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Research paper

Why is it important for male cardiologists to enroll more women in cardiovascular trials?

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Cardiovascular disease (CVD) is the leading cause of death among women, accounting for approximately 35% of total deaths in women in 2019 [1]. There are several important sex differences in the types, prevalence and impact of risk factors for the development of CVD, as well as important sex differences in the etiology, pathophysiology, presentation and clinical outcomes of CVD [2]. Much of the evidence base around the management of CVD is derived from randomized clinical trials (RCTs) that inform best practice for the prevention and treatment of CVD and shape clinical recommendations delivered through guidelines. The value of such trials in informing the management of both women and men depends on clinical trial populations that are reflective of the wider population that we serve, and whether trial populations reflect the prevalence of disease among different patient groups at the population level and the assessment of the efficacy and safety of interventions in both men and women.

Women are consistently under-represented in landmark clinical trials [3], reducing the ability to assess the safety and efficacy of therapies used to treat them, as highlighted later. Trial results that inform guideline recommendations for the prevention and management of CVD are based on predominantly male participants. This limits the potential for identifying sex-specific differences in important risk factors and outcomes, impeding the development of sex-specific strategies that could lead to improved therapeutic strategies [1]. With a focus on improving the external validity of clinical trials, the National Institutes of Health Revitalization Act (1993) legally requires the inclusion of women and men in clinical trials proportionate to the sex-related prevalence of the disease under investigation (important regulatory milestones affecting issues covered in the editorial recently overviewed [4]). This is necessary to provide appropriate data on the treatment effect of an intervention in both women and men. Despite the establishment of such legal frameworks, recruitment of women into RCTs remains suboptimal across a broad spectrum of CVD, from prevention, to therapeutics and interventions. For example, in a systematic review of randomized controlled trials of heart failure published in high-impact journals between 2000 and 2019, only one quarter of trial participants were women, with over 70% of trials under-enrolling women [3]. Similarly in a study examining enrolment of women in landmark CVD trials supporting 36 drug approvals from 2005 to 2015 submitted to the U.S. Food and Drug Administration (FDA), the proportion of women enrolled was significantly below the prevalence estimates of individual CVDs, with participant to prevalence ratio (PPR) for heart failure (0.5 to 0.6), coronary artery disease (0.6), and acute coronary syndrome (0.6) below what is considered desirable (0.8–1.2) where <0.8 represents under-recruitment and >1.2 represents over-recruitment of women [5]. Interestingly, safety results by gender were only recorded in 31 of 36 drugs studied (86%) with 3 drugs used in the treatment of hypertension Aliskiren, Amlodipine/Olmesartan and Aliskiren/Hydrochlorothiazide reporting significant sex differences in safety [5]. The importance of reporting sex differences in safety of therapies used to treat cardiovascular diseases is highlighted by the U.S. Government Accountability Office that reported that 8 out of 10 drugs removed from the market due to unacceptable health risks between 1997 and 2001 were more harmful to women than men [6]. The report makes a distinction between drugs that cause higher rate or severity of injury in women than men when equal numbers are treated compared to situations where women are more likely to be prescribed the drug. Interventions that have proven efficacious in clinical trials with predominantly male participants have been shown in subsequent observational studies to have unexpected adverse effects in women [7]. Furthermore, there are potential safety issues surrounding side effects of prescribed medications from potentially incorrect sex-appropriate dosing of pharmaceutical agents in women as they are under-represented trials.

Current guidelines for the management and prevention of CVD are largely based on trial data quantifying the efficacy of therapies in men.

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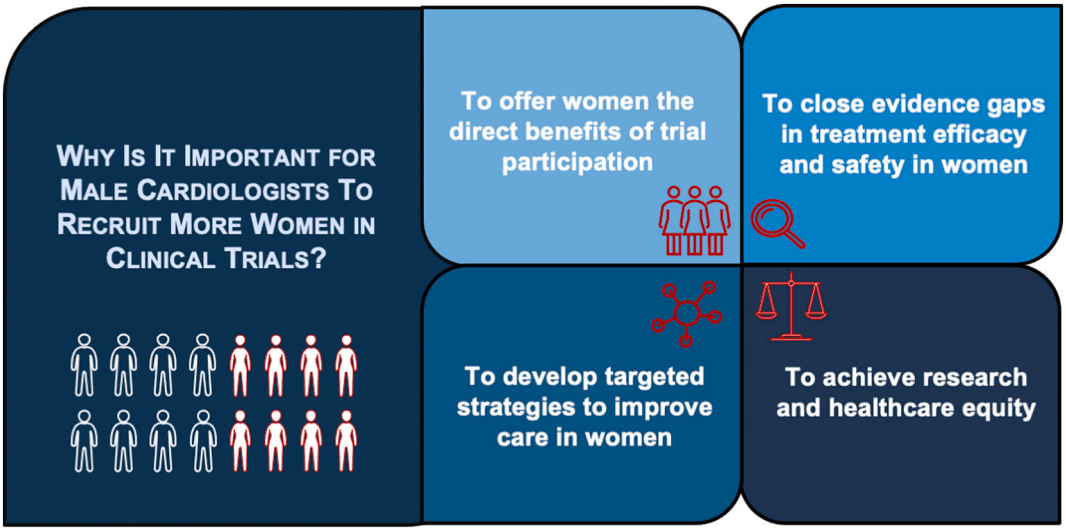

Fig. 1. Why is it important for male cardiologists to recruit more women in clinical trials?

Many landmark trials do not report sex specific outcomes and do not report the *p*-value for sex interaction [8], with clinical uncertainty around the efficacy of treatments that we currently offer women. So where does this leave us with the question posed by the editorial, "Why is it important for male cardiologists to enroll more women in cardiovascular trials?" Is there literature to support that men are less likely to under-enroll women? And why do men need to show leadership in closing this gender gap?

Previous work has suggested that after adjusting for other factors, trials led by men have 30% greater odds of under-enrolling women relative to disease prevalence [3], highlighting that there is a significant gender gap in optimizing recruitment strategies to facilitate greater representation of women as trial participants. Women are under-represented in clinical trial leadership, with more than half of cardiovascular trials published in high impact journals lacked women on their executive committees, and only one in ten of these trials are led by a woman investigator [9]. There will be a significant lead time lag even if strategies highlighted to narrow gender disparities in trial leadership such as recommendations for early, mid and senior career cardiologists, academic and departmental leadership, industry and grant funding agencies and journals [10] are implemented immediately. It will take many years to reverse decades of underfunding, poor mentorship opportunities, inequalities in promotion, structural sexism and reversal of the leaky pipeline that have acted as barriers to trial leadership by women. We therefore cannot wait until there is greater representation of women in trial leadership positions before we work towards implementing strategies that are effective in increasing trial recruitment of women such as achieving greater diversity in trial teams, trial design and institution of policies that facilitate equity and diversity at the industry, funding agency and the journal level [11]. The onus on increasing recruitment of women trial participants must fall mainly on male trialists who currently lead 90% of clinical trials and are currently under-performing in this regard in the first instance, although penultimately a more diverse and representative research leadership will be the most effective means to achieve greater recruitment of women into trials.

In addition to closing the evidence gap that underpins disparities in clinical outcomes in CVD, there are several further advantages to increasing the enrollment of women in clinical trials. Under-enrollment in clinical trials deprive women of the widely known benefits of trial participation. Trial participants more frequently receive contemporary evidence-based therapy, are more likely to be prescribed guideline-directed medications and receive better quality medical care and closer clinical follow up and have been shown to have fewer adverse effects and better outcomes than those of eligible non-participants [12].

Many of the institutional interventions that have been shown to improve recruitment of women into clinical trials serve to reduce structural sexism often embedded within institutions, leading to greater retention of women, and serve to reduce the impact of the leaky pipeline in research leadership and harness the potential of half the academic population to close the sex and gender gaps among research participants [10]. The training and hiring of more women investigators and educators will foster greater trust among women participants and increase diversity across an institution. Indeed, trial leadership by women is associated with greater enrolment of women as well as historically under-represented ethnic groups. Inclusion of women on clinical trial staff, particularly women reflecting the ethnic or racial composition of the target population may serve to sensitize staff members to the unique needs of women in clinical trials, which may increase trial recruitment and perhaps, more effectively retain trial participants through to the end of the follow-up period.

Recruitment of more women into clinical trials will contribute to reducing the global burden of CVD in women [1], and implementation of solutions at an institutional level to achieve this will serve to reduce barriers for women around structural sexism and provide for a more diverse workplace, thereby encouraging more women into positions of trial leadership. The question should not be of "Why is it important for male cardiologists to enrol more women in cardiovascular trials?" (Fig. 1) but rather "Why is it not happening now?

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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