

Jane Reusch: Welcome to the American Heart Association Getting to the Heart of Stroke podcast series. I'm Dr. Jane Reusch, a professor of medicine, integrative physiology, and bioengineering at the University of Colorado and the Rocky Mountain Regional VA and an endocrinologist.

Before we begin, let's review the learning objectives specific for this podcast. They are, first, to understand the indications for lipid-lowering therapy in multi-risk patients with atherosclerotic cardiovascular disease. Next, to understand female-specific cardiovascular risk modifiers for stroke. And third, to appreciate the guideline for lipid management in the secondary stroke prevention. We are joined today by our distinguished colleagues, Dr. Sidney Smith and Dr. Seemant Chaturvedi. Dr. Smith, why don't you start by introducing yourself? And then Dr. Chaturvedi will introduce himself. From now on in the podcast, we will call me Jane, Dr. Smith, Sid, and Dr. Chaturvedi, Seemant. Thank you. Dr. Smith.

Sidney Smith: Thank you, Jane. I'm Dr. Sidney Smith, a professor of medicine cardiology at the University of North Carolina. I am a clinical cardiologist with a major research focus in the development of evidence-based guidelines, especially relating to cardiovascular prevention.

Jane Reusch: Seemant, could you please introduce yourself?

Seemant Chaturvedi: Yes, I'm Seemant Chaturvedi. I'm a neurologist and professor of neurology at the University of Maryland School of Medicine and I'm the system director of stroke across the hospitals of the University of Maryland Medical System. I have special research interests in carotid stenosis management, sex differences in stroke, and intensive medical therapy for stroke prevention.

Jane Reusch: So as you can see, we come from a number of different disciplines and each of us are going to discuss today a case that we frequently see in our clinic that specifically speaks to strategies whereby we can decrease stroke in people. Sid, if you could take the first case, please?

Sidney Smith: Thank you, Jane. I'd be happy to do so. I'd like to present a 70-year-old South Asian female. And I start off because I see an increasing number of patients from Asia here in the research triangle, North Carolina, both South Asian and East Asian. And, of course, the South Asian patients have a higher incidence of diabetes and a slightly different dyslipidemia. So we're going to take a South Asian woman, 70 years old with type 2 diabetes. Also has high blood pressure and recent acute coronary syndrome six months ago, which was a non-STEMI and also had an ischemic stroke 14 months ago. So at age 70, she's had two manifestations of atherosclerotic vascular disease, once the ischemic stroke and secondly the non-STEMI. She came to clinic now for return visit and in this setting, of course, we are focusing on preventing her from having a second clinical manifestation, either neurologic or cardiovascular. In going over her symptoms, her only complaint on this visit is of a left hip soreness. She's been stable with no symptoms of angina and no neurologic symptoms. Of course, this complaint of left hip discomfort in patients that are on statin therapy always raises the question of a myositis. So that's in our

minds.

Now, on physical examination, we see that her blood pressure is 128/72. This is excellent. Well under the systolic goal of 130 for patients with the diabetes and hypertension. She's in regular sinus rhythm with a heart rate of 74. The rest of her physical exam is normal. Her electrocardiogram shows a normal sinus rhythm with some lateral ST-T changes, no Q waves, and her echocardiogram on current medical therapy shows an ejection fraction of 50%, which is just mildly reduced. Laboratory tests are very important here. Total cholesterol, 155, LDL cholesterol of 70, the HDL of 60, and triglycerides are 125. Importantly, it raises a question because we have a total cholesterol, 155, well below 200 and close to 150, looking very good, and an LDL is right at the range of 70, which, in primary prevention, might be okay, but it raises some questions that we'll get into. Her HDL is 60 and the triglycerides are fine. Also, another important measurement, too, the thyroid studies are normal. This comes into play with dyslipidemia frequently and is very important to include in our patients as we evaluate their lipid panels. Also of importance is the CK, which was ordered earlier because of her hip discomfort. That's 190, which is within normal limits. Hemoglobin A1C, 6.8 is good, and their meds are losartan with 50 milligrams, metformin, 500 milligrams, empagliflozin, 10 milligrams per day, atorvastatin, 80, clopidogrel, 75, and aspirin, 81.

So the question is, in this patient with well-controlled hypertension, who is on reasonable therapy for her diabetes, we may want to change that just a little bit. And on therapy for her mildly-reduced ejection fraction, MRF, what do we do about these lipids? Now, there's several considerations. We might say we're really worried about this back pain that's secondary to statin intolerance myositis. We're going to get her off statins, we're going to go to Bempadoic acid, an attractive new lipid-lowering agent for LDL. We might add PCSK9 inhibition to the statin therapy to drive her LDL to less than 40. We could consider ezetimibe to a current statin therapy to reduce the LDL to less than 55 or we might get out of all of this and go to rosuvastatin because we really do think that this is a statin-related myositis.

My answer to this question would be three. I would add ezetimibe to the current and statin therapy to further lower her LDL cholesterol to less than 55. I would not choose Bempadoic acid because of myositis because I think this isolated left hip pain in a 70-year-old woman with normal CK may well be related to osteoarthritis of the left hip and would not jump on that. And for that reason, I would not switch to rosuvastatin because of myositis. So we're left then with a question of how low to take the LDL cholesterol. In this setting, I would choose ezetimibe because I would expect about an 18% to 20% reduction in the current LDL cholesterol that would get her down to a range of 55.

And the interesting information that we have from studies with ezetimibe, the IMPROVE-IT trial, was that the subgroup in IMPROVE-IT, which is what really drove our guideline committee to move in this direction, concerned patient with diabetes. And in that subgroup with diabetes on ezetimibe and statin therapy, further reduction of LDL to a range of around 55 had a very significant reduction in cardiovascular outcomes and especially stroke. So this is where I would take this

patient with combined atherosclerotic and cerebrovascular disease, dyslipidemia, multiple risk factors. I'd look at getting her LDL down to a 55 area or so. And I would look to adding to the lipid lowering with statins, ezetimibe, which has some known benefits in patients with diabetes.

Jane Reusch: So let's say that you believed that this really was a statin-based myopathy, what would your expectation be for the LDL lowering with Bempadoic acid?

Sidney Smith: With Bempadoic acid ... And we're not talking about people with that age, which is where a lot of the data resides with Bempadoic acid. So I would think a switch to Bempadoic acid might get me to somewhere in the range of 55 to 70. That would not be achieved in a lot of the study patients which entered with LDLs much higher. And so it's a bit of a guess and I would be more likely to move to PCSK9 inhibition, where I'm pretty sure that I'll get a good reduction. I also want to point out that ezetimibe is not entirely without problems with myalgia and myositis. And so that's a good reason. If we really think this is myalgia and myositis, I think we're really into moving towards PCSK9 inhibition.

Jane Reusch: And Seemant, have you seen any myositis with PCSK9 inhibition?

Seemant Chaturv...: No, I have not. And I think the studies would also back that up that it appears to be very rare. But one thing I did want to comment on with Sid's case is that I think for our listeners, it's very important that they keep in mind patients with polyvascular disease or disease in more than one territory because I think there's increasing data that we need to be more vigorous and attentive to lipids in patients with polyvascular disease and should shoot for a lower target.

Jane Reusch: Well, thanks. I mean, I think that everybody learned a lot from that case. And in the theme of going forward in short of comments about women, I'm going to move us forward to two decades earlier. My background is in cardiovascular disease and the study of sex differences and particularly women who have excess cardiovascular disease in the context of pregnancy.

So my case is a 52-year-old woman who presents to establish care. She's not giving any complaints other than hot flashes and her last menstrual period was 18 months ago. She also has some poor sleep related to those hot flashes. Her past medical history reveals hypertension, which has been well controlled since her late 30s, but she did develop it in her 30s. She has had obesity throughout her adult life, and with menopause, she has had some increased weight gain. She's Gravida 3, Para 3 with hypertension in two pregnancies and gestational diabetes in her third pregnancy, which was controlled with diet and physical activity. All pregnancies were term and normal birth weight. Her menstrual age was onset at age 12. Menopause was around 50 as noted above and she always had regular periods with no diagnostic criteria for PCOS. In her family, she has obesity, type 2 diabetes, hypertension, and cardiovascular disease, not formally premature, 60s in her mother, 70s in her father, and prostate cancer in her father.

She is married, an attorney, no tobacco ever, occasional alcohol, rarely cooks but

enjoys healthy food, and has a nanny to run children's sports activities that helps her cooking. She goes to the gym once on the weekend and she's just busy during the week. Her step counter does not seem to show how busy she is. She falls asleep around 10:00 p.m., often awake from 2:00 to 4:00 a.m., sleepy during the day, in the morning in particular, but does not nap or fall asleep with TV watching. Her medications include losartan 50 milligrams a day, metformin for her pre-diabetes, 50 milligrams BID. She is obese with a BMI of 31. She's five foot three, weighs 180 pounds. Her BMI has increased over the last few months. Her blood pressure is well controlled and she has a normal thyroid exam and basically no signs of severe insulin resistance and no acanthosis, no arterial insufficiency or venous insufficiency in her lower extremities. Her fasting glucose is 97. She has a total cholesterol of 291, triglycerides of 82, HDL of 83, and an LDL of 192. She has an ALT that is normal. Her A1C is 5.6 and her creatinine is normal.

So in this 52-year-old female with well-controlled hypertension, obesity, if you were to do a Framingham risk analysis, would she specifically require lipid therapy? Well, yes, she would because of her LDL of 192. But the reason that I gave her an LDL of 192, these are actually my lipids, is because this 52-year-old woman with numerous comorbidities, if she had an LDL of 160, on the risk engine, she would not meet criteria for statin therapy right now or she'd be in that never-never land. So my real points in discussing this case is beyond the LDL of 192, what are the risk factors for this patient and how should you discuss them with her in terms of her LDL goal? And she specifically has the risk factor of two pregnancies with hypertension and one with gestational diabetes. These sometimes happen all together, but those are what have been termed for women risk modulators. So they're not specific risk factors that go into the classic risk engines, but we're supposed to think about them when we're in the clinical setting. We're supposed to say, "This woman with an LDL of 192, should she have an LDL of below a hundred, 70, 55, how low are we going to try to help her go and what else do we need to worry about?"

She is very concerned about medication. She's 52. She's already on metformin and losartan and she wants to know, is there a way to manage this all with lifestyle? What about that medication on TV with weight loss is her question. So I would just say that this is a woman with multiple cardiovascular risk factors, including a ... Well, she has formally been diagnosed with prediabetes, obesity, hypertension, and these hypertensive and diabetes disease of pregnancy, such that we would want to be very aggressive with her. We do not have a formal prospective study in her exactly that is adequately powered for women using a GLP-1 receptor agonist. But this could be quite an exciting way to help her get off of other medications so we could treat her with a statin because she is not going to get away without formal lipid management in this instance in the setting of this LDL lowering therapy that she needs right now. And so I would like to open up this particular case to ask first Seemant, when you are meeting a younger woman with multiple cardiovascular risk factors, how are you approaching this and how aggressively would you be treating her?

Seemant

Yeah, no, I think what you highlighted is correct that we look at the constellation of

Chaturv...: the total risk factors. And so in this case, we have the obesity, the pregnancy-related modulators as you mentioned, a poor sleep, which could be considered another cardiovascular stressor. And it seems that she has a stressful lifestyle, which certainly is probably not helping. Yeah. So I think I would have a frank discussion with her about which ones she thinks she can modify in the future and what are the prospects for making an impact on those risk factors. And I think the point you made in the third question is reasonable that a GLP-1 agonist could be beneficial in terms of weight loss and then helping with the other risk factors because we know the studies show that in patients with prediabetes, the GLP-1 agonist can be useful for preventing the onset of a full-blown diabetes. But I would certainly be concerned with an LDL of 192 given her other risk factors. And I would certainly lifestyle change and dietary change would be recommended, but I think she'll be not able to really achieve the desirable target with just dietary change alone.

Jane Reusch: Yes. And I specifically wove in there because I'm an exercise physiologist, the idea that she goes to the gym once a week. When you're approaching somebody with the idea of starting a statin and also considering a GLP-1 receptor agonist, what are you telling them, Sid, about diet and physical activity?

Sidney Smith: Well, you hit the right person when it comes to physical activity because it's number one on my list. I mean, I think there's no drug that you can have which does more than physical activity in terms of blood pressure, lipid panel, weight. You also get some anxiety relief. And physical activity is absolutely number one for me and, in my opinion, needs to be daily. I tell my patients that you brush your teeth once a day, you have breakfast in the morning, you should look at physical activity. That's part of the daily life that we have to live or that we should live. And don't think that it has to all be on an elliptical trainer. You can walk with a close friend for half an hour at a rapid pace. There are many things that you can do that will reach a physical activity goal. So I would lean hard on that. In a sympathetic encouraging way, I'd be after weight loss here. It's hard, but it takes discipline. And I tell her that I think she's got it. I think she can do this.

Now, the other thing that can be helpful in my practice is the coronary calcium scan. If we were to do a calcium scan in her and we found the presence of coronary calcium, I think that would be a further incentive for her. You've already got changes here and you are at risk already in your coronaries. That would be helpful. If it came out at zero, it gives us a little time, and I might tell her, "We've dodged a bullet here, but we know that you're at a point now that you're in 50s, you get outside of the menopause, you're in a different situation in terms of cardiovascular risk. So this is our chance to make a difference with a change in your life." So physical activity would be at the center of all my recommendations and I'd look for some adjunctive tests that might help point us in one direction or another.

Jane Reusch: In terms of how low to go. And I think that we often ... And I buried the lead intentionally here because I think that when we look at any of our pharmacological interventions, none of them will do as much as physical activity moving from nothing to something. And so that is definitely where I wanted to head with that.

And at age 52 with already a decade and a half of hypertension, that really escalates the risk in women more so than men, I just recently saw a study on that. And I think that we need to be so aware that we might miss the opportunity to take care of women as intensively as possible if we're not asking all of these pregnancy-related issues. So they gave me a bandstand and I stood on it. So we're going to go, Seemant, to the next case and I'll have you take it from there.

Seemant
Chaturv...:

Sure. So this is a case which is fairly common in my practice, and this is a 60-year-old man with a history of hypertension and diabetes. And he presents to the emergency room after having had a 30-minute episode of left arm heaviness and slurred speech. His blood pressure in the emergency room was 180 over a hundred and he's found to be in sinus rhythm. And his neurologic exam has returned to normal in the emergency room.

And so he's admitted to the hospital with a diagnosis of transient ischemic attack and further evaluation shows 90% right internal carotid artery stenosis. And his lipid profile is notable for an LDL of 198 milligrams per deciliter. Total cholesterol is 240, HDL is 38, and his triglycerides are 260. And the hemoglobin A1C is 8.1. And so he's not on a cholesterol-lowering medication at the time of this event. And so what should our approach be to managing his dyslipidemia?

And so I would say that he has a definitely evidence for a large vessel atherosclerosis, and with the 90% right internal carotid artery stenosis and somebody with recent symptoms, he would definitely be someone who would be evaluated for potential revascularization with a carotid endarterectomy. But even if he goes for a carotid endarterectomy, we need to consider his lifelong risk of future vascular events. And so I think he would definitely warrant a pretty aggressive LDL target and the 2021 AHA/ASA guidelines, of which I was a member of for secondary stroke prevention, that recommended an LDL of less than 70. So I think that would be a reasonable initial target. One could argue that perhaps we should go even lower, maybe less than 55, given the diabetes and the large vessel disease, but definitely less than 70 would be an initial starting point. And he is starting with a very high LDL of 198. And I would be interested in your comments, Jane and Sid, about whether we should consider familial hypercholesterolemia in this patient with that high level.

And so I would definitely put him on a high potency stat and initially see where that gets you, but realizing that he may need adjunctive medications either in the form of ezetimibe or a PCSK9 inhibitor.

Sidney Smith:

That's a great question, Seemant. And I ... The one thing I see in this patient, which Jane dodged the bullet with her patient, is the hemoglobin A1C. And her patient, it was down around 5.2 or so. But we've got a hemoglobin A1C of 8.1 and the area I'm interested in is whether or not better control of diabetes would not improve that lipid panel. In fact, I think it would. So I would not move to really aggressive lipid lowering at this point nor do I think this is FH without strong family history, without getting the diabetes under better control and seeing what happens to that lipid panel.

Jane Reusch: Yeah. So with that triglyceride being what it is that in A1C ... We used to see triglycerides in the 200s to 300s very commonly when poor control of diabetes was an A1C of 10 or 12. With an A1C of 8.1, we definitely think it's a factor, but I would just say it's always an option to back off on that intensive statin therapy later. But for right now, I would be going after both together. And so, in this person, my question then becomes, what else do I know about them? In terms of an A1C of 8.1, I can easily get that down with either empagliflozin or a GLP-1. So what else do I know about them? They're not really on a lot of medications at all, to start with. So we've got a long way to go with lifestyle and some of the simpler medicines. I don't recall, and I'm looking at you guys instead of the case, what his BMI was.

Seemant Chaturv...: Yeah, I don't think it's specified, but I think for the sake of argument, maybe we can say 32.

Jane Reusch: Okay. All right. So we would love some weight loss. We would love to get his diabetes under control. He's already presenting with atherosclerotic disease, so we can definitely go with either a GLP-1 or an SGLT2 agent. And we just want to ... That will lower some things. Definitely, that's going to probably help those triglycerides, but I wouldn't count on it to get the LDL where I want it, as opposed to Sid, because we have to have a little controversy here. I would probably start that statin right away, but be going very aggressively after the diabetes, which in some people who present with a first stroke or TIA, it's more terrifying, I think, to a person than a heart attack. And it's usually an incredible window of opportunity for lifestyle change.

Sidney Smith: No, I totally agree. Carpe diem here. There's no better time to get a patient to change their behavior when they've just had symptoms of a stroke. And so I'm in total agreement here. This is secondary prevention here. This is a patient that has evidence for a lesion in the right carotid artery that's had a TIA and they should be on high-dose statin therapy. The area that I would maybe pull back on is whether I'd be adding ezetimibe or thinking about a PCSK9 inhibitor until I'd gotten the diabetes under control. Those triglycerides, you and I and Seemant have all seen higher triglycerides than 260, granted they're above 150 or even 135, but they're not at 500, 800, or a thousand. So I think we'll be able to move it a little bit with better diabetes control. But totally agree, patient has a manifestation of cerebrovascular, atherosclerotic vascular disease, and needs to be on maximal statin therapy at this point.

Jane Reusch: All right. Seemant, do you have any other questions for us?

Seemant Chaturv...: No, I appreciate those perspectives and I think we're in agreement on maybe 98%.

Jane Reusch: Yeah, absolutely. So ... Well, I just would like to thank everybody for sharing their experiences with us today and it has been my great pleasure to meet the two of you and to be able to talk about something that we're all quite passionate about. The HCA Healthcare and the HCA Healthcare Foundation are a national sponsor of getting to the heart of stroke. The views and opinions in this activity are those of

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