmatic clinical trials, which typically follow the approval of a new drug, device, or procedure, are carried out in real-world clinical settings to investigate the effectiveness of an intervention in broad patient populations. Pragmatic trials are especially amenable to recruitment of older individuals, despite comorbidity and polypharmacy, making these late-phase trials particularly relevant to heart diseases that tend to affect women later in life than men.

In mixed-gender clinical trials, investigators should routinely look for sex/gender influences on research outcomes. The Bayesian statistical approach is an alternative to traditional frequentist methods for testing hypotheses about gender differences.⁴⁵ The Bayesian approach, which formally integrates prior information with newly acquired data, is especially promising for testing gender differences in more complex study designs, including adaptive clinical trials, post-marketing pragmatic trials, synthetic cohorts that creatively combine data from multiple sources, and meta-analyses. Regardless of how gender-based analyses are conducted, there is a need for expanded gender-specific reporting of clinical-trial results.⁴⁵ Otherwise, the benefits of clinical trials cannot be fully realized for the women and men who participated in the research, nor will the broader biomedical community know to whom the results are most applicable. Even when analyses fail to find evidence of sex/gender differences, researchers should report descriptive statistics disaggregated by sex/gender—via tables, by way of plots ideally with points color-coded by sex/gender, or in online supplementary appendices. Such information is important to inform sample-size calculations for subsequent studies.

5 | SEX AS A BIOLOGICAL VARIABLE IN PRECLINICAL RESEARCH

The design of clinical research is informed by the foundations of pre-clinical and translational research, which are fueled, in turn, by even more fundamental discoveries in basic science. These connections across the research continuum are critical to well-designed and well-executed clinical investigations—not only in cardiology,⁴⁶ but in all areas of biomedical research.⁴⁷ The many differences in heart health and disease between men and women have their origins in factors ranging from biological (including genetic, molecular, and physiological factors) to psychosocial. Indeed, the sex-chromosomal complement influences many fundamental mechanisms of CV structure and function, which are apparent across preclinical research models, including cells in culture, isolated tissues, and animal models.⁴⁶ Therefore, in all preclinical and translational research that precedes CV clinical trials, it is necessary to consider the possibility of sex differences, to investigate them when appropriate, and to report such results regardless of whether sex differences are present or absent. In fact, sex influences are so widespread across medical disciplines, and knowledge of them is so critical to scientific rigor and reproducibility, that the National Institutes of Health (NIH) expects sex as a biological variable to be factored into research designs, analyses, and reporting in NIH-funded vertebrate animal and human studies.⁴⁷

6 | CONCLUSION

There are many reasons to strive for balanced gender representation in clinical trials and to make the most of the data generated by those trials. Heart diseases and diseases across many other organ systems manifest differently in men and women. Disease symptoms are often reported differently by men and women, and the normal ranges for disease biomarkers can differ substantially by sex. Moreover, sex-based differences in the pharmacokinetics and pharmacodynamics of drugs are common. Definitions of many therapeutic outcomes vary by sex/gender, and men and women often respond to interventions differently. In addition, adverse-event profiles are likely to differ as well, because women generally tend to report more adverse events than do men.

When it comes to sex and gender in clinical research, clearly the one-size-fits-all approach cannot provide definitive answers to clinically important questions for everyone. It is time to move beyond simple inclusion in clinical trials to enhance the fidelity of the biomedical research continuum by threading sex and gender considerations from point to point throughout the entire research spectrum. Doing so will improve the efficiency of translation. The enhanced sex- and gender-attentive approach to biomedical research will expand our knowledge base on female and male biology, minimize risk of harm to both men and women, and accelerate the drug-development pipeline. This approach will also provide the sex/gender-relevant evidence necessary for clinicians to practice truly evidence-based sex- and gender-appropriate medicine and deliver individualized clinical care.

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Conflicts of interest

The authors declare no potential conflicts of interest.

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