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### ASCVD Risk & Women: Investigating Impact on Female Patients

Dr. Brown:

Atherosclerotic cardiovascular disease, or ASCVD, for short, typically presents 10 years later in women than in men. And while many risk factors for ASCVD are the same for men and women, do we truly understand the workings of non-traditional risk factors for women?

Welcome to *Heart Matters* on ReachMD. I'm Dr. Alan Brown, and joining me today to discuss ASCVD risk factors, and lipid management in women is Dr. Erin Michos, an Associate Professor of Medicine, and Director of the Women's Cardiovascular Health Center at Johns Hopkins School of Medicine. Dr. Michos, welcome, and thank you for joining us today.

Dr. Michos:

Thank you for having me on your program.

Dr. Brown:

So a couple of things that we discussed in the introduction; number one women tend to have their cardiac events about 10 years later than men. And number two, unfortunately, a little-known fact is they have an equal amount of cardiovascular morbidity and mortality to men. And traditionally, I think over the years, there was this sort of myth that women didn't get heart disease as much as men. So, can you illuminate that situation a little bit and talk to us about the overall risk of cardiovascular disease in women?

Dr. Michos:

Yes, so you know, unfortunately, cardiovascular disease remains the leading cause of death in women. And since 2013, we're no longer seeing a decline in cardiovascular disease mortality, there's actually been a slight uptick. The fastest growing heart disease death rate is for women ages 45 to 64, middle-aged women, which is increased 7 percent since 2017. So this needs special attention. And we want to make sure women have their risk factors screened for and treated, but we know that women tend to be undertreated, and they are less likely to be offered statins and treated to guideline intensity statins for prevention.

Dr. Brown:

Yeah, I'd like to talk a little bit about those disparities today. It's something that's been, known for several years, and yet we still have a gap that we have to close. Why do you think middle-aged women have had such an uptick in cardiovascular morbidity in recent years?

Dr. Michos:

Right, so as you mentioned, the cardiovascular health of the U.S. population, including women has been getting worse over time with the epidemic of obesity and, diabetes, increased cardiometabolic risk. So that's also contributing to this earlier onset in women. And one of our recent papers published in the *Journal of the American Heart Association*, we showed over a 10-year period that cardiovascular disease and risk factors are being diagnosed in younger ages in women suggesting, that they're becoming less healthy over time. I think one of the concerns is the association with adverse pregnancy outcomes. But, women on average are starting to have pregnancies at later ages. And often there's more underlying comorbidities and risk factors with elevated body mass index and blood pressure, and dyslipidemia that sets them at risk for adverse pregnancy outcomes.

And when there is a, preeclamptic pregnancy, that preeclampsia affects 5 to 8 percent of pregnancies. And having chronic hypertension is a major risk factor for the development of preeclampsia during pregnancy. But having a preeclamptic pregnancy is associated with a fourfold increased risk of heart failure in the mother, you know, a twofold subsequent risk of cardiovascular disease. So this is a major red flag of risk in women. And there's also risks associated with preterm delivery, small-for-gestational-age infant, spontaneous pregnancy loss, that we also see with, older maternal age, and gestational diabetes, which affects 1 in 10 pregnancies, that's associated with a 25 percent increased risk of subsequent cardiovascular disease.

So I think these adverse pregnancy outcomes, as well as worsening cardiovascular health is leading to this earlier onset of ASCVD in women.

Dr. Brown:

Now, that's very interesting. I know that, you know, over the years, we've seen sort of underrepresentation in clinical trials of women. Seems like in the past decade or so, we've seen greater percentages of women in particularly the lipid-lowering trials with somewhere around 30 percent of the participants being female. What are your thoughts on that?

Dr. Michos:

So actually, I reviewed this alongside my co-author Dr. Safi Khan. We published this in *JAMA Network Open* last year. We reviewed 60 randomized clinical trials of lipid-lowering therapy over a 30-year period from 1990 to 2018. This was over nearly 500,000 participants. So over this 30-year period, there was an uptick in the enrollment of women in these lipid-lowering trials. But the overall representation was still low. It was only around 29 percent of these trials had women. Now we know for some disease conditions like acute coronary syndrome, or ASCVD, that women are less likely to have this at a given age than men. So what we did is we benchmarked it to this participation to prevalence ratio. So a ratio of 1 would mean adequate representation to the disease burden in the population. But what we found was participation to prevalence ratio about 0.5, particularly for ACS trials, and stable CVD trials.

So, in summary, women were underrepresented relative to their disease burden. And this really has important implications in determining the efficacy and safety of these cardiovascular therapies. And it may impair generalizability of trial results to routine clinical practice. Because even if there's no interaction by sex, if there's not enough women in those trials, you may be underpowered to see any sex specific, you know, interaction for both efficacy but also for safety.

So we really need to undertake new strategies to improve optimal recruitment. And one of the things I've been really passionate about was trying to increase the diversity of trial investigators. There is some data suggesting that the more women who are on steering committees of trials and these leadership roles and authors of these studies, is associated with the higher enrollment of women patients in trials. So efforts to recruit and retain women trial investigators, may be a mechanism to help lessen disparities in both areas.

Dr. Brown:

I want to just take you back to one of the topics you didn't touch on. We talked a little bit about the risks of pregnancy and preeclampsia, etcetera. What about menopause? We kind of used the perimenopausal, the time of developing menopause if it's early, a risk indicator for cardiovascular disease later in life. What kind of data do we have on those perimenopausal years? And do we have enough data?

Dr. Michos:

Yeah, so interestingly, total cholesterol is similar for women and men under the age of 35. However, after that age, there's really a sex-specific differences by age. So compared to men, actually women ages 35 to 49, still sort of premenopause, have a lower total cholesterol than men. But after the age of 50, which is around the average age of menopause, women have higher cholesterol levels than men. So at the menopause transition, women have this acute rise in total cholesterol and LDL cholesterol, and drop in HDL cholesterol with a sudden cessation of estrogen. And so this is really an acute change in lipids that, of course, men don't experience. But this is also in contrast to other risk factors, like hypertension and diabetes. And women seem to be much more age dependent and not relative acute change at the time of the menopause transition. So women tend to have a little bit more dyslipidemia later in life. And some have postulated that this may be one of the reasons why women on average might have this 10-year delay of having cardiovascular disease later in life than men. But, premature menopause, women who got the menopause early, is an independent risk factor of cardiovascular disease, sort of in a linear fashion below the age of 45. And women below the age of 40, who went through menopause, that's associated with a 36 percent increased risk of cardiovascular disease, even after you adjust for traditional risk factors, such as blood pressure and lipids and diabetes.

So, that's why in our, recent ACC, AHA, with our cholesterol guidelines and our primary prevention guidelines, we have listed both premature menopause and those adverse pregnancy outcomes I mentioned earlier, as risk-enhancing factors. So after you estimate 10-year risk, for those women who are at borderline or intermediate risk, the presence of risk enhancers might favor a statin initiation. Although sometimes it's still not clear what a cardiovascular risk is,

you know, it might not be clear whether all women, who've had these risk factors should start on a statin. And so in this case, if there is indecision about the net benefit of statin therapy, our guidelines say you could use coronary artery calcium scores to help refine risk further and guide treatment decisions, and primary prevention as part of shared decision making. So some of these women, will actually get coronary calcium score, if they have one of these, red flags of risk, like premature menopause or a history of preeclampsia.

Dr. Brown:

For those just tuning in, you're listening to *Heart Matters* on ReachMD. I'm Dr. Alan Brown, and I'm speaking today with Dr. Erin Michos about lipid management and the risk of atherosclerotic CV disease in our female patients.

So before we wrap up, Dr. Michos, I want to just focus on female patients with this elevated ASCVD risk. And maybe pretend you're sitting with a patient in your office, who may have had preeclampsia or maybe going through early menopause, and you're discussing with them whether or not you should prescribe a statin. What kind of things do you say to them?

Dr. Michos:

Well, first of all, I think there's still some misconceptions out there that statins don't benefit women. I still hear this being brought up. And that's not really true. Some of the earlier primary prevention trials didn't have enough women in the trials and, of course, women being lower risk, you needed, you know, a sufficient number of patients to show there was a benefit. But now we have a lot of meta-analyses. Dr. Khan and I performed one recently; 53 randomized clinical trials of LDL-lowering therapy, statins, ezetimibe, PCSK9 inhibitors and really showed for every 1 millimole per liter, which is 39 milligrams per deciliter reduction in LDL, you can reduce the risk of major adverse cardiovascular events by 15 percent in women. There was no interaction by sex. So we saw women benefit in statin trials with ezetimibe and IMPROVE-IT with the PCSK9 trial. So the implication is that therapy should be used in appropriate patients without regards to sex. So first of all, I emphasize that we do have data that women benefit. Unfortunately, data from the PALM Registry suggests that women are less likely to be offered statins, and they're more likely to decline. And we also know that women are more likely to have muscle-related symptoms with statins, and stop the statins due to these muscles symptoms compared to men.

So this can be a challenge. I think encouragement, reinforcement, so I have them assess any baseline muscle aches and pains that they may have so that they can notice any difference. I talk about the benefits. I think the important thing is that we listen to patients and we take their symptoms seriously. And most patients who reported statin-associated muscle symptoms, we can get them back on some statins with rechallenge. So rechallenge should always be tried. But the good news is at least we have some new tools available. We have new lipid-lowering therapy, LDL-lowering therapy that we can use if patients are truly statin intolerant. The PCSK9 inhibitors for high-risk patients, we also have bempedoic acid. So we have some more options that can help if we truly can't get patients on statins, but reassure that women's do benefit from statins. But unfortunately, they remain under treated.

Dr. Brown:

Well, I just want to thank you for all the efforts that you've put in in this area. I think, you know, your work has really illuminated this issue and brought it back to the forefront. I hope you will continue your diligence on that. Thank you for sharing your wisdom with us today. And it's certainly encouraging to know that there's continued research and teaching efforts around the treatment of women with atherosclerosis.

Then to the audience, I want to thank my guest, Dr. Erin Michos, for joining me in this very important discussion, and providing all of her wisdom. Dr. Michos, was great having you on the program.

Dr. Michos:

Thank you so much for having me today.

Dr. Brown:

I'm Dr. Alan Brown. To access this and other episodes in our series, visit [ReachMD.com/HeartMatters](https://ReachMD.com/HeartMatters), where you can Be Part of the Knowledge. Thanks very much for listening.