Announcer: Welcome back to the Mayo Clinic cardiovascular podcast series, interviews with the experts. I'm your host, Sharonne Hayes. I'm a non-invasive cardiologist and vice chair of faculty development and academic advancement for the Department of Cardiovascular Medicine here in Rochester, Minnesota. Today I'm joined by Dr. Regis Fernandes. He is division chair of Preventive Cardiology and comprehensive cardiology at Mayo Clinic Cardiology in Arizona. He's also director of the lipid clinic and does lipid research. Today our topic is how to integrate non-statin therapy in your practice with updates from the latest 2022 LDL Cholesterol lowering guidelines. Welcome Regis.

Dr. Regis Fernandes: Thank you Sharonne. Happy to be here.

Dr. Sharonne Hayes: So tell us a little bit, just maybe a high level overview about the new FDA approved non-statin drugs for lipid lowering.

Dr. Regis Fernandes: Yeah, happy to do that. So one of the things that drove the development of this cholesterol guideline or expert consensus is that new drugs are coming up in the market. These drugs have been FDA approved. There has been some research backing up the use of these drugs and this is developing quite fast. So it was important for the ACC, AHA to come up with a document that summarizes some of these new findings for providers.

Dr. Sharonne Hayes: You and I both see lots of patients who either they're not at goal, they have statin intolerance, they have lots of reasons why we've been looking for alternatives to statins, even though statins are still our mainstay. So who and when should we consider these alternatives or additions to statins?

Dr. Regis Fernandes: Yeah, great. So lemme just touch about first a little bit on some of these new drugs that people may not be familiar with and they have some questions and then we can get onto who and when we should be using this drug. So I think most people here should be familiar with ezetimibe and PCSK nine inhibitors, which are non-statin drugs that have been supported in the previous guidelines. But new drugs are coming up. I think two that are worth mentioned is bempedoic acid and inclisiran. So I'm gonna start with bempedoic acid. This is an oral drug. It's a very interesting drug, was pretty much designed for patients with statin intolerance. It's actually administered as a pro drug and it doesn't get activated until it gets to the liver. So Harry, it basically has no effect in the skeletal so whatsoever. So no statin, myo, no myalgia from any type in there. It does lower the production of cholesterol in a similar way that statins do it. It kind of blocks a little bit a higher level of that cascade of events. But again, it is activated in liver. It, it does not affect skeletal muscles. It lowers LDL cholesterol by about 10 15%. So it's very robust. It's like ezetimibe. But the company did market also the beady acid in combination with ezetimibe together in one pill. So when you put them together you can get 35% reduction LDL or up to 40%, which is similar to a moderate intensity statin. So it's very attractive for people that cannot take statins and need that kind of, that kind of reduction. Main side effects. Comparing to placebo in the

clinical trials, one important one to know is gout. It looks like bempedoic acid can increase uric acid levels a little. So it's recommended to check uric acid levels and let patients know about it. But the incidence was really very small, but it was noteworthy and was statistically a little bit higher than placebo. Another very exciting drug is inclisiran. inclisiran is a medication that decreases PCSK nine and therefore have the same end effect as PCSK nine inhibitors by helping with the recycling of the LDL receptors and lowering LDL cholesterol. That's the mechanism of action. The interesting thing about it is that inclisiran is a small interfering RNA, which is a very smart way to do drugs nowadays. Other drugs are being developed in lipidology and other areas in medicine with the same technologies, basically blocking the information of the DNA into the RNA in building proteins. So it's a way to decrease the production of a protein that should don't want to make in this case here, PCSK nine from the liver. Logistically, some interesting fact facts about enis it, one important is that it, it, it can be given in the clinic only clinic setting only. So it's not something that patients take home and inject themselves. It has to be given in the clinic because that's how the FDA approved the drug. So it's very important to know that. And the medication, the good thing about it, it's given every six months. So you get one first dose, a second dose in three months and after that every six months. So it's very appealing for patients. Can you imagine Sharrone, you have high cholesterol, you have familial hypercholesterolemia, and now you need to do is give yourself a shot every six months. So it's very good for compliance, it's very good for preventing people from missing dosages, et cetera. So very exciting field in lipidology. Those are the two main ones that people in this podcast will probably, probably have questions about it.

Dr. Sharonne Hayes: Yeah, and and what kind of percentage LDL lowering do we get with inclisiran?

Dr. Regis Fernandes: That's a fantastic question. And you get about 50%. So high intensity statins, you get 60. Besides kind inhibitors, we get around 60 the same. So this is a little bit less 50, but clinically it's a, you know, within that high intensity statin reduction, 50% reduction. So it's really good for that.

Dr. Sharonne Hayes: Anybody who's not providing this in their clinic now, are there any hoops or challenges to, to providing this if you are a lipid clinic or maybe just a general cardiologist or internist?

Dr. Regis Fernandes: I would say it comes down to the, to the pre-approval process. So we have to follow the FDA indications for the medication. And it's similar to PCSK nine, which came from the trials where they, how they, they tested the drug. So patients with familial Hypercholesterolemia or patients with clinical A-S-C-V-D, they don't get to be a goal, et cetera. But there are some challenges in, in getting, you know, pre-approval. So most of these drugs, just like PCs nine inhibitors, they require pre-approval and, and that takes time from providers. It takes times from your staff. So that that is definitely a, a, a barrier to prescribing these medications because of the amount of time that it takes to get that approval. So here at Mayo Clinic, Arizona, we're working on processes, we're fortunate to have pharmacists and pre-approval, PA prioritization groups of people that work with that, that can help us out. But I can see how that will be a challenge in a, you know, in for most providers outside.

Dr. Sharonne Hayes: Yeah. So I, you know, we've kind of alluded to these two medications might be appropriate for somebody with statin intolerance. How about somebody who's just not at goal and, and so what are some of these thresholds that we might use and, and can they be used in combination with statins and have you, what experience do you or the, the guidance from the the '22, 2022 guidance?

Dr. Regis Fernandes: Yeah, so that, going back to when you asked before to whom and, and when should be considered, I would answer with a, a sentence that is very helpful to have in this PA processes and is actually in the guidelines, which it says exactly that for patients that are not at goal after maximum, maximum tolerated dosages of statins, which would be, could be zero. Some people don't tolerate any, right? So when you get to that level in an appropriate diet, so you have to be, you have to document patients are on an appropriate diet and they have tried ezetimibe, okay. And they have tried smaller tolerated doses of statins. 'cause a lot of people with statin tolerance can tolerate smaller doses. If you have done all of that and your patient's still know at goal, that's the patient that we should be considered non statin, non statin therapy. Another one, possibly more in an acute setting, which is something new. But something to think about is patients that come in with an acute coronary syndrome share on, and they are already on a high intensity statin, right? They will require an additional 50% reduction independent of what the L is at the time, you know, in order to get a 50 cent, 50% in addition to a high intensity statin. Ezetimibe alone may not cut that. So you may have to go into some of these other drugs that are used. So those are all new developed new things that are, are coming up. But those will be the most, the two most common reasons for who and when you should go to a non-statin therapy.

Dr. Sharonne Hayes: You talked about the 50%, but what, you know, what's the update on thought on LDL targets or thresholds for treatment depending on the type of patient? Do you wanna give us a, a review of that?

Dr. Regis Fernandes: Historically it has been a LDL of 70 or less for patients that have clinical as CVD. So I'm gonna try to focus on the patients we see most, most often in cardiology. So secondary prevention, so the new guidelines have a new threshold and that's very important from that. So the new threshold is 55 milligrams per deciliter or less for patients that are considered this very high risk group. So we can talk about later what is the recommendations for patients with statin toes in general. But the guideline divided similar to the previous guideline, they divided patients in in group risks groups or different group risks with A-S-C-V-D and also in primary prevention. So for patients that are considered very high risk, so the, the key word here, Sharon, is very, okay, so very high risk because they also have a group that is not at very high risk. So for very high risk patients, the threshold is 55. Now how do you identify the very high risk patient? Well, it's basically almost the majority of the patients that we give in cardiology. I'll give an example. So very high risk requires similar to the Duke criteria for endocarditis. So a major and some minor criteria. So major criteria is any patient that had an MI in their life, any documentation of a myocardial infarction or a stroke or peripheral arterial disease or someone that had an ACS history,

especially within the last year or so. So anyone in that category fits one of those criteria is a major criteria. The minor criteria are very broad and it is almost every patient who seen cardiology on age over 65 patients that have diabetes, hypertension, smoking, all these traditional risk factors. So it's not very difficult to see that patients with clinical ASCVD, I would say the majority of them would fit into that very high risk group. So I think it's safe to say that if you have clinical SCVD, unless someone is very stable, had bypass surgery 10 years ago, something like that, all of these other groups would consider them very high risk and use a, use a threshold of 55 or less for LDL cholesterol.

Dr. Sharonne Hayes: 55 is the new 70?

Dr. Regis Fernandes: That's correct.

Dr. Sharonne Hayes: Okay. All right. So, so we're gonna aim for a lower target on the vast majority of our patients. You know, statins are still the mainstay and the vast majority of our patients do tolerate them and we, and, and a lot of them we can get to goal. But what are some of the new thoughts and tips and tricks on dealing with statin intolerant patients?

Dr. Regis Fernandes: Fantastic. So first of all, let's not put down statins. The statins are still great. They have tremendous value. If we look at how much they cost and what do you get from them, nothing beats them. There are still, they, they still have the best value in the market. But with the new statins, we have to think in terms of value too. We have medications that are not expensive, but they don't lower LDL much like ezetimibe and we have medications that are very expensive and lower LDLA lot. So when you put in that equation value, you see how they compare with statins, but unfortunately some people don't tolerate. So how do we use that? How do we combine value? How do we combine cost, how we combine effectiveness and how do we combine evidence-based? Because after all we have, we want to use recommendations that have in outcome. It's just not evidence based in okay, lowers by 50%, great, wonderful, but does it reduce the risk of heart attacks? We all wanna think it does the lower the better for LDI in preventing events. But have they, have they done placebo control randomized clinical trials on this stuff? Right? So when you combine all of that, I think the guideline did a good job. They have actually a diagram at the end. They kind of put it all together and I think it pretty much can kind of helps providers to decide where to go next. So I can tell you pretty much together putting together, if we use for instance clinical A-S-C-V-D, let's try to focus on these patients because those are the ones that we see more often in cardiology. So if you have someone who's at a very high risk, okay and you want to bring their LDL down or someone that has let's say familial hypercholesterolemia and has that very high risk, so the first line therapy would be ezetimibe and or a PCs can nine inhibitor. Okay? As a first choice. If that doesn't work, then you can get into Bempedoic acid inclisiran as a third line. And the reason why it has to do with outcome data that we don't have yet. With inclisiran for instance, by the way, right after, not after, but a few months after this was published, at the end of last year in March, they released some outcome data with Bempedoic acid. So maybe now can Bempedoic acid can be put up a little, so you see how fast this field moves. But anyhow, the first line is ezetimibe or or PCSK nine inhibitor and or it

depends on how much reduction you want. And the reason for that is because of the outcome data that they had at the time the guideline was written. Okay, for the patients that don't have this very high risk, you want don't, don't need to go to 55 70, kind of the same thing. First line is ezetimibe and or a PCSK nine inhibitor and then second line will be Bempedoic acid and inclisiran. Okay. Now for patients that have, they don't have a CVD, let's talk very quickly about those primary prevention. We have to talk a little bit about primary prevention because a lot of folks listen to these are in that area. So for primary prevention, if you have familial Hypercholesterolemia or FH your net FH range, LDL over 190 again for non statin first line therapy, ezetimibe and or PCSK nine inhibitor. And then again PDO acid includes running, it kind of goes like that. If you have, let's say diabetes now things are a little bit different because the data is different. So for diabetes the first line is ezetimibe and second, second line. Then we get into things like bio acid sequestering that we don't use as much, but it can be used bepadoic acid. There's no PCSK nine inhibitor in clone in there because that population was never studied with this drugs as far as outcomes, right? It doesn't mean it cannot be used, it just means that it's more difficult to prescribe a PCSK nine inhibitor or inclisiran in the primary care setting. Same thing for patients. The majority of patients that you wanna start a statin in primary care, they just have risk and, and, but they cannot take statins or they're not at goal first. Retinal therapy again is ezetimibe and then comes after that something else to lower cholesterol and eventually bepadoic acid. But the injectables are not in there because they are not under the FDA approval for primary care use. So it's difficult to get it approved for them. One, perhaps expression ex exception for that could be perhaps patients they have an extremely high coronary calcium score, a lot of plaque burden. You might be lucky enough to get it approved for these patients, but it's just more difficult to approve.

Dr. Sharonne Hayes: Yeah, I mean there's always been the, is that really primary prevention, right? If they've got, if they've got-

Dr. Regis Fernandes: Exactly.

Dr. Sharonne Hayes: Absolutely. But I think it really, it, it, it does present additional barriers if they have not had a clinical event, as you say. Correct. Hopefully there will be more evidence available to us to be able to support treatment because even though we don't have the data, I think extrapolating the data from what we know about statins and what we know about these drugs and other conditions, they're, they're likely to be beneficial.

Dr. Regis Fernandes: Oh, absolutely. There is no doubt on that. Yes, correct.

Dr. Sharonne Hayes: Yeah. So this has been great because I think needing an update and particularly for these drugs that, that some in the audience may have never prescribed but are thinking about it and certainly have the patient population in their practice that they'd be thinking about them. This will be a very helpful jumpstart and I think the takeaway is the knowledge about the new agents as well as the

new targets because we all get numbers stuck in our head. And, and I do think that that 55 for that very high risk and recognizing that most of our patients are in that category, particularly among cardiologists. So this wraps up this week's episode of interviews with the experts and I'd like to thank Dr. Fernandez for joining me today and discussing this important topic. We look forward to you joining us again next week with for interview with an Expert, be well.