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Research paper

Underrepresentation of women in cardiac imaging trials: A review

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ABSTRACT

Inclusion and equal representation of women in cardiovascular imaging trials are essential to provide insight into the factors impacting women's heart health and outcomes. Despite heart disease being the leading cause of mortality for women in the United States, women have been underrepresented in cardiovascular clinical trials, including imaging trials. Research demonstrates that women have key sex-specific differences in the pathophysiology of cardiovascular disease, the evolution of disease state, and disease manifestation (Solimene, 2010; Nevsky et al., 2011 [1,2]). This understanding and acknowledgment come decades after clinical providers have extrapolated data from cardiovascular disease clinical trials conducted primarily on Caucasian men, assuming the data were generalizable to sex, race, and ethnicity. The current cardiology society guidelines, which recommend optimal medical therapies for various cardiovascular diseases, are based on trials predominantly focused on men rather than women.

Sex-based research, governmental and institutional task forces, and policies on gender equity have made inroads into the disproportionate number of women's enrollment in clinical research. The National Institutes of Health in the 1990s set forth requirements on incorporating women and minorities in research, including clinical trials (Mastroianni et al., 1994; Mieres et al., 2014 [3,4]). Continued progress is imperative to improve the gap in the number of women enrolled in clinical research trials.

1. Introduction

The lack of female representation in cardiovascular imaging trials has far-reaching implications in diagnosing and managing female patients with cardiovascular disease (CVD), the leading cause of death among women. Studies demonstrate that women have an increased risk of death or heart failure after a heart attack [5]. Still, despite this sobering statistic, women have historically been underrepresented in cardiovascular trials [6]. Jin and colleagues systematically screened cardiovascular trials registered on [ClinicalTrials.gov](https://clinicaltrials.gov) from 2010 to 2017. They identified 740 trials for analyses of women's representation, finding the overall representation to be low at 38%, with men continuing to predominate among current decade cardiovascular trials [6].

Pathophysiological differences in CVD development and progression in women contribute to a disproportionate burden of death and disability from cardiovascular disease in the United States [1,5,7]. Despite critical differences by sex in clinical presentation, evaluation

and treatment, the clinical approach to men and women with CVD has historically been homogeneous [8]. In the *State of the Science in Women's Cardiovascular Disease*, Norris et al. cites the stunning lack of research oriented explicitly to women and the under-representation of women in CVD research studies as significant contributing factors to the disparate care of women with CVD [9]. Their paper also highlights that while differences in sex-specific pathophysiology, diagnostic tests, and treatment efficacy are often acknowledged by physicians and researchers, its influences on the clinical care of women have been slow or absent [9].

Cardiovascular imaging trials play an essential role in addressing this disparity. Imaging trials establish normative values, diagnostic test characteristics and a method to evaluate the safety and efficacy of drugs and devices. Trials also provide evidence-based approaches to developing and evaluating novel therapeutics and ultimately shape practice guidelines. Considering known differences in the presentation and treatment of heart disease in women, there is increasing recognition of the need for cardiac imaging modalities to provide sex-specific risk assessment and prognostication. Over the past decades, various

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initiatives, law reforms, and revised research policies have helped increase the number of women in clinical CVD trials. However, the overall enrollment of women still lags behind men in clinical CVD trials, notably when excluding sex-specific trials. Without thoughtful and intentional inclusion of women in CVD imaging trials, the gap in sex outcomes is likely to persist and potentially widen further.

This paper aims to review the history of under-enrollment of women in cardiovascular imaging trials, to assess the progress made thus far in diversifying clinical trial enrollment, to discuss the barriers to the proportional inclusion of women in cardiovascular imaging trials, and finally to address the importance of closing this gap between the sexes and emphasize the relevance and impact on current clinical practice.

2. Review

2.1. Historical context

Participation of women in clinical trials has been fraught with longstanding bias founded on fear. In the 1960s, evidence emerged linking fetal malformation to thalidomide, broadly used in Europe. The Federal Drug Administration (FDA) subsequently blocked approval of this drug in the United States for concern that its use would cause similar deleterious effects in American women of childbearing potential. This caution led to broad hesitation to include women of childbearing years in clinical trials. In 1977, the FDA formalized this sex-based exclusion in published guidance recommending that women of childbearing potential not be included in Phase I or Phase II clinical trials, ostensibly protecting women if they become pregnant [10]. Consequently, women were not included in any early phase drug safety tests until 1993, when the National Institutes of Health (NIH) Revitalization Act addressed this longstanding bias by legislatively prioritizing the inclusion of women in clinical research and trials [3].

In the interim, male-dominated cardiovascular trials continued to be conducted, extrapolating results to women. Many influential studies of cardiovascular disease have notably not included any women participants. The Multiple Risk Factor Intervention Trial Research Group (MRFIT), the Coronary Drug Project (CDP), Lipid Research Clinic, and the Physicians' Health Study (PHS), all excluded women, and all have a widespread and prominent influence on the treatment and prevention of heart disease [3,11]. The extrapolation of these results to women is flawed. They overlook significant physiologic differences in men and women and disregard the salience of these differences in the natural history of cardiovascular disease [3,11]. Applying non-generalizable sex imbalanced research has persisted and has significant implications in the health and wellbeing of women with cardiovascular disease.

Two critical reports served as pivotal catalysts for creating and passing the NIH Revitalization Act: the 1985 U.S. Public Health Service Task Force on Women's Health Issues and the 1992 General Accounting Office (GAO) report on sex differences in pharmaceutical research. The 1985 U.S. Public Health Service Task Force report reviewed the historical lack of research in women's health. It criticized the scientific community for compromising the quality of health information available and health care quality to women [12]. This was followed by the 1992 GAO report, which stated that due to physiological differences, men and women could respond differently to the same drug, cardiovascular drug metabolism could differ between men and women. In addition, women's natural hormones and interaction with oral contraceptive hormones could cause varying responses to certain cardiovascular drugs.

The GAO report also highlighted that women were infrequently included in clinical trials despite the evidence supporting significant differences in how sex can affect drug response. Drug trial data were not studied for potential sex-related differences in the therapeutic response [13]. These impactful reports were followed by the 1993 FDA Guidance Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs which withdrew the 1977 restriction on the participation of women of childbearing potential in Phase I and Phase II clinical trials. In

addition, the critical 1993 NIH Revitalization Act required NIH-funded clinical trials to include women and minorities as participants and assess outcomes by sex and race or ethnicity [14]. The FDA and NIH actions brought awareness to the importance of sex inclusion in clinical research and highlighted a gap in clinical care.

2.2. Current state

Nearly thirty years after the 1993 NIH Revitalization Act, cardiovascular clinical trials continue to underperform in achieving sex parity. The field of cardiovascular imaging has been hampered chiefly by three factors: 1) the lack of imaging trials evaluating sex-specific differences, 2) the persistent underrepresentation of female participants in clinical trials, and 3) vague language in current policy and lack of enforcement of current policy from national agencies in charge of regulating and approving clinical trials, pharmaceutical drugs, and medical systems and devices.

2.3. Sex differences in cardiovascular imaging

Intrinsic anatomical sex differences may result in differing sensitivity and specificity of noninvasive testing [15]. Women have smaller aortic dimensions, left ventricular chamber size and pulmonary arteries even after adjusted for body size [2]. Compared with men, women have smaller coronary artery sizes, potentially limiting the visualization of distal coronary artery segments on imaging [16]. In addition, breast tissue attenuation and prosthetic breast implants may alter the quality of the anterior wall imaging with echocardiography and Single-Photon Emission Computed Tomography (SPECT), which may require different post-processing methods for analysis [17]. Sex-based differences have also been demonstrated with coronary vasomotor dysfunction and microvascular dysfunction [1,18–22]. Pregnancy causes significant changes in heart rate, blood volume, cardiac output, and vascular resistance. In pregnancy, the heart is displaced upward and laterally secondary to the enlarged uterus [23]. Echocardiograms and cardiac magnetic resonance imaging (MRI) without gadolinium contrast are preferred imaging modalities during pregnancy. Moreover, computed tomography, nuclear medicine, or invasive coronary angiography are judiciously used during pregnancy due to the risk of ionizing radiation on the fetus weighing against the benefits to the mother.

When evaluating sex differences in valve disease, aortic stenosis is the most studied and studies have revealed critical differences [24]. Women tend to have less valvular calcification and more fibrosis than men, which remains significant after considering the smaller size of women's hearts and aorta [24]. Cardiac MRI studies evaluating aortic stenosis demonstrate that men are more likely to develop eccentric hypertrophy than women with a similar degree of aortic stenosis, whereas women display concentric remodeling and hypertrophy [24,25]. Interestingly, concentric hypertrophy is an independent predictor of mortality in women and not men [24–26]. In addition, women have lower indexed left ventricular (LV) mass but a greater extent of diffuse myocardial fibrosis and higher estimated filling pressures (E/e') [24,25]. Women more frequently present with paradoxical low flow low gradient aortic stenosis despite preserved LV ejection fraction [24,27,28]. Men are more likely to have reduced LV ejection fraction with low flow, low gradient aortic stenosis [24].

2.4. Imaging trials evaluating sex-based differences

Noninvasive cardiac imaging has become essential in assessing, diagnosing, and managing cardiovascular diseases. Despite the reliance upon cardiovascular imaging modalities, not much work has been done to explicitly examine sex-based aspects in cardiac imaging. For the few imaging trials that examine sex-based differences, their outcomes may not translate to tangible practice changes [29]. For example, though echocardiographic data for left ventricular hypertrophy, ventricular

function, and strain remains variable and often contradictory, there has been no sex-based study to date that examines the sex differences in the development of left ventricular hypertrophy, diastolic dysfunction, and diastolic heart failure, disproportionately affecting older women with hypertension [30]. Studies on MRI have examined sex discrepancy in diagnostic performance in the context of the pathophysiologic differences [4]. Despite evidence showing cardiac MRI to have superior sensitivity, negative predictive value, and positive predictive value compared to SPECT in women, SPECT is consistently utilized in chest pain evaluation and diagnosis guideline algorithms [28–31]. SPECT underperforms partly due to spatial resolution limitations in evaluating women's smaller heart sizes [31–33].

According to the United States National Library of Medicine clinical trials database, nearly five thousand cardiovascular imaging trials were initiated. Nevertheless, there remains a persistent lack of sex equity in imaging trials as demonstrated and critiqued in a recent study on peer-reviewed articles of NIH-funded randomized controlled trials published in high-impact journals in 2015 [34]. The authors found that 15% of studies enrolled fewer than 30% of women. In addition, 72% of the studies reviewed did not include sex in their analyses [34]. The disparity is even more significant when separating out the trials that focus mainly on gender or sex-based research. One might postulate that enrollment inequality in research trials would galvanize an explosion of gender or sex-based clinical research trials. This has not borne out to be true. Our review of ongoing and recently closed cardiovascular imaging trials from [ClinicalTrials.gov](https://clinicaltrials.gov) showed merely twelve total trials with gender or sex-based research focus. After excluding imaging trials studying disease states specific to women, e.g., preeclampsia, the total number of women-focused cardiovascular imaging trials dwindles to just five.

2.5. Persistent underrepresentation of women in clinical trials

Despite trial guidelines and legal requirements put in place to ensure inclusivity, recent studies continue to demonstrate the underrepresentation of women in CV trials, the latest being a report from the American College of Cardiology Cardiovascular Disease in Women Committee [35]. The report's authors identified multiple barriers to the equitable representation of women in clinical trials, including lower rates of referrals to general cardiology and cardiology subspecialties resulting in fewer women being screened for potential enrollment in cardiovascular clinical trials [35]. Ageism, lack of awareness, and trust are additional identified barriers seen across sex lines [35]. Logistical barriers such as transportation concerns, childcare, and eldercare concerns tend to affect women significantly more than men, making the threshold to participation in clinical trials higher for women [35]. The lack of diversity among trial leadership is also a significant additional barrier [35]. The relative dearth of women in clinical trial leadership positions directly impacts the enrollment of women in clinical trials, with women-led trials recruiting more women participants [35]. Finally, pregnant women and women of childbearing years have historically been considered a vulnerable population, previously classed with children, prisoners, and the mentally impaired, with the needle slowly moving on the widespread inclusion of eligible women of this demographic in clinical trials [35].

2.6. Vague language and lack of enforcement

Increasingly, medicine is incorporating artificial intelligence systems with computer-aided diagnosis and image-based screening. Larrazabal et al. demonstrated a decrease in the performance of algorithms based on databases used to train artificial intelligence systems that lack diversity and gender balance [36]. Despite FDA published guidance regarding the importance of sex inclusion in the design and evaluation of clinical trials and medical devices, there is no explicit identification of sex as a relevant demographic variable. Many imaging datasets do not contain sex information at the patient level. Based on these findings, the

authors called for explicit sex balance and diversity recommendations from national regulatory agencies for the academic medical imaging community [36].

The Institute of Medicine Committee performed a comprehensive study of federal clinical research trial policies, historical practices, policy changes, and current criteria governing the participation and evaluation of women and men in clinical trials. In their book, *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, the committee criticized the lack of reliable, comprehensive information on the participation of women and various subgroups of women in clinical studies, today or in the past, putting forth recommendations to the NIH regarding the inclusion of information on the participation of women in clinical trials in an accessible registry [3]. Unfortunately, this strong recommendation from the Institute of Medicine has not yet resulted in a substantial increase in reporting results stratified by sex, suggesting noncompliance with NIH policies [37].

Efforts to increase women's representation in clinical trials were primarily due to the institution of large single-sex trials with no overall change in the sex composition in most cardiovascular disease trials [38]. This finding was echoed in a subsequent study on the enrollment of women in NIH randomized controlled trials. The authors argued that, excluding single sex-based trials such as the Women's Health Study and the Women's Health Initiative, NIH policies have not yielded success in bringing about a meaningful increase in women's enrollment in NIH-sponsored clinical trials.

3. Conclusion

Even with increasing recognition of crucial sex differences in cardiovascular disease, our review highlights the extent to which women are persistently underrepresented in cardiovascular imaging trials despite organized efforts to achieve gender parity in clinical trials. Recruitment of women as clinical trial leaders, acknowledgment and accommodation for sex-specific barriers to enrollment in clinical trials, and increased performance of sex-specific analyses will further our understanding of the pathophysiology of CVD in women and the varied manifestation across cardiovascular imaging modalities. Continued attention to this subject and interventions such as those mentioned above are needed to improve cardiovascular outcomes for women.

CRediT authorship contribution statement

Rachel-Maria Brown: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Catherine Weinberg:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Caroline Ong:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Jennifer H. Mieres:** Conceptualization, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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