Women in Clinical Research
What We Need for Progress

Emily M. Bucholz, MPH; Harlan M. Krumholz, MD, SM

This Go Red for Women® theme collection of articles in Circulation: Cardiovascular Quality and Outcomes presents several interesting studies focused on women’s health.\textsuperscript{1–10} 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\textsuperscript{11,12} and the Multiple Risk Factor Intervention Trial (MRFIT),\textsuperscript{13,14} studied only men. Concerns in the 1980s about sex equity in research led to 2 federal mandates for the inclusion of women in clinical trials. The National Institutes of Health Revitalization Act of 1993 required that all clinical trials funded by the National Institutes of Health include women as subjects and adequately power their samples to perform sex-specific analyses.\textsuperscript{15,16} Similarly, 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.\textsuperscript{17} These policies marked a seminal advancement in women’s health research and set the precedent for subsequent guidelines and reports.

Since the National Institutes of Health Revitalization Act, the absolute number of women in clinical trials has increased.\textsuperscript{18} However, recent reports show that women remain woefully under-represented in trials of cardiovascular disease prevention and treatment\textsuperscript{19–22} and that the relative proportion of women in mixed-sex trials has remained relatively stagnant.\textsuperscript{23,24} Part of the reason for the lack of improvement may be the absence of an established benchmark for adequate enrollment. Neither the National Institutes of Health nor the Food and Drug Administration guidelines identified a target recruitment proportion for women. Although studies have suggested that the ratio of women:men in trials should mirror that in the overall disease population,\textsuperscript{25} 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 under-represented. In addition, there are known sex differences in cardiac risk perception\textsuperscript{25} and referrals for cardiac testing and treatments,\textsuperscript{26,27} 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.\textsuperscript{18,24,28} 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 by 32% but had no effect on ischemic stroke.\textsuperscript{29} In contrast, aspirin in women had no effect on myocardial infarction but reduced the risk of stroke by 24%. Similarly, the recent debate on implantable cardioverter-defibrillators 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 implantable cardioverter-defibrillators significantly reduced mortality rates in men, there was no benefit in women.\textsuperscript{30} 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 2 such events. Cardiovascular risk varies greatly by age and menopausal status, and young

---

From the Yale School of Medicine, New Haven, CT (E.M.B.); Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT (E.M.B.); Robert Wood Johnson Foundation Clinical Scholars Program and the Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine and Department of Health Policy and Management, Yale School of Public Health, New Haven, CT (H.M.K.); and Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT (H.M.K.).

The opinions expressed in this article are not necessarily those of the American Heart Association.

Correspondence to Harlan M. Krumholz, MD, SM, Yale School of Medicine, 1 Church St, Suite 200, New Haven, CT 06510. E-mail harlan.krumholz@yale.edu

(Circ Cardiovasc Qual Outcomes. 2015;8:S1-S3. DOI: 10.1161/CIRCOUTCOMES.115.001756.) © 2015 American Heart Association, Inc.

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org
DOI: 10.1161/CIRCOUTCOMES.115.001756
women often present differently from older women for many disease types. Myocardial infarction is a prime example. Compared with men and older women, young women with myocardial infarction represent a higher risk population with higher rates of traditional and nontraditional risk factors, more atypical symptoms, and higher complication and mortality rates.\textsuperscript{31–34} Moreover, they more frequently experience atypical disease processes, including disease of the coronary microvasculature\textsuperscript{35,36} and spontaneous coronary artery dissection.\textsuperscript{37,38} 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 premenopausal versus postmenopausal women. Certainly age-by-treatment interactions have been reported for men and women collectively with procedures, such as carotid artery stenting versus carotid endarterectomy\textsuperscript{39} and coronary artery bypass grafting versus percutaneous coronary intervention.\textsuperscript{40} 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 naive. Diseases such as spontaneous coronary artery dissection, Takotsubo 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, they 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 subgroups of women. Only with rigorously designed, adequately powered studies to detect and explain the differences will we make true progress.

**Sources of Funding**

E.M. Bucholz is supported by an F30 Training grant F30HL120498-01A1 from the National Heart, Lung, and Blood Institute. Dr Krumholz is supported by grant U01 HL105270-05 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute.

**Disclosures**

Dr Krumholz works under contract with the Centers for Medicare & Medicaid Services to develop and maintain performance measures. He is the recipient of research grants from Medtronic and from Johnson & Johnson, through Yale University, to develop methods of clinical trial data sharing and chairs a cardiac scientific advisory board for United Healthcare. E.M. Bucholz reports no conflicts.

**References**


10. Arnett DK. Plugging the leaking pipeline: why men have a stake in the recruitment and retention of women in cardiovascular medicine and research. Circ Cardiovasc Qual Outcomes. 2015;8:S63–S64. DOI: 10.1161/CIRCOUTCOMES.115.001757.


20. Arnett DK. Plugging the leaking pipeline: why men have a stake in the recruitment and retention of women in cardiovascular medicine and research. Circ Cardiovasc Qual Outcomes. 2015;8:S63–S64. DOI: 10.1161/CIRCOUTCOMES.115.001757.


**Key Words:** clinical trial ■ sex