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### A Closer Look at Women, Atherosclerosis, and Lipids: What Is Different?

Announcer:

Welcome to CME on ReachMD. This activity, entitled "A Closer Look at Women, Atherosclerosis, and Lipids: What Is Different?" was presented during Omnia Education's Women's Health 2021: Beyond the Annual Visit.

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Dr. Pokrywka:

Okay, welcome everyone, and thank you for sharing some of your time today with me. My name is Gregory Pokrywka, and I am the Director of the Baltimore Lipid Center, a center which specializes in cardiometabolic risk reduction. I also have a very strong interest in women's healthcare. I'm one of the only lipidologists in the country who's also certified in menopausal medicine by the North American Menopause Society. So I have 3 quick objectives with this talk today. I want to get across to you a sense of urgency, a sense of awareness, and a sense of hope. Urgency, because someone dies a cardiovascular death every 45 seconds in this country, so it's one of the most important issues in preventive medicine. A sense of awareness, because you want to talk about how to assess risk, particularly focusing on women's issues. And hope, because we want to talk about some of the wonderful new science and evidence-based strategies that we have to reduce this cardiovascular risk. So with that said, we'll move on to the first slide.

Heart disease remains the number one cause of death, as you can see from this very up-to-date data from 2021. As a matter of fact, 2 of the top 5 causes of death in this country are cardiovascular in nature, that is heart disease and stroke. And you can make a strong case that Alzheimer's is also a vascular disease, and you can see that comes in at number 7. So again, a real sense of urgency in preventing these most common causes of death.

Now, the cardiovascular mortality gap between men and women has narrowed, but it's plateaued. As you can see from this United States data from the AHA Statistics Report, there's been a narrowing of the gap between approximately 2000 or so and 2012 between men and women. You also see that there's an uptick in the deaths in both men and women that occurs after 2010, and it's not clear why this is happening, but most of us feel that this is probably due to the impact of metabolic disease, such as insulin-resistant diseases, diabetes, prediabetes, etc. Now, what's responsible for this drop in deaths? It's not vascular-type procedures; it's not bypass surgery; it's not stenting. This is optimal medical care, the use of statins, better control of high blood pressure, cessation of cigarette smoking, etc. So optimal medical care works, and here's the proof in the pudding right here. And we can all do this in our practices, every day.

So let's talk about a wonderful article called female-specific risk enhancers across the lifespan of a woman. This is from the *American Journal of Preventive Cardiology*. I also have to mention the other key journal in this field is the *Journal of Clinical Lipidology*, from the National Lipid Association. These are really the 2 main groups I'd like to focus on that are leading the intervention strategies in terms of prevention of cardiovascular disease in this country. So you can see, in younger women, we've got issues such as early or late menarche, PCOS [polycystic ovary syndrome], which is something a lot of us may not think about that much in general internal medicine and family practice, but we have plenty of PCOS patients in our practice if you look for them. Use of OCPs [oral contraceptive pills] can influence risk, premature menopause, and primary ovarian insufficiency. When we shift to pregnancy, issues such as gestational diabetes, gestational hypertension, preeclampsia, and preterm birth are going to increase cardiovascular risk in women.

And then menopause itself seems to increase risk in older women.

So let's talk about APOs – adverse pregnancy outcomes – and future maternal CVD risk. About 5% to 10% of pregnancies have the complication of hypertension in one form or another. Remember, the difference between gestational hypertension and preeclampsia is that in preeclampsia you have not only hypertension, but you also have end-organ damage, most commonly in the form of proteinuria. When we talk about hypertension in pregnancy, the definition is a little bit different than we're used to in internal medicine and family practice based upon various guidelines. We now usually classify hypertension in our general practice as a blood pressure above 120 systolic, and then above 130 we're calling it actual hypertension. But in pregnancy, we're talking about systolic above 150 to 160. We're talking about a diastolic 95 to 110. So the criteria are a little bit different. As you can see, the risk of cardiovascular disease after a woman is diagnosed with gestational hypertension or preeclampsia goes up dramatically. Future hypertension goes up dramatically. You can see this occurs quite rapidly, often within a few years of the pregnancy-related event. When you go further out and look at greater than 10 years, you can also see increases in cardiovascular disease events themselves, hypertension, coronary artery disease, stroke, heart failure, and mortality. We have less data for the conditions known as small for gestational age and for preterm delivery (PTD), but you can also see what looks like short-term increases in cardiovascular risk and also long-term increases in cardiovascular risk.

So preeclampsia, preterm delivery, and subsequent maternal cardiovascular disease – here's a meta-analysis of greater than 20 studies with over 6 million women which shows significant increase in incident heart failure – a 4-fold increase if you have preeclampsia, and a 2-fold increase in cardiovascular disease, stroke, and cardiovascular death.

We also see preterm delivery associated with an increase in future maternal adverse cardiovascular outcomes, including a 2-fold increase in deaths caused by CHD. So the highest risks are occurring when the PTD occurs before 32 weeks of gestation or were medically indicated. So again, emphasizing not only the risk that our patients face, but the opportunity to pay more attention to screening and prevention in these patients identified as having an event during pregnancy.

Most of us are aware that gestational diabetes increases the risk of future diabetes in our patients long after the gestational period is over. But look at the risk of maternal CVD that we see in these patients, again, looking at risks that increase in the fairly short-term range, from 2 to 3 years out through the 5 to 7 year range and further out. We see a big increase in stroke, an increase in angina, and also an increase in myocardial infarctions. Again, the point here is that gestational diabetes identifies a patient at risk. We want to try to intervene as best we can to prevent and reduce that residual risk in the future by focusing on correction of risk factors in these women.

So this is a slide that I have used extensively in my teaching. I recently had a couple of nurse practitioner students with me, and we used this every single day on every single patient. This is the A, B, C, D, E, F, and even Gs, now, of preventive cardiology. And we could give a whole lecture based on this slide; it's got a lot of rich content, I think. But just to focus on a few things. A, I think of first, aspirin. We're using a lot less aspirin in primary prevention than we used to. We're using it really only in very high-risk primary prevention patients. We focus mostly on the use of aspirin for secondary prevention patients. We talk about A for anti-inflammatory trials and hopefully future therapeutic agents that we can use. But I also think of A for assessing risk. We have a number of different guidelines. We're going to focus on these in a subsequent slide.

Talk about B, we're talking about blood pressure. Obviously, we're trying to get almost everyone down below 130/80 these days, but we're beginning to even look at particularly lifestyle changes when we see someone whose systolic is above 120. We also use B for body weight. Body weight itself, not the greatest predictor of risk, but certainly we can use waist circumference and to a lesser extent BMI. And we'll talk in our case about how waist circumference risk differs based upon different ethnic backgrounds.

C stands for cholesterol. You can see a couple of the newer agents are listed here. Our highest risk patients, we're trying to get the LDL cholesterol down to less than 55. I believe there are distinct advantages in using a lipoprotein-related approach to management of cholesterol disorders as opposed to the standard LDL cholesterol approach, and we will, again, talk about that a little bit in the case. C also stands for cigarette cessation.

D stands for diet. We have a subsequent slide focusing on that. It also brings up digital health and some of the wonderful, new remote monitoring techniques and we can use to assess risk in our patients. We talk about diabetes – how we now have amazing new agents that not only reduce hemoglobin A1C and reduce blood sugar, but also have been shown to reduce cardiovascular events, and we're talking here about the SGLT2 inhibitors and the GLP-1 agonists. D also stands for dream. If we don't get enough sleep, it increases our mortality and increases insulin resistance significantly.

E stands for exercise. It also stands for EPA, which appears to be the cardioprotective omega-3 that we'll be talking about in Dr. Watson's portion of the talk.

F stands for factors of the environment. To me, it also stands for heart failure. Obviously, we want to try to prevent heart failure

whenever we can, and G stands for genetics. We have wonderful new polygenic risk scores around the corner. At the lipid clinic, we also do genetic testing for common disorders – much more common than most realize, such as familial hypercholesterolemia.

So premature menopause increases the incidence of cardiovascular disease. This is a UK biobank, but as you can see, premature menopause is associated with an increased risk of cardiovascular disease, of about 36% after adjustment for conventional risk factors. So this is something I have to remind myself constantly, to take a history in new patients. I saw 2 new female patients today; I made sure to ask them at what age they had menopause. So this is important. We're not really sure we understand the pathophysiology of this completely. Maybe it's the lack of the protective effect of estrogen, but there's no doubt that there is an increase in cardiovascular risk when a patient has premature menopause.

So the 2019 ACC/AHA guidelines for primary preventions talk about where statins are most useful, and there are 3 groups where statins are considered to be highly useful in first-line treatment for the primary prevention of ASCVD [atherosclerotic cardiovascular disease]. We're talking elevated LDL cholesterol in excess of 190 mg/dL. This is where your familial hypercholesterolemia patients will live. But really, most patients with LDL cholesterol above 190 have just a common polygenic form of hypercholesterolemia. Patients with diabetes who are age 40 to 75 years benefit from statin therapy, and those patients determined to be at sufficient ASCVD risk after a clinician-patient risk discussion will also benefit from statin therapy.

So when we look at risk-enhancing factors, these are factors that are going to shift patients perhaps to a higher risk level within a schemata of primary prevention. So family history of premature ASCVD – here, I'm talking about largely in first-degree relatives. Primary hypercholesterolemia – again this is where FH patients or patients with extreme LDL cholesterol elevations would fall. Metabolic syndrome – the more features of metabolic syndrome you have, the greater the number of atherogenic lipoproteins you have in the bloodstream, the greater your risk. I think we all are familiar with the metabolic syndrome parameters, so I won't go through that in great detail. Chronic kidney disease – seems like I see patients with stage 3 chronic kidney disease every other patient these days. I even know what the ICD-10 code is by heart, N18.3. So that's a risk-enhancing factor. And chronic inflammatory conditions, such as rheumatoid arthritis definitely would be considered a risk-enhancing factor for cardiovascular risk assessment.

History of premature menopause – we already talked about – before age 40 or pregnancy-associated conditions, such as the APOs that we talked about earlier. Certain race and ethnic groups have an increased cardiovascular risk, particularly South Asian patients in my practice, but you can see a few other groups in here, where we know that risk is increased. High-risk levels of lipids or other biomarkers where you have extreme elevations of, for example, LDL cholesterol or apoB or LDL particle count – whatever you're using to assess atherogenic particle burden. Persistent primary hypertriglyceridemia – a normal triglyceride level for a human is less than 100, but a third of Americans have triglycerides above 150. So I would consider that to be elevated hypertriglyceridemia. And if you're measuring some of these newer biomarkers, such as high-sensitivity CRP, lipoprotein(a), you could make a case should be assessed once in a lifetime of every patient. Apolipoprotein B is probably our best evidence-based way for assessing atherogenic particle count burden. And then ABI [ankle brachial index] – if you have peripheral arterial disease, your risk of a cardiovascular event is dramatically increased.

So how do you use a CAC score to guide statin therapy? Well, coronary artery calcium, there's actually an app called the MESA Risk Score, which you can easily download. I use it every day. A CAC score can be used to reclassify risk. If you have a zero score, just do a search on the internet or Twitter for evidence about the Power of Zero group. They have been very prolific and very vocal. If you have a coronary calcium score of 1, the horse is out of the barn, so to speak. The atherosclerotic process has started. And if you have a coronary calcium score of greater than 100, this is usually considered to be roughly equivalent to the 7.5% 10-year risk that we get from the pooled risk equations, where we really begin to think very seriously about statin therapy. Now you could certainly offer statin therapy to patients with a lower coronary calcium score, but again, here's where the risk-enhancing factors come into play. Here is where issues, such as how aggressive the patient wants to be, come into play.

We don't have as much evidence based from randomized clinical control trials for statin therapy in older patients, but the evidence here is starting to grow, and I certainly have a ton of healthy 70- and 80-year-old patients in my practice, who I offer statin therapy to every day. Many international guidelines, again, support coronary calcium scoring. It's most useful in patients who are at low or intermediate risk, where you're trying to get some additional data before you make your decision about what you're going to do with the patient's management.

So you can also download this risk calculator, the ASCVD Plus risk calculator. Again, we use it every day. You can see the 4 groups that patients are classified in with this calculator. We're estimating here hard ASCVD risk. We're not talking unstable angina, chest pain, or hospitalizations for chest pain. We're talking about nonfatal MI, CHD death, or stroke. And the app is designed to be used between the ages of 40-79, so that's one shortcoming. And it could be used for a lifetime risk assessment when you're 20 to 59. Again, it's not a hard and fast rule. I know some of you may have it built into your EMRs [electronic medical records], where it's automatically

calculated for patients. So there's no firm cutoff for statin versus non-statin use, but greater than a 7.5% hard risk of an event over the next 10 years is considered to be the usual criteria for statin eligibility. It's not mandatory prescription for a statin. There's no medical/legal precedent here you need to worry about. I mean, this is where we really begin to seriously discuss this with the patient, and it always has to be a physician-patient discussion. Once you've used a risk calculator, then you can use the ACC/AHA primary prevention guideline algorithms, which we don't have in our talk today, but the reference is in here somewhere where you can find that. I think the app has it right inside of it also.

So last couple of slides for me – nutritional lifestyle recommendations. We emphasize the Mediterranean diet here, but we use a twist on the Mediterranean diet, since most of our patients are insulin resistant, so we use a low-carb variant to the Mediterranean diet. I would point out to you if you become a National Lipid Association member at [lipid.org](http://lipid.org) you get access to some incredible tear sheets that you can use, with or without your dietitian, to help coach patients about improving diet. And these tear sheets are amazing. They have a lot of different kinds. There's some for different ethnic groups, etc.

We really want to try to decrease sugar and simple carbohydrate intake. I personally believe that high fructose corn syrup is one of the real demons here in our diet. It's in most processed foods. It's in standard sodas like colas and such. We really want to try to decrease that as much as possible. We want to increase fruit, vegetable, and fiber consumption. We want to try to limit fat intake. We want to promote the intake of fatty fish, particularly salmon and tuna. They're going to raise those omega-3 levels. You want to decrease those highly processed, preprepared foods, because they're very low in fiber. They often contain high fructose corn syrup, as I mentioned. We want to restrict sodium consumption, and we want to emphasize changes in dietary patterns, not fad diets or something that the patient won't be able to stay on for very long. So we really want to emphasize healthy eating for the entire lifetime.

Finally, physical activity – we want to average 40 minutes per session. We want to go for trying to get the patients to at least walk briskly, enough to work up a sweat. That would be defined as moderate to vigorous activity. Strength training, at least 2 sessions per week. That's very helpful in terms of prevention of future cardiovascular events and treatment of the insulin resistance that we see in a majority of our patients. You don't have to go to a gym or lift heavy weights. There's lots of ways you can do this with kettle bells and bands and readily available things that you can use in the home. So you have to find something that the patient thinks is fun, and often most patients like doing this with other people around, and that will enhance their ability to sustain regular exercise. Brisk walking, 30 minutes a day, 5 days a week – that's the way to go.

So with that, I'm going to end my portion of the talk. We'll turn it over to Dr. Watson.

Dr. Watson:

Thank you so much, Dr. P, for that great presentation. I'm really happy to get started now on my part of the presentation. I'm going to talk about evidence-based approaches for managing women at high risk for cardiovascular disease events.

First of all, there are so many preventive therapies we can do, but I want to put a plug in for statins. Statins have been some of our most cardio-protective medications in patients at high risk, so statin, statin, statin is what we should consider when we deal with a patient with high cardiovascular risk.

And I was a member of the 2013 guideline writing committee where we discussed statins as the primary therapy. And the other thing we did was we talked about the appropriate intensity of statin. So, we sort of arbitrarily said a high-intensity statin was something that got you a 50% or more LDL lowering. Only two drugs at two doses get you there – atorvastatin 40 or 80, or rosuvastatin 20 or 40. Moderate-intensity statin is pretty much all the other statins we commonly use, and low-intensity statins are just the lowest doses of the less potent statins. The other very important principle we put in that was the intensity of risk should match the intensity of statin therapy. So if you have a high-risk patient, you want high-intensity statin. Moderate-risk patient, moderate-intensity statin. The low-risk patient we said probably doesn't need anything, so we never recommended low-intensity statins, but high-risk patients, high-risk statins. Moderate-risk patients, moderate-intensity statins.

Now, statins are so well tolerated. It's very, very common that patients are tolerating statins just fine. But there are some patients who will have what they consider to be intolerable side effects to statins. We don't know the true prevalence of that – maybe 10% of your patients – but most patients can tolerate some dose of some statin. Statins are very effective at preventing your first cardiovascular event, your recurrent cardiovascular event, regardless of what your risk is driven by. If it's driven by smoking or low HDL or high blood pressure, statins work.

Now the risks of serious adverse events to statins are very, very low. The true risk that I ever worry about are a rhabdomyolysis – very, very, very rare. And there is a small but real increased risk of diagnosing diabetes. And it's not that the statin is giving you diabetes. If you happen to be teetering on the edge of diabetes, the statin may tip you over because statin therapy is typically associated with a 1- to 2-mg/dL increase in glucose levels. But this is something that someone who's going to develop diabetes eventually, the statin may

accelerate that slightly, but it does not cause diabetes.

Now, unfortunately, a large percentage of our patients will stop their statin within 1 to 2 years of it being prescribed, and many patients can't tell you why, exactly. Eh, no side effects. No, I could afford it; I just stopped taking it. And there are many patients who have a perception of having some side effect with statin, which when you look in randomized controlled trials, you just don't see.

So when I think about a patient with high ASCVD risk and dyslipidemia, I'm starting with statin, statin, statin. You get them on the appropriate intensity of statin therapy. Now our guidelines tell us – the 2018 guidelines – if a high-risk patient has an LDL cholesterol above 70, we want to add ezetimibe first to that maximum-tolerated statin. If it's still above 70, after max-tolerated statin plus ezetimibe, we should consider a PCSK9 inhibitor.

There are other therapies out there which can lower LDL, like bempedoic acid, but the evidence-based drugs are statins, ezetimibe, and PCSK9 inhibitors. Now, what if your risk, after you get the LDL controlled, is driven by high triglycerides? Well, then we have to start thinking about therapy for that. And right now, the best evidence base is for icosapent ethyl.

Now we know that LDL is the primary driver – lipid driver of atherosclerosis. But we also know that high triglycerides confer risk. This is data looking at people who are on a statin with a well-controlled LDL, but they still have high triglycerides. If you look over to the right, if your triglycerides are less than 150, the event rate in this cohort was 11.7. But in that same cohort, well-controlled LDL on a statin, if your triglycerides were over 150 – that's the bar to the left, your event rate was 16.5% – 41% higher. So even having a great LDL – in this study it was less than 70 – on high-intensity statin, high triglycerides still conferred risk.

And it's not just the high levels. So this is showing you data on what the relationship between triglyceride levels are and cardiovascular disease event rates. You see over to the left, even at very low triglyceride levels, there's a direct linear relationship between how high your triglycerides are and how high your cardiovascular disease event rates are. So down to a triglyceride level of 100 – you still see a linear increase in risk for each increase in your triglycerides. Now, that curve starts to flatten a bit as you get to triglycerides above 200, but there's still a direct linear relationship. The higher your triglycerides, the higher your risk.

And so this is how we classify triglyceride levels according to the American Heart Association and the National Lipid Association. Very high triglycerides are above 500. High triglycerides are between 200 and 499. Borderline high – 150 to 199. Normal is less than 150, but optimal is truly less than 100.

Now, we've always thought about fibrates and niacin as being the primary drugs to lower triglycerides. Unfortunately, our clinical trials have not shown cardiovascular benefit by adding either fibrate or niacin to statin therapy. So the ACCORD trial looked at patients who had newly diagnosed diabetes. Everyone got a statin. Half got fenofibrate, no benefit. The FIELD trial – mostly patients were just on fenofibrate. Some of them were on a statin, and there was no significant reduction in their primary outcome of nonfatal MI or cardiovascular disease death. Looking at niacin trials, the AIM-HIGH trial gave everyone a statin, and Niaspan was added to that. No benefit. In fact, a trend towards an increased risk. HPS2-THRIVE used – again, everyone got a statin, and half got extended-release niacin. Again, no benefit. So because these drugs are not conferring cardiovascular benefit, we do not recommend them.

What we do still have a lot of hope for, though, are omega-3 fatty acids. You heard about EPA. The other long-chain omega-3 fatty acid is DHA. And those 2 long-chain omega-3 fatty acids cause triglyceride lowering. For every full gram you can get in a patient of 1 of those 2 drugs, you can get about a 10% triglyceride lowering, up to 4 grams daily. But when we've looked at them and tried to see if there was any reduction in clinical events, especially with low-dose omega-3, we just don't see it. If you look over there to the forest plot over to the right, while it's really right along the line of unity, not really a benefit. Now some more recent trials have shown maybe a little bit more hope. VITAL trial and the ASCEND trial, but no statistically significant cardiovascular disease benefit. The one trial that's an exception, however, is the REDUCE-IT trial, there on the bottom, and I'll show you a lot more about that in a minute.

Well, EPA only – that's 1 of the 2 long-chain omega-3 fatty acids. There was a lot of reason to think that might be more beneficial than the DHA component. And I'll show you some of that data in a second. But let me show you the first study that kind of let us know that EPA-only might confer benefit. That was the JELIS trial. This was conducted in Japan. It took patients at high risk. Everyone got a statin, and half got EPA-only omega-3 fatty acids on top of that. They were also given 1.8 grams per day, so not the high dose that we typically think of now, but when they did that and they looked overall at this hypercholesterolemic population, they saw a 19% reduction in cumulative incidents of major coronary events.

Now, in the separate analysis, they looked at people who had only high triglycerides, above 150, or low HDL, below 40 – that's over there on the right side – and in that cohort, those who got the EPA omega-3 along with the statin had 53% reduction in clinical events.

Now what is it about icosapent ethyl that might make a difference? Well, whenever you give a patient fish oils or any lipid, really, those lipids will intercalate into the membrane of whatever lipid molecules they already have. Icosapent ethyl, via lipase, becomes EPA, and

that will intercalate into your cell membranes. But when it does that, it does a lot of things that could be beneficial. You get the EPA re-esterified in chylomicrons and then packaged as part of your lipid transport system, and they intercalate into new ones.

That brings us to the REDUCE-IT trial. Again, there were so many pieces of evidence that suggested that icosapent ethyl, or EPA-only fish oil, might be beneficial. So in the REDUCE-IT trial, they decided to study that formulation of omega-3 fatty acids only. So these were individuals who had elevated triglycerides between 135 and 500. They had to have higher cardiovascular risk. There was both a primary prevention cohort and a secondary prevention cohort, and everyone got statins.

Then, half were randomized to icosapent ethyl, and half to placebo which was mineral oil. In this study, the primary endpoint was cardiovascular death, MI, stroke, revascularization, or unstable angina, and they saw a very striking 25% risk reduction in the group that got the icosapent ethyl. If you look over to the right, a key secondary endpoint was the hard 3 – the big 3 we care about – MI, stroke, and cardiovascular death. And in that, they saw a really striking 27% relative risk reduction.

Now, if you look at what happened when people took those icosapent ethyl tablets, 4 grams daily, the dotted line shows you the levels of icosapent ethyl – EPA – that was achieved by taking the either placebo – over there, at about 27, or the icosapent ethyl. The EPA levels rose greatly, to about 150. That made sense. And then you saw this nice reduction in cardiovascular events, that were very strongly correlated to the achieved EPA levels.

Okay. So that's fabulous. This was one very positive trial. Do we have any other trials to corroborate it? Well, another trial, called the STRENGTH trial, was performed about the same time. This randomized 13,000 patients; they were similar in their backgrounds. They were higher cardiovascular risk, they have higher triglycerides, and they were randomized to an omega-3 fatty acid preparation that included EPA plus DHA or a corn oil placebo. And then they followed them up for events. Now this study was prematurely terminated because the DSMB [data and safety monitoring board] felt that it was futile to continue. There was no separation of the curves, and they could not see the curves separating, even with prolongation or continuation of the study. So it was stopped prematurely with a neutral result.

There you see it right there. Those lines are absolutely right together. No benefit. So that's odd. What's the difference? Well, one of the differences I told you is that the REDUCE-IT trial used an EPA-only preparation of omega-3 fatty acids, while the STRENGTH trial used a fatty acid combination of EPA plus DHA. That's what they did. Now, what is the difference between these two? Well, one you see right here. DHA has two extra carbons and one extra double bond. And DHA is what we primarily use to make most of our reproductive hormones, like testosterone and estrogen.

One of the other things that's different is how they intercalate into cell membranes. Remember I told you, every time you eat a fat, it gets intercalated into your existing cell membranes. EPA intercalates as a pretty straight molecule. It's membrane stabilizing. DHA intercalates as more curlicues, kind of disrupting the membrane, so it's membrane destabilizing. There are a number of other differences between the two lipids that might impact on the outcome.

So distinctly different lipids – DHA and EPA. EPA seems to be more membrane stabilizing. There are different resolvents that are engaged. These are enzymes that participate in the fluidity of the membrane. There's different activity in oxidized LDL, so you get more reduction in oxidation of LDL with EPA, and different anti-inflammatory effects on biomarkers, such as CRP. More anti-inflammatory properties as EPA as opposed to DHA.

So what have we learned? The REDUCE-IT trial, as I showed you, EPA-only – a lot of cardiovascular benefit. JELIS trial – I showed you – EPA-only, cardiovascular benefit. There are two other trials. Both of them were smaller, and both of them used imaging. The CHERRY trial used intravascular ultrasound, and the EVAPORATE trial used coronary CTA to show reduction in plaque with EPA on the background of statin therapy. All the top 4 trials were on background of statin therapy. Now, the 4 at the bottom, which used EPA and DHA, didn't show any benefit. Not one of them. Simply, you can think about, well is it just the DHA? It may be more complicated than that, but that is clear one difference between the trials that showed benefit and the trials that did not.

Okay, so how do we use this data? Well, REDUCE-IT showed us that icosapent ethyl at 4 grams daily can be used to lower cardiovascular risk in patients with moderate hypertriglyceridemia. Prescription icosapent ethyl has a unique, well-documented mechanism of action that has benefit on atherosclerotic cardiovascular disease, on plaque, on membrane stabilization, oxidation, endothelial function – a lot of things that could confer benefit.

So alone, our patients would be like, "Well, you know, I was at Walmart the other day, and I saw this omega-3. It's a lot cheaper. Can I get it?" And our answer at our lipid clinic is, "No, that's not what we recommend." If you look at over-the-counter omega-3 fatty acids, most of them are only about 30% to 50% long-chain omega-3, the remainder being typically some filler, like corn oil, most of them. The other thing is they have not been studied, and really, the FDA does not regulate them like we do drugs. So we really don't know what's in it. So a couple of reasons: they don't have the potency, and we probably aren't as comfortable with the purity of these, and they don't

have any outcome studies.

This is from my friend Preston Mason in Boston. He's shown that some of the leading over-the-counter fish oil supplements are contaminated with saturated fats, as you see there. Look at the prescription omega-3s, over to the right – nice and clear, and the dietary supplement – very cloudy. It shows you there are saturated fats there.

And again, as I said, the potency isn't as great, because omega-3 fatty acids given by prescription are typically 1 gram per capsule. To get that 4 grams daily, you only need 4 capsules. But because the over-the-counter omega-3s are typically only 30% or 50% long-chain omega-3s, you might need 15 of those to get the same 4 grams of long-chain omega-3s. Now there's a big push for this krill oil supplement. Krills are these little bottom dwellers on the ocean floor. They go around eating algae and that's how they get their omega-3s. But you need about 20 or 25 of them to get 4 grams of long-chain omega-3 fatty acids.

So what does the FDA say about this? So the FDA gave a new indication for icosapent ethyl, saying that it can be used as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarctions, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglycerides. And that's anything over 150 if they have either established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors. Before it was just given as a means to lower triglycerides. This new cardiovascular indication is based on data from the REDUCE-IT trial. And it's been incorporated into the guidelines as far as the American Diabetes Association, the European Society of Cardiology, the National Lipid Association, the American Heart Association. Know, though, that all 4 of the guidelines include a recommendation for triglycerides between 135 to 500. In the FDA package insert, it says triglycerides above 150. So the guidelines use the triglycerides that were used in the enrollment for the REDUCE-IT trial, whereas the FDA says above 150. Three of the four guidelines mention LDL control on a statin, but remember, the NLA says – and the FDA says – maximum-tolerated statin. That was not necessarily what was used in REDUCE-IT, but that's what the label says.

Okay. But again, if you have a patient at high cardiovascular risk, statin, statin, statin. If the LDL is still above 70, add ezetimibe. If it's still above 70, think about adding a PCSK9 inhibitor. If after getting their LDL under control, their triglycerides are above 150, think about icosapent ethyl.

Well, that was a rapid trip through this stuff. I think I have another interesting case. Let's call her Carla. She's a 68-year-old Hispanic woman. She has a 20-year history of type 2 diabetes and everything that goes along with it, including hypertension and dyslipidemia. But fortunately, she has not yet had a clinical cardiovascular event.

She had a random chest CT about 2 years ago, because of concern about pneumonia. They didn't find pneumonia, but what they did find were severe coronary artery calcifications. Now, she's a nonsmoker, but she does have a pretty strong family history of type 2 diabetes and hypertension, and also, her mom died of congestive failure at the age of 75. When you take a look at her, she feels pretty well, looks pretty well. Her blood pressure is too high – 148/80. It's the same in both arms. Heart rate's high – 90. She's a little overweight, actually very close to the obese category, with a BMI of 29, and her waist circumference is too high at 37.

You look at her lipids. So her total cholesterol doesn't alarm you too much, but then you look at her triglycerides, and it's 300. So you start to get alarmed. Also, her HDL is 42 – it's lower than you like to see in a woman. Her LDL is okay at 104, but still I think you might want that lower. Her non-HDL is a little high, too. Her glucose fasting is 150, and her A1C is 7.3, so she has diabetes. You see her medications over there on the right. Lisinopril 20, hydrochlorothiazide 12.5, metformin 1000 twice daily, and pravastatin 10 mg daily. Remember when I said there was low-intensity statins – that was the lowest doses of the weakest statins? That's exactly what she's on. Lowest dose of a weak statin. Do you guys think she needs any change to her lipid-lowering therapy?

Well, we said, you know, we definitely want you to encourage some lifestyle. We want you to start thinking about diet and exercise and losing weight. We said her pravastatin 10 is too low because, again, you match the intensity of risk to the intensity of statin therapy. She is a high-risk patient, so I want her on a high-intensity statin. So we change her to rosuvastatin 20, which is a high-intensity statin. When she comes back, everything looks better. So the cholesterol has fallen, down to 163. The triglycerides are still too high – 225. Her HDL went up a little bit. Her LDL went down a little bit – it's still about 70, so we might think about adding additional agents. Her non-HDL went down, and her hemoglobin A1C went down with just lifestyle. But what do you think now? Do you want to add anything else to her lipid-lowering therapy?

Okay, so let's transition now into a discussion, and let's hear what some of our colleagues have to say.

Announcer:

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