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Keys to Closing the Gender Gap in Stroke Trials

Dr. Wilner:
Although research suggests that women have a similar stroke risk as men, a new analysis of 281 stroke trials involving a half million participants reveals that women are often underrepresented in these studies. So why are fewer women participating in these clinical trials? And what implications does this disparity have on their treatment?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner. And joining me to talk about the underrepresentation of women in clinical stroke trials is Dr. Cheryl Carcel, neurologist and Senior Research Fellow at the George Institute of Global Health. She's also a senior lecturer on the Faculty of Medicine at the University of New South Wales in Sydney, Australia.

Dr. Carcel, welcome to the program.

Dr. Carcel:
Thank you for having me here today, Dr. Wilner. It's very exciting to be on ReachMD.

Dr. Wilner:
Well, thank you for joining us. Let's start with your background, Dr. Carcel. You've been a pioneer in the field studying sex differences in stroke epidemiology. Please share your experience and how it led to the current study.

Dr. Carcel:
Thank you. My clinical background is that I'm a neurologist. I did my training in the Philippines and then came to Sydney to do more specific training in neurophysiology and stroke. And after that fellowship ended, I happened upon the George Institute, was referred by a colleague, and I met Professor Craig Anderson, who is known for his clinical trials in stroke. And so I joined his team. I did my PhD on sex and gender differences in stroke, and from all these findings, I thought, what can we do next, you know? So this I thought could be an interesting next step looking at representation of women in clinical trials. Are there enough women in clinical trials? And if there aren't enough, what are the strategies to increase enrollment of women in clinical trials? So that's how I got here.

Dr. Wilner:
I did read your paper where you put all this together, so tell us about it.

Dr. Carcel:
The premise was in other cardiovascular disease trials, they found that women are underrepresented in some areas but also overrepresented in other areas, so we thought let's have a look at stroke. We've done some of our clinical trials. Some of them have pretty poor representation of women. For example, one trial that we did on hemorrhagic stroke, which was the INTERACT study, enrolled about 35, 36% women. So we thought we'd have a look generally. We went into clinicaltrials.gov database, which is one of the largest trial registries to find stroke trials with more than 100 participants. And we also looked at the Global Burden of Disease study for the prevalence of stroke in women per country. So the way we're looking at it is it's not just how many percent of women are in trials, but is it reflective of the burden of disease—or in this case the burden of stroke in the community, so comparing it with the participation of women in the trial by the prevalence of stroke in women in the population, so that means it's more reflective of what's actually happening out there.

So overall, we looked at 281 trials, and this was with at least a hundred participants. And then the trials were conducted between 1990 to 2020, so a good representation there. And we found a little over half a million participants, and 37% were women. The participation varied across individual trials. Some were 3% women, so very, very low and others were up to 78% women, but about an average or mean of 40% while the Global Burden of Disease study, as many of us will know, has prevalence of stroke in women about 48%. So

this means that when you calculated it with the prevalence participation ratio, majority of it was less than 1, which indicates that women in trials are enrolled less than the expected proportion of stroke in the background population.

Dr. Wilner:
When you broke down the results, it turned out that women were fairly equally represented when it came to stroke intervention trials but underrepresented when it was non-acute and in the rehabilitation trials. Any speculations why that might be?

Dr. Carcel:
Yeah, thanks, Dr. Wilner, for that question. And it's a difficult question to answer to be honest. We were a bit surprised with the results, and that means that for acute intervention, you think about endovascular trials or thrombolysis trials or anything really that enrolled participants within the 24 hours of acute onset, which is what our definition was. In other studies they found similar things. There was a *JAMA Neurology* paper that came out as well where trials with eligibility criteria of endovascular thrombectomy requirements also enrolled women. So in our paper, we discussed why this was and these are all sort of speculations really, but our thoughts were that when it's more acute trials and because women have more severe strokes, they may be more likely to participate in clinical trials because they see the need there. And this has been also validated in other studies where they didn't look specifically at women where the specific need is there to have a possible intervention that might change whatever you're having right now or the gravity of your illness.

Dr. Wilner
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. Cheryl Carcel about the underrepresentation of women in stroke clinical trials.

Now if we circle back to the findings of your study, Dr. Carcel, how can they affect the way women may be treated for stroke in the future?

Dr. Carcel:
I think this is really the most important question and thing that we need to explore with these findings because why are we doing this research anyway? The possible under-enrollment of women in these trials represents a threat to generalizability and in turn to the validity of the evidence base with regard to the treatment of women, and it also introduces a potential for unequal access to novel treatments. As an example, Dr. Wilner in 2015, when stroke treatment changed again when the endovascular therapy was recommended for large vessel occlusions—so this was sort of a big thing for stroke—another new treatment that could potentially change the lives of stroke patients.

So there were 5 trials that came out that year. One of the trials, MR CLEAN, put out a study and looked at it, and sex disaggregated their data. So this study enrolled 42% women, and they looked at the treatment effect, and it was null for women compared to protective in men, so women in the intervention group were more likely to die and as well as have serious adverse events. Then what they did was looked at it further. So those 5 large clinical trials, they put it all together in a meta-analysis looking at over 47–48% women in total now, and so they found out that there is really no sex differences in the intervention to endovascular thrombectomy, so it's equally effective in both women and men. There are no more serious adverse events for women. So I think if they stop there with the MR CLEAN publication then maybe the uptake for endovascular thrombectomy would not be as good in women.

Dr. Wilner:
So that being said, what recommendations do you have? What strategies can encourage women to participate in these clinical trials?

Dr. Carcel:
I think that's a really important question, and to do that we have to find out a few things. First of all, we need to find out what are the barriers for women attending trials. So we have all this data in cardiovascular disease, but we know that people with stroke may have different needs from people who have had an MI, for example, so we need to find out what the barriers are. And second of all, we need to find out if there are certain trial-specific factors that under-enroll women or disproportionately enroll women. And some of the things that we've found is that there are certain eligibility criteria, if you include that in your trial, you may end up under-enrolling women. An example would be age. So if you put an age cap in your clinical trial, women are generally older when they have had stroke, so you're generally more likely to enroll less women, so more research in that area is needed. And there's been some studies again in cardiovascular disease trials where if there is more gender diversity in leadership, then you get more diversity with your clinical trial population. The last bit would be to design trials that's very inclusive to everybody, including women. For example, if there is a trial, if there's an option to do it remotely, if it's too hard to for women to access the site, then you have a video conference as an alternative.

Dr. Wilner:
Before we close, Dr. Carcel, is there anything else you'd like to share with our audience today?

Dr. Carcel:
Yeah, I think it's upon us clinicians, academics, researchers, trialists, to encourage more diversity in our clinical trials, whether it be sex, gender, or race, and so that means that our trials are inclusive or generalizable to everybody that we want to treat in our clinics.

Dr. Wilner:
Well this has been an insightful look at how we can better improve representation of women in stroke trials, and I want to thank my guest, Dr. Cheryl Carcel, for shedding light on this important topic. Dr. Carcel, it was a pleasure speaking with you today.

Dr. Carcel:
Thank you for having me.

Dr. Wilner:
For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers, where you can Be Part of the Knowledge. Thanks for listening.