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Practical Considerations to Manage Residual ASCVD Risk

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Practical Considerations to Manage Residual ASCVD Risk," is provided by Medtelligence and is supported by an independent educational grant from Amarin Pharma, Incorporated. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Fazio:
Considerations are basically wrap-up, taking together all that has been discussed up to now, guidelines to give us guidance on cholesterol management, endorsement to use statins, clinical trials of ezetimibe, PCSK9 inhibitors for LDL lowering, and persistent efforts at figuring out what we use with triglycerides with the most recent REDUCE-IT trial that give us a tool to go after people with moderate hypertriglyceridemia. Perhaps the benefits are not because triglyceride levels go down, and they're going to be parallel therapy to LDL lowering. Those are my disclosures. You will see slides that've been seen before, so it's going to be very easy for me to just go fast through all the slides. I just want to just add a few points.

So, you remember a good conversation from Dr. Underberg about coronary artery calcium scoring. And here, I think, I will just highlight a few more things. You also heard a lot from Dr. Watson about the importance of lifestyle, diet, exercise, and smoking. And I would say that that is something we need to remember in our practice and actually goes beyond these three things. As you know, there's a lot more that we cannot capture – what is coming up as the polysocial risk factors, one that doctors need to be more and more aware of as we build up histories for our patients. So, you know, we have a risk estimate, and we can do whatever we can do, right, with the knowledge you have at a certain time. So, as long as you know that our risk calculators are not completely comprehensive and accurate, it's a good starting point.

Next slide shows you that, as Dr. Underberg was saying, if we deal with people who have not had prior cardiovascular disease and you are dealing with a primary prevention setting, you have different buckets to place them in, and you have to use the information that is considered primary, and that's risk modifiers. The primary risk factors is what he has already shown you, age, sex, race, blood pressure, cholesterol, HDL, LDL, history of diabetes, smoking, and use of some medications. As you remember from Dr. Watson's presentation, though, lots of things are missing here from what is considered primary. Like, you wouldn't know about body weight; you don't know about Lp little a; you don't know about triglycerides, don't know about physical activity. Then about family history – there is so much out there, so that's why it shows you, pretty much, a series of risk modifiers that is actually not all-inclusive. There is a lot more than that, though. But as a good doctor, you want to be aware of family history or early CVD, the fact that the hypercholesterolemia may not be a common one, but a more severe one, perhaps primary, perhaps inherited, the presence of the metabolic syndrome or the factors that probably increase risk in more ways than just by virtue of one variable like triglycerides or HDL, the presence of kidney disease, inflammatory conditions – and you can probably read faster than I can mention these bullet points – but there are actually a lot more.

As I was saying, recently, I went to Bangkok where I am helping a group of hospitals create a network of preventive cardiology clinics. And I was surprised everybody there was wearing a little device here, nurses, doctors, and, you know, many patients. And those were electromagnetic repellants for what they call particulate matter of size bigger than 2.5 microns, which is a real problem in Bangkok

because of pollution, but it's a problem many see in the US as well. And that's an additional factor that's part of the polysocial risk exposure. And I think one day we'll need to be aware of that, and maybe we can quantify it one day.

So, while we look at biochemistries as ways to enhance our knowledge of risk for a patient, we have several things that we should test at least once or several times depending on the values, and some of them are in the imaging realm. There is no time to discuss ABI and CIMT, but I want to say a few more words about coronary artery calcium scoring. So, as was said before, if you test for a non-contrasted CT of the chest in the right patient population, you can use all of the information for practical purposes. You can use a zero as an impetus to de-risk the patient and decide on a different strategy for long-term management. And if you have a number different than zero, and depending on where the threshold goes, you may consider initiation of statin therapy or even go for the lowest possible LDL goal. But it also goes beyond that. As you probably know if you're using it regularly, is that the calcium – the presence of calcium in any position in the coronary tree flags a plaque, a cholesterol plaque. And so the positioning of the calcium deposits in the coronary arteries are also sometimes platforms for further diagnostics or interventions. The European Society of Cardiology Guidelines come out strong in recommending the use of calcium scoring for risk assessment. In the US, you know, we have the problem of most insurances not covering it, and so what I recommend to private practitioners or people in hospitals is to see whether there's a way to control pricing for patients. This is what we have done in my hospital. We have a very low price that makes it actually feel just like a high co-pay for our patients.

The guidelines continue to put a lot of emphasis on the LDL side of things by endorsing not only the statin as before, but also the use of adjuncts like ezetimibe and PCSK9 inhibitor for further LDL reduction to expect additional cardiovascular risk reduction. There was not guidance on what to do with triglyceride lowering, particularly because the REDUCE-IT trial results were presented the same time as the society guidelines. And so, I think the way you should see it in the spectrum of what we call the cardioprotective drugs out there that can be given only to diabetics or only to people with certain presentations. You have the interventions for dyslipidemia. And there are two routes that are supported by clinical trials. The route of LDL lowering, starting with statin and going to ezetimibe and the PCSK9 inhibitor, and the route of triglycerides, starting with statin and going the route of icosapent ethyl, with the caveat that it's not just for triglyceride reduction. You don't have the target of triglyceride threshold to reach.

So, you have seen from Dr. Miller that the fibrates and niacin trials have not been giving us evidence for interventions when there's too many patients for the sake of reducing cardiovascular events in people taking a statin. But we have that information for ezetimibe and PCSK9 inhibitors, and those are, in general, considered to be medications that work a good pathway. And the good pathway is the one that is linked to an upregulation of the LDL receptor. And now there is another drug that can do that, and it's bempedoic acid. It came into the market two months ago, and bempedoic acid is an oral agent, one pill a day. And it targets an enzyme that is farther upstream, not downstream of the HMG-CoA reductase. So it's on the same line but actually works well with statins, works well with ezetimibe. The power on LDL cholesterol is not very much, 20%, 23%. But it's going to be an additional agent to be used for the strategy of placing LDL to go down further in patients at high risk. It doesn't have, of course, a cardiovascular outcome trial, and we'll see how the market adopts the new entry here.

Now I want to just finish with the guidelines that I've taken – the information of the REDUCE-IT trial. And I don't know if you remember from the guidelines that were shown before – I think it was Michael Miller who showed that some of the guidelines were cutting triglycerides at 175, but the REDUCE-IT trial was cutting at 150 and then ended up enrolling patients with triglycerides as low as 135. So, the FDA has approved the use of icosapent ethyl for people with triglycerides above 150 for cardiovascular risk reduction, but most guidelines have actually taken the 135 as the recommended threshold. So, there's a little bit of a discrepancy between guideline endorsement and FDA approval, which creates a little bit of a problem with insurance coverage and cost to patients, as you know. So, keep that in mind. In our practice, it's been difficult to get patients approved if they are below 150, even if they're above 135, but things are always fluid in the world of insurance denials.

Many people take fish oil. So, the one advantage of recommending a drug like icosapent ethyl is that, as you describe it to the patient, the patient is absolutely willing to take it. There is no resistance to taking a natural molecule like icosapent ethyl. The big challenge – another one – is that many patients say, "I'm already taking it," and they're not taking it. They're taking dietary supplements that contain who knows what, but definitely not enough amounts of the EPA. And they like – the EPA is to be unchallenged by the DHA in order to work. And so I think for all the patients that qualify, the prescription of icosapent ethyl will be warranted to ensure that 25% risk reduction that was seen in the REDUCE-IT trial.

The supplements, as I said, are all over the place, and they may or may not contain what's declared in the label in the back because there is no FDA oversight of batch-to-batch quality assurance during production. And there is a possibility of other substances are there, the fat going rancid. And even if one was saying, "I'm going to take enough to raise my EPA levels to the point of protection seen in the REDUCE-IT trial," that's very difficult. If you just go around purchasing supplements at the grocery store, you need a handful of dietary supplements to achieve the levels ingested of reported EPA and DHA levels that could produce the benefits, even though it is

not really expected a supplement will do that.

A look at cost-effectiveness for PCSK9 inhibitors: they started out as being not very cost-effective, but as prices have gone down recently, that has changed our view of the cost-effectiveness of PCSK9 inhibitors. For IPE, it's much more clear-cut. It is cost-effective. It hits all the targets for cost-effectiveness, even when you set it at the lowest amount of $50,000 US dollars for quality-adjusted life-years. So, the guidelines have taken note of this evaluation, and the most recent professional society recommendations all mention the use of icosapent ethyl either with terms like can be considered, should be considered, or is recommended by the National Lipid Association.

So, next slide is just a summary slide. For the sake of time, I will not repeat what I just said. And I will stop here. Thank you.

Announcer:
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