Clinical trials provide the most reliable data supporting the efficacy and safety of cardiovascular (CV) disease treatments. Generalizability is an important attribute of a clinical trial. In practical terms, you want to know that the patient you are about to treat was adequately represented in a trial demonstrating safety and efficacy. CV trials that exclude women or in which women are inadequately represented thus fall short of the ideal. This statement also holds true for older adults, people of color, and disadvantaged groups.

The tradition of excluding women from cardiovascular trials began long ago. A US Food and Drug Administration (FDA) guideline published in 1977 recommended that women of childbearing potential be excluded from phase 1 and early phase 2 clinical trials, and this directive is considered to have had a chilling effect on their access to phase 3 trials. In 1993, the FDA explicitly reversed their 1977 recommendation and called for trial data be analyzed to assess gender effect. The importance of CV trials for women was highlighted by the unexpected failures of hormone replacement therapy to reduce CV events in both primary and secondary prevention in postmenopausal women. Studies over the last 2 decades have broadened our understanding of sex and gender differences between women and men and how they might influence outcome differences for a variety of treatments.

**Participation Rates of Women in Cardiovascular Trials**

Four large studies were recently published documenting the rates of participation of women in CV trials. A study from the FDA’s Office of Women’s Health reported on trials supporting drug approvals from 2005 to 2015. The proportion of women enrolled overall was 46% (range, 22%-81%). Participation to prevalence ratio (PPR), defined as the percentage of women among trial participants divided by the percentage of women in the disease population, was within the desirable range of 0.8-1.2 for atrial fibrillation (0.8-1.1), hypertension (0.9) and pulmonary hypertension (1.4), but was low for trials in heart failure (0.5-0.6), coronary disease (0.6), and acute coronary syndrome (0.6). Across these trials the authors found little indication of clinically meaningful gender differences in efficacy or safety.

In a larger, more recent report, the investigators studied 740 completed CV trials registered at ClinicalTrials.gov between 2010 and 2017. PPR was higher than 0.8 for hypertension and pulmonary hypertension, and lower (0.48 to 0.78) for arrhythmia, coronary disease, acute coronary syndrome, and heart failure trials. The most recent period, 2013-2017, saw increases in PPR for stroke (P = 0.007) and heart failure (P = 0.01) trials compared with the previous period.

The third large recent study included 60 randomized trials of lipid-lowering therapy with 485,409 participants reported from 1990 to 2018. Enrollment of women increased from 19.5% between 1990 and 1994 to 33.6% between 2015 and 2018. PPR for lipid trials of diabetes (0.74), heart failure (0.27), stable coronary disease (0.48), and acute coronary syndrome (0.51) were low. However in trials of hypercholesterolemia, women were overrepresented (PPR 1.27).

In a study covering 598 CV trials published between 1986 and 2015 in 3 major journals, the proportion of participants who were women increased from 21% in 1986-1990 to 33% in 2011-2015. As reported in the other 3 studies, women participated at lower rates than expected based on their proportion of the disease population.

The results of these 4 studies are roughly congruent, although details differ. Women participate less often than men, and their PPRs are lower for most conditions. Participation rates have improved more recently in studies where different periods were compared.

**Reasons for Low Rates of Trial Participation in Women**

A limited number of studies have investigated potential explanations for lower willingness to participate (WTP) in women. In a small Canadian study, 54% of 270 postmenopausal women stated that they would not participate in a CV trial, and 46% indicated that they would. Motivations...
Improving Participation Rates for Women

Many CV trials aim to improve participation rates of women, and some set specific targets, yet in most cases these efforts are not serious and are not accompanied by any practical steps that are likely to make a difference. An initial practical step is to scrutinize inclusion and exclusion criteria to be certain that women are not being unintentionally excluded. Applying study entry criteria to a group of potential “real” study participants, men and women, can be a useful exercise to discover who will be excluded and why, before the study is initiated. Often initial entry criteria are too restrictive, recruitment lags, and entry criteria are then relaxed.

Women are underrepresented in leadership positions in CV trials. As a result, the orientation of trials tends to ignore the perspective of women. As previously noted, women have different issues related to trial participation compared with men, and it is reasonable to assume that these issues have not been adequately addressed when recruitment of women falls short. Although study coordinators are usually women, they may take their cues from male principal investigators and not be adequately trained to address the concerns of potential participants who are women.

Investigators who are serious about recruiting an adequate proportion of women into a trial should set a target and stop recruitment of men early if projections show that the target for women will not be met. In the recent heart failure trial in which this approach was adopted, 52% of participants were women (n = 2,479) and a strong sex-by-treatment interaction was observed, with greater benefit in women than in men with heart failure and preserved ejection in the sacubitril plus valsartan group compared with the valsartan alone group (interaction P < 0.006).

Older Adults, People of Color, Disadvantaged Groups

Most of the statements made about women in this review also apply to older adults and other subgroups of interest. Most older clinical trials had an upper age limit, with the result that scant or no trial data was available to guide decision-making in patients older than 75 or 80 years. Such patients comprise a rapidly growing proportion of the population. Because drug metabolism is slower and more variable in older adults, and for other reasons too, efficacy and safety might be different than for younger populations.

In the African-American Heart Failure Trial, self-identified Blacks with heart failure were randomly assigned to placebo or a fixed combination of hydralazine and isosorbide dinitrate. The trial was stopped early due to a 43% reduction in all-cause mortality in the active treatment group.

The justification for limiting the trial to Blacks is that such patients respond less well to angiotensin-converting enzyme inhibitors than do non-Blacks.

Race is a poor marker of genetic differences among populations; however, including different races in CV trials and reporting results by racial subgroup is important if the treatment under study will be used in that subgroup. Racial differences in outcomes may also be a result of environmental or behavioral differences between groups.

In Canada, CV risk is higher in certain racial and ethnic groups—South Asian, Afro-Caribbean, Chinese, and
Hispanic, particularly in women. Canadians living in remote, rural, northern, or on-reserve locations; those with lower socio-economic status; and persons with disabilities also have an increased CV risk. Overcoming barriers and enrolling such patients in CV trials demonstrates inclusivity and is respectful of others.

It is tempting to conclude that the treatment of women, older adults, people of color, and other disadvantaged groups in clinical trials mirrors their treatment in the broader world. Adapting trials to the perspectives and needs of all potential subjects, not just middle-aged white guys, will make trial results more accurate and useful.

**Funding Sources**

The author has no funding sources to declare.

**Disclosures**

The author has no conflicts of interest to disclose.

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