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Editorial

Women in Cardiovascular Clinical Trials—What Are the Barriers to Address to Improve Enrollment?

Christine Pacheco, MD,[a] and C. Noel Bairey Merz, MD[b]

[a] Hôpital Pierre-Boucher, Centre intégré de santé et de services sociaux de la Montérégie-Est, Longueuil, Québec, Canada

[b] Barbra Streisand Women's Heart Center, Cedars-Sinai Smidt Heart Institute, Los Angeles, California, USA

See article by Gong et al., pages 653–660 of this issue.

Although the prevalence of cardiovascular disease (CVD) among women is similar to that of men, women have been historically under-represented in clinical trials. This under-representation represents a barrier in the application of treatments to women, and likely continues to contribute to the knowledge gaps in the understanding and treatment of CVD in women. Indeed, contemporary data show increasing rates of hospitalizations for acute myocardial infarction (AMI)[1] and stagnation of cardiovascular mortality in women younger than 50 years,[2] suggesting that persistent hurdles in diagnosis, treatment, and care of women still exist today.

Have We Made Progress?

Past calls to action led to a required inclusion of women in studies funded by the US National Institutes of Health, enacted into policy in 1993. It is therefore imperative to question whether inclusion of women in trials has improved over time. In this issue of the *Canadian Journal of Cardiology*, a systematic review entitled "Temporal trends of women enrollment in major cardiovascular randomized clinical trials" by Gong et al. addresses this question.[3] The authors identified 598 trials published in 3 selected high-impact journals between 1986 and 2015, and reported that enrollment of women in randomized trials in CVD increased from 21% between 1986 and 1990 to 33% between 2011 and 2015. Women were enrolled at a relatively lower rate in procedural trials, in which only 26% of participants were women, as compared with device trials, in which women represented 29% of those enrolled. Female enrollment was highest in pharmacological trials, but women still made up a smaller percentage of participants, representing only 31% of those enrolled. Furthermore, the authors report that trials with a female corresponding or first author had a significantly higher proportion of women enrolled (32.0% vs 27.0%, compared with trials with male corresponding or first author, respectively, $P = 0.004$). Although limited to 3 major scientific journals, this study suggests that some progress toward representative inclusion of women has been made in CVD trials, however it has been limited, suggesting that policy alone is insufficient. A better understanding of the barriers to recruitment of women into trials is needed.

Why Are Women Underenrolled?

A potential contributor to underenrollment is trial inclusion and exclusion criteria that disproportionately exclude women. Differences in clinical features at presentation with coronary artery disease (CAD) including advanced age and diabetes might reduce enrollment of women in clinical trials and account for under-representation in trials, which most often recruit younger patients with fewer comorbidities.[4] In pharmacological trials, in which women are best represented, female participation with respect to disease prevalence in women is variable.[4] In 36 drug approvals conducted by the US Food and Drug Administration from 2005 to 2015, sex representation with regard to disease prevalence was within or above expected for pulmonary hypertension, atrial fibrillation, and hypertension, but below expected for CAD, heart failure, and acute coronary syndrome.[4] Although AMI is more prevalent in men,[5] some of this difference is because of the long-standing use of male-standard biomarker thresholds, which fail to detect 1 in 5 AMIs in women,[6] rendering women less likely to be eligible for acute coronary syndrome and AMI studies. We have previously called attention to the sex, death, and diagnosis gap—although an equal number of women and men now die of CVD, fewer women receive a CVD diagnosis before death using male standard thresholds of symptoms, electrocardiogram, and biomarkers.[7] Enrollment in clinical trials proportional to accurately determined disease prevalence should be a primary objective in cardiovascular clinical trials. Furthermore, improving the proportion of female participants will improve power of analysis in the assessment of the risks and benefits of study treatments in women. Although favourable for women in some disease populations, the improvement of inclusion/exclusion criteria to include female-specific disease features could help improve representation in others.

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Corresponding author: Dr C. Noel Bairey Merz, MD, Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Smidt Institute, 127 S San Vicente Blvd, Suite A3206, Los Angeles, California 90048, USA. Tel.: +1-310-423-9680; fax: +1-310-423-9681.

E-mail: merz@cshs.org

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Lower rates of use of interventional therapies in women in clinical practice might result in fewer women referred for trial screening.[4] This might account for the observed trend of declining numbers of women enrolled from pharmacological trials to CAD to devices trials, where women are most underrepresented. Arrhythmia device trials have been documented to underenroll women because of the male standard thresholds including QRS and body surface area measures that exclude women.[8] Further examples include ischemic heart disease trials in which women have lower prevalence of obstructive CAD, an entry criteria for these trials.[9] Gong et al. report that underenrollment was highest in heart failure trials (28%),[3] in which women represent a large proportion of patients, which might be explained by a reduced ejection fraction (heart failure with reduced ejection fraction) criterion, whereas women more often have heart failure with preserved ejection fraction.[10]

Also, eligible women might be less often approached to participate. Previous work suggests implicit bias, where perceived cardiovascular risk burden is lower compared with actual risk in women,[11] with perceived risk attributed to body weight rather than evaluation of risk factors of greater prognostic significance.[12] Implicit bias can lead to inaccurate risk assessment in women, and consequently a reduction in women deemed eligible for trial participation.

Finally, women who are screened and meet criteria might not be enrolled in the trial. In an analysis conducted on screening logs of 15 major CVD trials, Martin et al. report that age and female sex were associated with subsequent nonenrollment after screening.[13] This is puzzling, because contemporary women-only studies (**W**omen's **I**schemia **S**yndrome **E**valuation [WISE],[14,15] **Imp**rove Diagn**o**sis and Treatment of **W**omen With Angina P**e**ctoris and Mic**r**ovessel Disease [i-POWER],[16] Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) female-arm[17]) have enrolled on time as designed. Inspection of these studies suggests that female inclusion criteria directed by female leadership, indicated by authorship might contribute to successful female trial enrollment. The prospective VIRGO study, which aimed to evaluate risk factor profiles in women younger than 55 years who present with AMI, focused on AMI in young and middle-aged subjects, and aimed for a 2:1 female to male recruitment ratio. A total of 2349 women were included, who had higher rates of CVD risk factors, lower quality of life, presentation and treatment delays, and higher rates of depression than men.[17] In this study, as well as i-POWER and WISE, first authors were women, corroborating the findings of Gong et al.[3] that studies with female first authors and corresponding authors had a higher proportion of female participants. Such studies with specific goals for the enrollment of women have been successful.

What Can Be Done?

Gong et al. confirm that women continue to be underenrolled in CVD clinical trials, and future directions for identifying strategies for improvement is key. Previous work suggests existing solutions that can be deployed to improve these issues for women. AMI scores that include variables that differ according to sex accurately predict risk in women compared with scores without sex-specific variables that do not.[18] The proper identification of potential female-specific risk factors[18] and integration of these variables into study inclusion criteria might increase the number of eligible women. The use of standardized protocols for emergency triage and AMI management protocols improve outcomes in women.[19,20] Protocolized approaches to ST-elevation AMI diagnosis and treatment lead to shorter first medical contact-to-device and door-to-device times[21] with a resultant mortality reduction in women.[20]

The development of appropriately sized devices designed with the generally smaller body surface areas of women could lead to an increase in female participants. Although Gong et al. report that women are most underenrolled in device trials, women represent more than 50% of participants in landmark transcatheter aortic valve replacement clinical trials,[22] and continue to represent more than half of subjects who undergo transcatheter aortic valve replacement in international registries.[22] Women are more often at higher surgical risk,[22] driving their eligibility for earlier trials conducted in nonoperable subjects, possibly leading to appropriately sized and designed devices given this consideration. Equal sex representation in device trials is therefore possible when sex-related aspects of disease are taken into account.

Increasing female leadership in cardiovascular clinical research might represent an opportunity to increase research in women with CVD and their participation in clinical trials. As the findings of Gong et al. suggest, female investigators recruit higher proportions of women, and they, along with female research staff, might foster greater understanding among potential female participants.[3] Furthermore, women represent a small proportion of interventional cardiologists, which might contribute to lower rates of female recruitment in trials, especially in device or procedural trials.[23] Only 20% of women in academic cardiology currently achieve leadership positions,[23] and better representation could help reduce the gap in the recruitment of female trial participants.

A summary of the issues and possible solutions is provided in Figure 1. Knowledge gaps remain and it is imperative that future research aims at closing them. Specifically, further research is needed to confirm and expand how the current CVD clinical trial designs exclude women, and to test how integration of female-specific scores, appropriate device-sizing, and female investigator leadership might contribute to a greater enrollment rate for women and close the sex, death, and gender gap in CVD

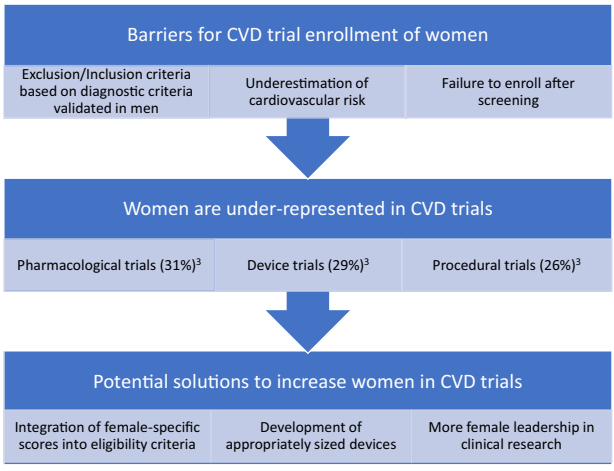

Figure 1. Barriers and solutions to improve enrollment of women in cardiovascular disease (CVD) clinical trials. Data from Gong et al.[3]

trials. Women represent a social and economic driving force, and developing mechanisms to improve equity in CVD research for women should be a priority.

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References

1. Arora S, Strassle PD, Qamar A, et al. Trends in inpatient complications after transcatheter and surgical aortic valve replacement in the transcatheter aortic valve replacement era. Circ Cardiovasc Interv 2018;11:e007517.
2. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. Circulation 2015;132:997-1002.
3. Gong IY, Tan NS, Ali SH, et al. Temporal trends of women enrollment in major cardiovascular randomized clinical trials. Can J Cardiol 2019;35:653-60.
4. Scott PE, Unger EF, Jenkins MR, et al. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. J Am Coll Cardiol 2018;71:1960-9.
5. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56-66.
6. AlBadri A, Wei J, Mehta PK, et al. Sex differences in coronary heart disease risk factors: rename it ischaemic heart disease! Heart 2017;103:1567-8.
7. Bairey Merz CN. Sex, death, and the diagnosis gap. Circulation 2014;130:740-2.
8. Taqueti VR, Bairey Merz CN. Sex-specific precision medicine: targeting CRT-D and other cardiovascular interventions to those most likely to benefit. Eur Heart J 2017;38:1495-7.
9. Pepine CJ, Ferdinand KC, Shaw LJ, et al. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. J Am Coll Cardiol 2015;66:1918-33.
10. Nelson MD, Wei J, Bairey Merz CN. Coronary microvascular dysfunction and heart failure with preserved ejection fraction as female-pattern cardiovascular disease: the chicken or the egg? Eur Heart J 2018;39:850-2.
11. Mosca L, Hammond G, Mochari-Greenberger H, et al. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. Circulation 2013;127:1254-63. e1251-9.
12. Bairey Merz CN, Andersen HS, Shufelt CL. Gender, cardiovascular disease, and the sexism of obesity. J Am Coll Cardiol 2015;66:1958-60.
13. Martin SS, Ou FS, Newby LK, et al. Patient- and trial-specific barriers to participation in cardiovascular randomized clinical trials. J Am Coll Cardiol 2013;61:762-9.
14. Merz CN, Kelsey SF, Pepine CJ, et al. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. J Am Coll Cardiol 1999;33:1453-61.
15. Ahmed B, Bairey Merz CN, Sopko G. Are we 'WISE'r? Findings from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation study. Womens Health (Lond) 2006;2:57-64.
16. Mygind ND, Michelsen MM, Pena A, et al. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER Study. J Am Heart Assoc 2016;5:e003064.
17. Bucholz EM, Strait KM, Dreyer RP, et al. Editor's Choice-Sex differences in young patients with acute myocardial infarction: a VIRGO study analysis. Eur Heart J Acute Cardiovasc Care 2017;6:610-22.
18. Shah RU, Merz CNB. Publicly available data: crowd sourcing to identify and reduce disparities. J Am Coll Cardiol 2015;66:1973-5.
19. Wei J, Mehta PK, Grey E, et al. Sex-based differences in quality of care and outcomes in a health system using a standardized STEMI protocol. Am Heart J 2017;191:30-6.
20. Huded CP, Johnson M, Kravitz K, et al. 4-Step protocol for disparities in STEMI care and outcomes in women. J Am Coll Cardiol 2018;71:2122-32.
21. Pacheco C, Matteau A, Bastiany A, et al. Can a "physician-less" system of automated prehospital STEMI diagnosis and catheterization laboratory activation reduce the treatment delay gap between men and women? Circulation 2017;136:A19267.
22. Pacheco C, Henri C, Forcillo J, Asgar AW. Transcatheter aortic valve replacement for severe aortic stenosis in women: clinical characteristics and outcomes. Can J Cardiol 2018;34:422-8.
23. Ghare MI, Chandrasekhar J, Mehran R, et al. Sex disparities in cardiovascular device evaluations: strategies for recruitment and retention of female patients in clinical device trials. JACC Cardiovasc Interv 2019;12:301-8.