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Women in Clinical Research: What We Need for Progress

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This Go Red for Women theme collection of articles in *Circulation: Cardiovascular Quality and Outcomes* presents several interesting studies focused on women's health.[1-9] The publication of this grouping provides an opportunity to reflect on the state of research into women's heart health, the challenges ahead, and what is needed for progress.

Despite the many successful campaigns raising awareness about heart disease in women, the inclusion of women in cardiovascular clinical research is a relatively recent occurrence. Before 1993, many large cardiovascular trials, including the Physicians' Health Study[10, 11] and the Multiple Risk Factor Intervention Trial (MRFIT),[12, 13] studied only men. Concerns in the 1980's about gender equity in research led to two federal mandates for the inclusion of women in clinical trials. The National Institutes of Health (NIH) Revitalization Act of 1993 required that all clinical trials funded by the NIH include women as subjects and adequately power their samples to perform sex-specific analyses,[14, 15] and the Food and Drug Administration's “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs” called for the examination of sex differences in pharmaceutical trials.[16] These policies marked a seminal advancement in women's health research and set the precedent for subsequent guidelines and reports.

Since the NIH Revitalization Act, the absolute number of women in clinical trials has increased.[17] However, recent reports show that women remain woefully under-represented in trials of cardiovascular disease prevention and treatment[18-21] and that the relative proportion of women in mixed-gender trials has remained relatively stagnant.[22, 23] Part of the reason for the lack of improvement may be the absence of an established benchmark for adequate enrollment. Neither the NIH Revitalization Act nor the Food and Drug Administration guidelines identified a target recruitment proportion for women. Although

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studies have suggested that the ratio of women to men in trials should mirror that in the overall disease population,[22] this approach may yield low numbers of women, particularly in trials of younger patients. Because women present with heart disease later in life and older patients are often excluded from clinical trials, women may be less likely to be recruited. Additionally, there are known sex differences in cardiac risk perception[24] and referrals for cardiac testing and treatments,[25, 26] which may limit the inclusion of women in trials. Thus, it may be necessary to intentionally "oversample" women in many of these studies.

Despite federal mandates to specifically examine drug and treatment effects in women, sex-specific analyses are frequently not performed and most clinical trials are underpowered to examine such effects.[17, 23, 27] Moreover, studies reporting sex-specific analyses are often conducted post-hoc without regard to whether the initial trial was adequately powered for such analyses. Underpowered subgroup analyses can produce false negatives and incorrect conclusions, which can lead to the institution of ineffective or even harmful treatment strategies in women.

In fact, there is growing evidence that women and men respond differently to drug therapies. Aspirin for the primary prevention of cardiovascular disease is one such example. A meta-analysis of 6 trials found that aspirin in men reduced the risk of myocardial infarction (MI) by 32% but had no effect on ischemic stroke.[28] In contrast, aspirin in women had no effect on MI but reduced the risk of stroke by 24%. Similarly, the recent debate on implantable cardioverter-defibrillators (ICDs) in women has raised concerns about sex differences in procedure and device outcomes. A meta-analysis of 5 trials and 934 women found that although ICDs significantly reduced mortality rates in men, there was no benefit in women.[29] These examples highlight the need for sex-based analyses to be prospectively planned and adequately powered if they are to identify differences in treatment effects and unwanted side effects. Simply enrolling women into trials is not sufficient. Clinical investigators should be specifying *a priori* sex-based analyses and ensuring that trials are adequately powered for such investigations in both men and women.

Even beyond sex-based analyses, there may be subgroups of women that warrant particular attention. Although women, as a whole, are often considered to be a "subgroup" in clinical research, they represent a diverse and heterogeneous population. Compared with men, women have unique biological life events, which may alter their risk of cardiovascular disease and response to therapies. However, these events have largely been ignored in cardiovascular trials.

Menopause and pregnancy are two such events. Cardiovascular risk varies greatly by age and menopausal status, and young women often present very differently than older women for many disease types. MI is a prime example. Compared with men and older women, young women with MI represent a "higher risk" population with higher rates of traditional and non-traditional risk factors, more atypical symptoms, and higher complication and mortality rates.[30-33] Moreover, they more frequently experience atypical disease processes including disease of the coronary microvasculature [34, 35] and spontaneous coronary artery dissection.[36, 37] Although virtually no studies have evaluated differences in drug or therapy effects by age specifically in women, it is reasonable to think that certain therapies may be

more or less beneficial for younger versus older women or even for pre- versus post-menopausal women. Certainly age-by-treatment interactions have been reported for men and women collectively with procedures such as carotid artery stenting versus carotid endarterectomy [38] and coronary artery bypass grafting versus percutaneous coronary intervention.[39] However, almost nothing is known about the effectiveness of these therapies in specific female subgroups.

Without these subgroup analyses, our knowledge of certain cardiovascular disease subtypes will remain inexcusably naïve. Diseases such as spontaneous coronary artery dissection, Takosubo's cardiomyopathy, long QT syndrome, pulmonary arterial hypertension, and postpartum cardiomyopathy have a strong female predominance or are exclusively found in women and as a result, have been largely understudied.

To effectively translate research evidence into clinical practice, all populations must be adequately represented and studied. We cannot dismiss such trials for being too expensive. Once we acknowledge that sex interactions – even with subgroups of women – are likely, we must find ways to study these differences explicitly and with adequate power, not as an afterthought with whatever data are available. We must also be thoughtful and deliberate in recruiting larger percentages and specific subgroups of women. Simply adding women in proportions to their disease prevalence will fail to provide us with the necessary sample sizes.

Although we have made significant strides in bringing women's heart disease into the national spotlight and promoting the inclusion of women in clinical trials, we have considerably more to learn about cardiovascular disease prevention, diagnosis, and response to therapy in this population. To continue progress in this direction, it is not enough just to include more women in the studies, even though we should. It is not enough to publish more subgroup analyses by sex, even though we should. What is needed is to turn the spotlight on the imperative that studies be designed at the outset to address important differences between men and women, and among women. Only with rigorously designed, adequately powered studies to detect and explain the differences will we make true progress.

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