Improving Enrollment of Women in Peripheral Vascular Trials

Dr. Chung discusses takeaways from a recent study in *Journal of Vascular Surgery*, the impact of female underrepresentation on trial outcomes, barriers and potential solutions to female trial participation, improving the diversity of study principal investigators, and what future studies should address.

With Jayer Chung, MD, MSc

In an article in *Journal of Vascular Surgery* (*JVS*), you and colleagues analyzed data from the last 12 years on the representation of women in United States clinical trials of common vascular diseases, identifying a low participation rate in these women, with no improvement since 2008.[1] Can you share your main goals for and takeaways from this study?

Our main goals were to (1) quantify the severity of underrepresentation of women in clinical trials (both externally funded and industry-sponsored) relative to the prevalence of disease by gender—we need a benchmark to measure progress/regression in order to more precisely guide efforts to rectify female representation in clinical trials; and (2) determine if there had been any improvements/worsening over time. The National Institutes of Health passed the Revitalization Act of 1993 in an effort to improve female and underrepresented minority participation in clinical trials. Theoretically, if legislation works, we would be able to see if there have been improvements over time.

Can you summarize the impact that underrepresentation has on female vascular patients and trial outcomes? How would you describe the connection between gender-related outcomes disparities in these vascular diseases and trial representation?

Modern medicine means precision medicine. Underrepresentation proscribes our ability to provide precision medicine to women. Instead, we are forced to generalize our recommendations and quality metrics from data gathered about male patients. The ultimate effect of underrepresentation on health care disparities is that precision medicine is impossible for women. The magnitude of this disparity is unknown because the alternative (using data that appropriately represent females) has not been performed adequately.

The relationship between female representation and the trial funding source is explored in depth in your paper, with median participation-to-prevalence ratios (PPRs) of 1.04 for university-funded trials, 0.67 for industry-funded, 0.60 for extramurally funded, and 0.02 for Veterans Affairs–funded trials. Why do you think university-funded trials have a higher PPR compared to the other trials, which have PPRs that do not reflect similar representation?

The main limitation of our paper is that we cannot explain why females remain underrepresented in clinical trials. We could only benchmark how we are doing to date. Our conjecture is that university-funded trials had a more representative study base compared with those from other funding sources. Clearly, this is the next area where research should be focused—on understanding why women are not being enrolled in clinical trials. We began to explore some of the early research exploiting qualitative methods that showed some of the barriers to female enrollment. These are the first steps, with future trials focusing on appropri-

ately powered, multiethnic female cohorts across the socioeconomic spectrum from diverse geographic settings to isolate the effects of female gender on trial enrollment in the context of other factors that may impact trial enrollment.

There appears to be room for improvement across funding sources. How can those in charge of funding trials ensure better representation in their patient populations?

I think that this is the wrong question. Our data, as well as data from other series, have shown that simply attempting to legislate appropriate representation in clinical trials is inadequate. Hence, asking funding sources to bear responsibility for improving representation ignores the most pressing question highlighted by our data: Why aren't investigators recruiting females to clinical trials at the same rate as males?

To me, the next most logical steps include research specifically focused on the etiology of persistent underrepresentation and testing solutions to the recruitment problems. However, I do not think that those in charge of funding sources should shoulder the brunt of the responsibility for female underrepresentation. Instead, I think all of us in medicine have to honestly (and uncomfortably) bear ownership of this problem. This will take in-depth study and thoughtful sustained efforts to responsibly correct.

One area where funding sources can help is to increase funding for studies examining the etiologies and solutions for gender underrepresentation (and other underrepresented groups) in clinical trials. Without funds, those in academia who want to study health care disparities are left without the means to accomplish their goals.

The *JVS* paper notes that representation of women in cardiovascular risk factor trials has increased, while women were underrepresented in all four of the common vascular diseases studied (carotid artery stenosis, peripheral artery disease, thoracic aortic aneurysm, abdominal aortic aneurysm). What do you think is the reason for this difference? Are there lessons trial investigators can learn from the cardiovascular trials?

The etiology of female underrepresentation in clinical trials was impossible to explore within our data. Yet, when one examines other works a bit more closely, several cardiovascular risk factor trials enrolled only females, and these trials may be driving the overall perception that female representation is improving (for instance, in trials studying the effect of antihypertensive medication in females). However, the fact remains that the majority of clinical trials (including cardiovascular risk factor trials) continue to underenroll women. Female-only trials are not an adequate solution, as the marginal impact of female gender on outcomes remains impossible to quantify.

Can you share some common theories about the barriers and potential solutions to female trial participation?

Recently published literature espouses some of the more common theories underpinning female underrepresentation, the first of which is the misperception that women are somehow protected against cardiovascular disease. Unfortunately, the demographics of our population would suggest otherwise. There has been an increase in the proportion of postmenopausal women in the overall population. A concomitant increase in the proportion of women among patients presenting with vascular diseases has magnified the data deficit regarding women in vascular trials.

Common restrictive entry criteria for clinical trials are another potential etiology. For instance, patient age is often used as a cutoff for clinical trials. Many past trials attempted to limit patient entry based on menopausal status, stating that it was important to homogenize the patient population to obtain a clear signal. This is false, as much of the statistical techniques and analytic power can capitalize on data heterogeneity to discern signals. In fact, heterogeneity can improve the resolution of a given data signal. Hence, many of the prior statistical reasons for restrictive entry criteria that systematically limited female enrollment are invalid.

Others have published different solutions, but we still need to study these solutions within vascular trials. An example is removing the barriers to trial enrollment to make participation easier for all involved, such as less complex recruitment materials, streamlining the research follow-ups and aligning them with standard clinical follow-up visits, or including telehealth follow-ups.

Although beyond the scope of your paper due to their inconsistent and/or lack of reporting in the analyzed trials, race and ethnicity are an important part of the representation conversation. How can intersectionality be ensured when making efforts to increase female participation?

Intersectionality is exceptionally important and is the ultimate goal of precision medicine and clinical trials research. I do not have all of the answers, but in my opinion, optimizing intersectionality mainly requires (1) dedicated, thoughtful planning and execution by the principal investigators (PIs), including a careful analysis of the study base prior to enrollment to ensure that the site can actually enroll a sufficient number of patients that accurately mirror the prevalence of disease in the popu-

lation, and (2) increased funding to support resources necessary to optimize intersectionality. For instance, if there were a disease with an increased prevalence among non-English speakers, the study would need more interpreters or interpretation services to appropriately enroll and consent patients. Again, further investigation into the etiology of the lack of enrollment is required before we can attack the problems. We hope that our work will spur further efforts to understand the etiology of underrepresentation of all groups so that we can improve the precision of our data.

How might improving the diversity of PIs affect that of trial populations, and what is the best way to see improvement in this regard?

We attempted to study the effect of the gender of the PI on the PPR within our study, and those data were somewhat unreliable. However, the data that we did obtain showed that the gender of the PI did not significantly impact the PPR. On the other side of the coin, there have been several qualitative studies examining some of the reasons why females felt discouraged from participation in clinical trials. Some women have expressed concerns for their own safety when all of the investigators and study personnel are male. My personal opinion is that this does play a role. In an analysis of heart failure trials, female investigators enrolled significantly more female patients as compared with male investigators,[2] and so, diversifying the group of people designing and leading the trials may make a difference in recruitment. I would like to see further research into appropriately quantifying the extent that the PI's gender plays on female enrollment in clinical trials.

What is the role of legislation and advocacy?

Legislation has played a role. Unfortunately, what we and other investigators have shown is that legislation alone is limited in its ability to optimize adequate female enrollment. Advocacy is also important. Yet, despite an abundance of advocacy, our data show that female participation remains inadequate and largely unchanged for the past 12 years. Further studies investigating the etiology underpinning persistent female underrepresentation are required to more efficiently optimize female enrollment. Given our data and that of others, I am dubious that further legislation and/or advocacy, while noble in intent, would be the most effective method to improve female participation in clinical trials.

The paper concludes with a call to action: "We need studies that identify the root causes of this persistent female underrepresentation and then mitigate them." What would such a study look like?

Studies that appropriately stratify by race, ethnicity, and gender are ultimately required to provide precision medicine to all patients. I think that this can be achieved with a methodical approach. The first step for our group was to try to quantify the severity of the problem, as well as to raise awareness of the persistent underrepresentation of females. The next step for our group is to perform qualitative analyses to determine barriers to entry for female participants within clinical trials. We endeavor to include all relevant stakeholders—the patients, spouses/significant others, caregivers, research coordinators, and past/current PIs. The goal from this would be to ensure that the stakeholder group adequately represents stakeholders that mirror the racial, ethnic, and socioeconomic composition of our local population. From this, we can then test possible solutions and measure metrics of participation.

What are the common myths related to this issue, and what are the priorities for future research?

I think the main myth we need to dispel is that cardiovascular disease is most importantly a male disease. Heart disease is the number one cause of death in females in the United States. Stroke and diabetes are also among the top ten causes of death. Clearly, atherosclerotic processes are driving the most mortality and morbidity for females in the United States. I think that we need a frameshift in understanding the importance of studying cardiovascular diseases in women. In terms of priorities for future research, I think we need to move toward an improved understanding of why female underenrollment remains a problem. We need to diagnose the problem before we can fix the problem. I think this will most efficiently optimize the data and precision of vascular care for women. ■

1. Mayor JM, Preventza O, McGinigle K, et al. Persistent under-representation of female patients in United States trials of common vascular diseases from 2008 to 2020. J Vasc Surg. Published online August 24, 2021. doi: 10.1016/j.jvs.2021.06.480
2. Harris DJ, Douglas PS. Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. N Engl J Med. 2000;343:475-480. doi: 10.1056/NEJM200008173430706

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