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Commentary

## Underrepresentation of women in cardiovascular trials- it is time to shatter this glass ceiling

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### ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in women, with underrepresented minority (URM) women experiencing the highest mortality rate. For decades, there has been an underrepresentation of women in CVD trials. Although more recent studies have increased the number of women enrolled in these trials, systematic reviews have demonstrated that this enrollment is still low. The National Institute of Health along with other agencies have boosted their efforts to increase enrollment of women and URM populations in CVD trials. Despite these efforts, there still remains a gap. This paper reviews the magnitude, implications and causes of the underrepresentation of women in CVD trials. A proposed multifaceted approach to solving this issue is also outlined in this commentary. Hopefully, implementation of these proposed solutions may facilitate the increase of women, including URM women, enrolled in CVD trials. It is anticipated that this will improve CVD outcomes in these patients.

### 1. Introduction

Cardiovascular (CV) disease is the leading cause of mortality for women worldwide [1,2]. In the United States women bear a disproportionate burden of death and disability from CV disease [1,3,4]. African-American women in the US bear the greatest CV mortality burden relative to other ethnicities [5]. Despite this fact women including women from underrepresented minority populations (URM) are still consistently poorly represented in research studies [6]. This has widespread consequences in the overall evaluation, stratification, and treatment of women with CV disease, as prior research based on male participants should not be extrapolated to women. A study by Jin, et al., found that out of 740 completed CV trials including a total of 862,652 adults, only 38.2% were women [6].

This under-representation extends to multiple CV research areas, particularly imaging trials as was outlined in the review article by Brown, et al. published in this edition of the Journal. Cardiac imaging is a natural starting point for the assessment of disease burden. In the most recently completed CV imaging trials, the PROMISE trial included the greatest proportion of women (52.7%) [7]. However, in other imaging trials, women still only represent a minority of the subjects [8–10]. This commentary will review the magnitude and implications for the

underrepresentation of women in CV trials as well as the proposed causes potential solutions of this underrepresentation.

### 2. Magnitude of the problem and its implications

The continuing work to advance the health of women has included advocacy for increasing the representation of women in clinical studies. It has been reported that even when women have been included as subjects in clinical research, the influence of sex and ethnicity are not widely analyzed and reported for various health outcomes [11].

Historically, advocacy for increasing women's health can be drawn back to a milestone in 1990 when the National Institute of Health (NIH) Office of Research on Women's Health was formed in response to congressional, scientific and advocacy concerns. The lack of systemic and consistent inclusion of women in NIH-supported clinical research was concerning as this could result in clinical health-care decisions being made for women based solely on male predominant study findings, without any evidence that they were applicable to women [12].

This recognition of female underrepresentation led to the NIH Revitalization Act in 1993, which aimed to increase enrollment of women and URM in clinical trials [13]. Despite all these efforts and other public initiatives to raise awareness about women and heart

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disease, recent data continue to show that enrollment of women including URM women still lags behind that of men [6].

There have been published studies that illustrate consistent findings highlighting the underrepresentation of women. These studies include the landmark Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial, which enrolled over 40,000 patients to evaluate the safety and effectiveness of fibrinolytic therapy in acute myocardial infarction (AMI). In this study, women constituted only 25% of the trial participants [14]. A systematic review of 325 CV trials published in three leading medical journals from 1997 to 2009 estimated that 1 in 3 participants were women [15]. After accounting for age- and sex-specific differences in disease prevalence, however, the enrollment rates of women were lower than expected, estimated at 3% to 13% across the spectrum of CV diseases [15].

A more contemporary systematic review indicates that this underrepresentation of women in CV trials persist with women representing approximately one third of the study population in most studies [6]. Participation to prevalence ratio (PPR) is a measure to describe the representation of women in a trial with respect to their proportion in the disease population Fig. 1 [16]. The ideal PPR is considered to be 0.8–1.2, which indicates a good representation of women in a study [16]. Even after adjusting for prevalence, it has been shown that trials related to heart failure, acute coronary syndromes, and coronary artery disease (CAD) have consistent underrepresentation of women with PPR <0.8 [6]. Trials related to device placement, procedures and multi-interventions had lower representation of women compared to trials focused on lifestyle and medications, and trials conducted in the Americas had better representation than those conducted in Europe and the Western Pacific [6]. Besides NIH sponsored trials, government sponsored trials had lower enrollment of women [6]. Additionally, low representation of women was particularly seen in women 61–65 years of age [6].

Recent CV imaging studies also had low enrollment of women. In the SCOT-HEART trial, investigators reported 44% of the study population being women [8], the ICONIC trial reported 36.3% of the acute coronary syndrome patients being women [10] and the ISCHEMIA trial reported 22.6% women [9]. This is of critical importance because the presentation, imaging, and pathophysiology of CAD in women are different from that of men. Compared to men, women are more likely to have diffuse non-obstructive epicardial CAD with lower coronary flow reserve (CFR) [17]. Women had fewer calcified lesions and higher plaque density compared to men [18], and women have smaller sized coronary arteries. Therefore, less plaque burden is required to result in flow limiting stenosis [19]. In view of these sex differences in the pathophysiology of CAD, the extrapolation of the findings from these imaging trials to women may not be appropriate.

It has also been established that the treatment pharmacokinetics for women are different from that of men [20,21]. Despite this, there is continued underrepresentation of women in CV research studies and the results of these studies are often extrapolated to women. This extrapolation may lead to potential harm and greater side effects for women [22]. This underscores that low representation in clinical trials can lead to poor CV outcomes for women.

$$\text{PPR} = \frac{\text{Percentage of women among trial participants}}{\text{Percentage of women among disease population}}$$

Fig. 1. Calculation of the participation to prevalence ratio (PPR)  
An outline of the calculation of the participation to prevalence ratio (PPR) [16].

### 3. Proposed causes of the underrepresentation of women in clinical trials

Although there is growing awareness, significant gaps persist in sex-specific research and many questions of clinical importance remain unanswered. To discover the basic understanding of this dilemma, we must focus on answering the main question: why are women not participating in trials at the same extent as men? An exploration of the causes of this underrepresentation is not complete without including causes unique to URM women as this population bears the greatest CV mortality among women [5].

A randomized study of patient willingness to participate in CV prevention trials found that men had 15% greater willingness to participate than women [23]. Among the reasons for this gap was the fact that women perceived a greater risk of harm from trial participation. Women had also been shown to take fewer risks than men under stress, and major health-based decisions could certainly be a source of stress [24].

Additionally, financial stability, sociocultural environment, patient education, community engagement as well as the health care system are all important factors influencing CV health in women [25,26]. These factors also play an important role in decision making when it comes to clinical trial participation [27]. Distrust of the healthcare system and of medical research also negatively impacts the enrollment of URM women [28,29].

Women are likely more swayed by their surrounding social and family environments [6]. Women may take more time to plan and they may require more sources of input with decisions influenced by friends, family, researchers, or other external influences [6]. They are also more likely to have their decisions influenced by altruistic motivations given that most women are caregivers [6].

Equally important, a lack of awareness, leadership, and engagement on the part of investigators may be a cause of poor enrollment of women in clinical trials [27]. Several recent studies have reviewed female authorship for CV disease clinical trial publications and found that women are significantly underrepresented in clinical trial leadership [27]. Although the proportion of women in trial leadership has increased over the past decade, the upward trend has been slow [27].

### 4. Proposed solutions for addressing underrepresentation of women in clinic trials

As noted previously, the reasons for underrepresentation of women in clinical trials are multifactorial and addressing this issue will require a multifaceted approach. This multifaceted approach requires interventions at a patient care level, clinical care team level, governmental/funding level, societal level as well as at the level of research investigational leadership and authorship. Table 1 outlines the causes and potential solutions to underrepresentation of women in CV research trials.

### 5. Conclusion

Underrepresentation of women including URM women in CV trials remains dismally low despite efforts by government organizations to increase the enrollment of women and URM in these trials [6]. This underrepresentation leads to the extrapolation of study results from predominantly male trials to women which have been shown to lead to more side effects and potentially worse outcomes [22]. The causes for the underrepresentation of women in CV trials are multifactorial [6,27–32]. Therefore addressing these causes should be multifaceted at the levels of the patient, clinical care, government/funding, societal and research study leadership, and authorship.

### CRedit authorship contribution statement

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**Table 1**  
 An outline of the causes and proposed solutions to underrepresentation of women in cardiovascular (CV) research trials [6,27–32].

<b>Proposed Causes for the Underrepresentation of Women in Cardiovascular Trials</b>	<b>Proposed Solutions to Address the Underrepresentation of Women in Cardiovascular Trials</b>
<b>Patient Related Causes</b>	<b>Patient Related Solutions</b>
Lack of patient awareness of available CV studies among women [27, 29]	Instituting outreach initiatives to raise awareness of available ongoing CV trials. These initiatives should be customized to the target communities by using frequently used media outlets such as social media, internet radio, television, and print media.  Engaging and actively involving primary care providers and cardiologists in the dissemination of information about available ongoing CV trials.
Financial barriers to participation in CV trials [27, 29]	Monetary reimbursement to the patients enrolled in the trial for their time spent in trial participation and cover any associated costs for trial participation. The monetary reimbursement process should be as simple as possible so that all trial participants can be reimbursed fairly.

<p>Systemic barriers to participation in trials such as caregiving responsibilities, lack of transportation, and long work hours [27, 29]</p>	<p>Trial designs should aim to breakdown systemic barriers to trial participation such as maximizing use of telehealth for patient follow up in lieu of in person visits, increasing the number of satellite trial sites and making these sites more accessible by strategically locating satellite sites in more local communities rather than at large regional tertiary centers.</p> <p>Extending the hours of operation for the trial sites to allow employed patients to be able to attend before or after work and to include weekend hours as well.</p> <p>Provision of onsite childcare at trial centers to encourage mothers of young children to participate in trials. Providing transportation to and from the trial center for trial participants.</p>
<p>Decreased willingness of women to participate in clinical trials due to perceived increased risk of harm [6]</p>	<p>Patient centered open discussion between the research site staff and patient when discussing enrollment in the trial. This should include full disclosure of risks and benefits of trial participation.</p> <p>It may also be helpful to include a trusted family member or friend in this discussion if approved by the patient.</p> <p>A series of discussions may be useful.</p>

	Involvement of the patient’s primary care provider or cardiologist may also be helpful.
<b>Clinical Care Causes</b>	<b>Clinical Care Solutions</b>
Decreased referral of women for appropriate specialty care, appropriate procedures, and therapies [30].	<p>Provider education and raising awareness to guide providers on the appropriate patients to refer for specialty care, therapies, and procedures.</p> <p>Having a referral call center and coordinators arranged at specialty care centers so that local providers can readily arrange referrals for appropriate patients when needed. This referral call center information should be shared with local medical community via emails, social media, print media, local television, and brochures.</p> <p>Use of electronic medical record alert systems to notify providers when patients meet criteria for referral to specialty care, procedures, or therapies.</p>
<p>Females especially those who are underrepresented minorities (URM), often have decreased trust in the healthcare system due to poor interaction and communication with health care providers [29].</p> <p>Amongst URM women there may also be a greater medical researcher distrust and a greater perceived risk of harm [28].</p>	Raising awareness and educating providers on the importance of and how to establish and cultivate a trusting patient-provider relationship in which care is patient focused.

	<p>Ensuring that patients are treated with dignity and respect with an appreciation of their cultural sensitivities and norms</p> <p>Ensuring that communication with the patient is effective. Language barriers should also be broken down with use of effective interpretation strategies.</p> <p>In the discussion of CV trials with the patient, it may be helpful to include a trusting close family member and the patient’s primary care provider in the discussion. This will assist in guiding the patient in their decision on trial participation.</p>
<p>Lack of ethnic and gender diversity in the cardiovascular workforce [31]resulting in sociocultural barriers in the female patient-provider interaction[27].</p>	<p>Creating an environment within the healthcare institution that promotes diversity and inclusion at all levels of the cardiovascular workforce.</p> <p>Creating an effective Office of Diversity and Inclusion that ensures recruitment of a diverse cardiovascular workforce. This office will also encourage and promote talented cardiovascular team members into positions of leadership who will be able to make decisions and effective changes within the institution focused on diversity and inclusion.</p>
<p><b>Government/Funding Causes</b></p>	<p><b>Government/Funding Solutions</b></p>

<p>Although government particularly in the US have aimed to increase enrollment of women and URM [13] a reasonable PPR of (0.8-1.2) has not been mandated.</p>	<p>Government and industry funded research trials should mandate that a reasonable PPR (0.8-1.2) is achieved with regard to the enrollment of women.</p>
<p>Decreased funding of cardiovascular trials [32]. This may have implications for funding of sex specific cardiovascular studies.</p>	<p>Government legislation in Congress would be helpful to allocate increased funds for government sponsored sex focused CV trials.</p> <p>Encouraging industry funding of high quality unbiased cardiovascular trials.</p>
<p>Reporting of sex specific results and a breakdown of sex specific loss to follow up (including reasons for loss to follow up) in CV trials have not been mandated in government sponsored trials[27].</p>	<p>Government sponsored trials should be mandated to include analysis and reporting of sex specific results and a breakdown of sex specific loss to follow up (including reasons for loss to follow up) in all CV trials [27].</p>
<p><b>Societal Level Causes</b></p>	<p><b>Societal Level Solutions</b></p>
<p>Lack of community engagement with URM female populations [27, 29]</p>	<p>Meeting members of URM communities where they are, such as places of worship, salons, and youth centers are important in order to create a connection with the community. This connection with the community will cultivate trust which will lead to better engagement.</p>

<p>Lack of awareness of available trials within the community [27, 29].</p>	<p>Share trial information with and include community leaders such as pastors and hairdressers, in outreach events with the community. These community leaders could serve as ambassadors to assist with informing the community of ongoing CV trials and the importance of study participation.</p>
<p>Lack of awareness within the community of the impact of study trial results on the type and quality of healthcare provided</p>	<p>Creating outreach events with inclusion of community leaders such as pastors and hairdressers to inform the community of the importance and impact of CV trials in improving healthcare.</p>
<p><b>Research/Investigational Causes</b></p>	<p><b>Research/Investigational Solutions</b></p>
<p>Lack of ethnic and gender diversity among the principal investigators in the study design and enrollment strategy planning [27].</p>	<p>Improving the professional pipeline of research investigators to include an ethnically and gender diverse group of talented principal research investigators. These investigators should be promoted into research leadership positions who will assist in study design and enrollment strategy planning.</p>
<p>Lack of ethnic and gender diversity among the local research staff at the various study sites [27].</p>	<p>Recruitment of ethnically and gender diverse local research staff would be helpful to address the lack of diversity.</p>
	<p>Planning outreach recruitment events writing the local communities where study sites are located would assist in recruiting a diverse research staff with regard to ethnicity and gender.</p> <p>Having a Diversity and Inclusion officer as a part of the research leadership team would assist in creating a diverse research staff at each local site.</p>
<p>Lack of ethnic and gender diversity in the lead authorship of CV studies who are also responsible for study analysis and reporting [27].</p>	<p>Research leadership development programs</p> <p>Mentorship programs</p> <p>Formal scientific research training</p> <p>Formal training in writing scientific papers</p>



**Madison Kocher-Writing** - Original Draft, Writing - Review & Editing.

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#### 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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