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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Adopting the New Therapeutic "Lineup" to Manage ASCVD - Central

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Adopting the New Therapeutic Line-up to Manage ASCVD," is provided by Medtelligence. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Ballantyne:
We have a really outstanding faculty tonight. We have Greg Pokrywka. He is the director of the Baltimore Lipid Center, and Assistant Professor of Medicine at Johns Hopkins University School of Medicine. We have Joe Saseen, who is a professor in the Department of Clinical Pharmacy, University of Colorado, and Karol Watson, who is a professor also of cardiology, and Co-Director of the UCLA Program in Preventive Cardiology, in Los Angeles.

Our learning objectives are to apply the key findings in large-scale Omega-3 fatty acid clinical trials to clinical practice, for the reduction of ACVD events, look at the clinical trial evidence of EPA to the care of patients with established CVD who are on statins and at risk – at high risk for future events, and also identify the various of im – for implementation of effective long-term management of ASCVD. We'll go through a – a – several presentations, which are shown here. I'll begin with the burden of heart disease, and we'll go through a number of these, and finish up with some cases. So let's move right into it. Ne – and here's a polling question, and this is how you can answer the question here, and let's go to the question.

After an ACS event, what percent of your patients have optimized lipid management at one year? 10%, 30%, 50%, 80%, or 100%. And so this is actively polling. If you can join at the slido.com. Alright, so, our answers are 50%. (pause) See we can move on. And I think we've passed up.

Alright, so, you know, we had been focused for good reasons in the last two years on COVID because it has been a pandemic. It's changed the way that we were living, and the way that everything was done for us in medicine, and all fields of – of life. But, it is important to remind everybody that heart disease remains the number one cause of death. Cancer is number two, and stroke is also the fifth leading cause of death.

So cardiovascular disease – tremendous cause of pain, suffering and death in this country. It's the biggest cause of it. It's also a worldwide epidemic. And this has been increasing pretty dramatic, with changes in lifestyle. An estimated – about 18 million people died of cardiovascular disease in 2019. That's about a third of all global deaths. So this has really become something that's not only important – we used to focus this on western countries; it is not. Currently it is a race between South Asia, India and China, Pakistan – as to who will have the most diabetics in the world. Those t – those two areas have had huge increase in diabetes, and tremendous increase in the risk for cardiovascular disease.

We've made a lot of progress, in terms of our treatments, but this is some data that shows that basically, you take a look at older individuals who have events. It's about a one-third chance of having a recurrent event in the first year post-ACS, if you're over the age of 74, and have high-risk characteristics.

We are very effective now, in terms of our treatments for LDL. We've got statins new here. We've also got non-statins, so usually

between these, we're able to get LDLs at low levels. This is some data from FOURIER that even if you got LDLs to extremely low levels even down to 20 – less than 20 milligrams per deciliter, you still had a substantial residual risk for cardiovascular events.

So what we'll be focusing on tonight is really your patients with ASCVD, and in terms of one of the fundamental changes has been we used to think of everyone the same, just primary and secondary prevention. In the same way where we target the high-risk primary prevention, we also know that the risk is not the same for everybody who has clinical disease or has had an event. So it's important to understand who are these individuals, how do we manage these patients, and how do we optimize their management for risk reduction. So I'll turn this over to Greg, who's gonna talk about atherogenic dyslipidemia and new approaches to risk assessment for ASCVD. Greg.

Dr. Pokrywka:
Thanks a lot, Christie. It's a – well-deserved. Christie is one of my lipidology heroes down through the years, so it's an honor to follow up and speak after him. I run a lipidology consultation practice in Baltimore, so I see patients 90% of the time, and I hope I can relay some of that wisdom to you guys in your daily treatment of patients. So we're gonna talk about the atherogenic dyslipidemia, and we typically think of that as low HDL, high triglycerides lots of ApoB-containing lipoproteins. We often see this in insulin-resistant patients. We're gonna talk about that a bit for the next few minutes.

So, when we talk about what makes a patient high risk, you can see on the left part of this slide, the number of factors that can drive this high risk – they can have high LDL, they can have a hyperthrombotic state.

They could be diabetic, they could have LP(a) – something that we're beginning to talk about more and more as – as some new landmark therapies come into play. And then there can be an inflammatory component. So tonight, we're gonna focus really on the residual cholesterol risk, which we manage with a surrogate biomarker, called LDL cholesterol. Remember, there's no such thing as an LDL. It's either LDL cholesterol, or the LDL lipoprotein, and we count the LDL lipoprotein by counting ApoB as a biomarker. We talk about residual triglyceride risk, the simplest biomarker that we use is the – the standard triglyceride level that we get in a lipid panel. But what we're really looking is the number of triglyceride-rich lipoproteins, and we're gonna talk about how atherogenic those lipoproteins are. And there's a number of other causes for residual risk that we're not gonna spend as much time on tonight.

So, when you're seeing a patient, sitting across the desk from you the algorithm that we should be using to evaluate risk is to use the app from the 2018 ACC/AHA multispecialty guidelines, and everybody can download this app. You probably have it on your smart phone, you may not even be aware of it. It's very easy to use, it's free. So this estimates 10-year hard ASCVD risk for ages 40-79, and also gives you a lifetime risk estimate. So, it's not designed to be used as a hard cutoff, as to whether you get a statin or not. It's – it's used to provoke discussion, okay? 7.5% 10-year risk is widely considered as as a typical threshold for initiating statin therapy, but that's not carved in stone. The – the app is designed, and the algorithm is designed to promote discussion.

Then you wanna use your ACC/AHA prevention guideline algorithms to guide your next step. So, statin therapy is gonna be first line treatment for the big four clinical indications. We all know these from the previous, 2013 guidelines. So, clinical ASCVD – no brainer. Elevated LDL cholesterol levels that are dramatically elevated, such as your heterozygous FH patients – we're gonna start a statin. Diabetics, age 40-75, with an LDL cholesterol greater than 70 – again plenty of evidence there. And then, if you're age 40-75, but you are deemed to be high risk by using the calculator, these are patients we're gonna consider a statin.

Now, we also had these – the concept of risk-enhancing factors such as family history, primary hypercholesterolemia, metabolic syndrome – everybody knows what that is here, I think. Chronic kidney disease – something that we see more and more frequently, and then chronic inflammatory conditions. And when you have a risk-enhancing factor, it kicks you up into the next tier of risk. It might kick you from borderline risk to intermediate risk, for example. So that's how we use these risk-enhancing factors. And there is some more – some are – are specific to women, such as premature menopause before age 40, pregnancy-associated conditions that increase ASCVD risk, like preeclampsia or hypertension in pregnancy, etc. Certain ethnicities are a much higher risk, and these are risk-enhancing factors, such as South Asian ancestry.

If your trigs are greater than 175, if you have some of the other biomarkers listed here – a very high ApoB, if you have LP(a) above these cut points, if you have high sensitivity CRP which elevated, and then if you have ankle brachial index which is low, PAD is – is a devastating form of atherosclerosis. It really increases your risk. So again, these risk-enhancing factors may kick you up into the next category.

So, we can use coronary calcium scoring judiciously, not in patients with known ASCVD, but patients in these intermediate risk categories, to further refine that risk. And I like using the MESA app, because it really places into context the age of the patient and other

clinical factors such as what their lipids and lipoproteins are doing. I – I don't like these lab reports myself. Our lab will say you got a coronary calcium score of – of three or something, and – and that's considered low risk, etc. I think you have to put it in the context of the patient's age and situation, always. You could make a case, if you have a coronary calcium score of one, that favors statin therapy. The cat's out of the bag. You know, it's not normal for a human being to have coronary calcium score of one. that means the process is already occurring.

Now how do we define a very high risk ASCVD patient? This is a subgroup of patients who already have known ASCVD. The definition is multiple major events, or one major event and greater than or equal to two high-risk conditions. So I'm not gonna read off the entire list, but if you think about it, most patients who've had an event are high risk patients, or very high risk patients. Think about it. When's the last time you saw somebody with a clinical ASCVD event, like a heart attack or revascularization who didn't have one of these high-risk conditions? So, most of our ASCVD patients are gonna be in this very high risk category. What do we do with them? We're gonna use the tools we have – statins, ezetimibe, PCSK9 inhibitors – aggressively until their LDL cholesterol is less than or equal to 70. Remember, 70 is – is a threshold. It's not like we're trying to get everybody to 69. 70 is a threshold for action. You know, if you've got somebody – I've put many patients on PCSK9 inhibitors who have an LDL cholesterol of 79. You know, their LDL cholesterol might go down to 49. It might go down to 39 or 29. But, look at – at that LDL-C of 70 as a threshold for further action. Don't look at it as a target. There's a subtle difference, which I hope I helped clarify.

Now, tonight we're gonna focus a little bit more on non-LDL atherogenic lipids and lipoproteins. Remember that all the guys on the top – the VLDLs, the IDLs, the LDLs – these all contain ApoB. One ApoB on each one of these lipoproteins. So you wanna count all the atherogenic lipoproteins you can measure ApoB. ApoB, you know, people used to argue that it wasn't readily available, that it cost too much. it's five bucks to get an ApoB now, in most of the commercial labs in the Baltimore area, and probably also around here. And it's very cost-effective.

Just Google Allan Sniderman and ApoB, and you can see plenty of cost-effective studies about how good ApoB is for counting these atherogenic lipoproteins.

Michael Miller, my colleague from the University of Maryland, did this excellent analysis. We used to think, well, if we nuke the LDL-C dam, we're done. But that's not true, if you have hypertriglyceridemia. As you can see, the subset of patients in the PROVE-IT trial who had trigs greater than 150, while having a well-managed LDL cholesterol on statin therapy – they had a much greater risk, a 41% increased cardiovascular risk, just from this seemingly mild hypertriglyceridemia. There are many, many studies that have replicated this. So triglyceride elevations do matter, even after you've nuked the LDL cholesterol level down as low as you want it.

Now, the risk for cardiovascular events from hypertriglyceridemia steeply increases, as you can see once the trigs get much above certainly in the 100 to 200 range. You can see a very steep curve, maybe even below 100. So, we used to think, ah, you know, we don't worry about triglycerides unless they're 500 or more. Don't think that way anymore. You can see that there's a rapidly increasing risk for cardiovascular events from hypertriglyceridemia, even in the range from 100 to 200. And this is from the ARIC and Framingham offspring studies.

So, why are these triglyceride-rich lipoproteins causally related to ASCVD? What's the evidence? Well, we have major genetic studies, like Mendelian randomization trials, which show that LDL and triglycerides are both related to cardiovascular risk. HDL is not. HDL cholesterol is not. And, we see some of the apolipoproteins that – that influence the triglyceride levels here – in APOA5 and APOC3 lipoprotein lipase, etc. These are the enzymes, and apolipoproteins that are gonna control the serum levels of hypertriglyceridemia that we see. So, the triglyceride-rich lipoproteins promote inflammation more than the LDL lipoprotein. That's important, and we're gonna show you a couple of slides on that in a moment. And remember that remnant lipoproteins accumulate where the action is, as Bill Cramer would say. where the party is – that's in the arterial intima. That's where the macrophages that drive the process of – of a plaque formation – that's where they occur, and that's where the remnant lipoproteins are gonna create inflammation.

So here's a simplistic scenario of the atherogenic pathways, by which triglyceride-rich lipoproteins increase your risk. They often have APOC3, which is very pro-inflammatory. They often carry saturated fatty acids and they also carry cholesterol. And you can see that these three factors will drive foam cell formation, they'll recruit leukocytes into the subendothelial space, and they'll promote inflammation.

If you look at the rate of hypertriglyceridemia in statin-treated Type 2 diabetic patients, or cardiovascular risk patients, a lot of patients out there still have residual hypertriglyceridemia. You can see, one in four CVD patients, with LDL cholesterol less than 100 still have at least a modest elevation of hypertriglyceridemia. You can see one in three statin-treated diabetic patients will have trigs greater than 150. So there're plenty of these patients out there. Plenty of residual risks that we can potentially reduce.

So, this very complex slide shows us the different pathways from the recently published 2021 ACC Expert Consensus Decision Pathway

on management of hypertriglyceridemia. All of these pathways are gonna start with identifying secondary factors that are raising the trigs, and then they're also gonna implement effective lifestyle changes, which we're gonna talk about. So that's common to all these pathways. The one I wanna point out, is when your trigs are above 500, you – you stop right there, and you really focus on getting the trigs down by whatever mechanism you need to use. Combination of diet and drug therapy, because obviously, we're worried about pancreatitis in these patients with trigs above 500.

So, what are the major secondary causes? I won't read the whole list, but the number one thing I think we see in clinical practice is gonna be insulin resistance. You know, I teach my patients – most patients don't know what triglycerides are. The – the NLA did a poll where 90% of Americans don't know what triglycerides are, or don't know what their own triglycerides are. And I tell them that they're basically the trigs are – are a form of fat storage, and – and – and – and stored energy, but they're also a waste product of disordered sugar metabolism. That seems to resonate with my patients. So diabetes and insulin resistance is gonna really be the number one cause secondary cause of hypertriglyceridemia. And then you can see numerous other conditions, like chronic kidney disease, chronic liver disease.

Often, medications are the culprit. One of the easiest consults we get as lipidologists would be switching a woman over from oral estrogen to transdermal estrogen, for example. That is – the transdermals are not gonna raise your trig level. I've seen two cases in the last six months of tamoxifen-induced hypertriglyceridemia in my breast cancer patients, and that dramatically resolved once we got them off the tamoxifen.

So second, we're gonna optimize diet and exercise. Trigs are the easiest lipid to normalize, or at least to reduce, when you follow a goal-directed lifestyle change. We're talking about low carbohydrate eating, we're talking about weight loss, we're talking about concepts such as insulin sensitizing diets where you're trying to reduce glucose consumption, fructose consumption. I myself, in my practice, do a lot of time-restricted feeding, intermittent fasting type concepts.

Exercise, even without weight loss, will lower triglycerides in many cases, substantially. Just trying to get our patients to move. you can see every five to ten percent decrease in weights gets ab – in weight, gets about a 20% reduction in triglycerides. Just asking patients how much processed food they're eating. You know, it's – it's incredible the amount of sugar, high fructose corn syrup, etc., that's in processed foods.

And this is my – honestly, my favorite slide, when – when I look through this slide set, because I think there's a lot of wisdom here. You know, obviously, unless you're using a dietitian, which we're fortunate to have in the lipid clinic, you just wanna pick out a couple of these things to focus on at office visits with patients. You know, how much are you drinking as far as sugar-sweetened beverages? How much alcohol are you drinking? Maybe you need to stop drinking that glass of wine every day, and make it just a treat, a couple times a week. You know, have you gained any weight in the last year? What kind of physical activity are you doing? You know, the majority of our patients, unfortunately, sadly aren't doing much at all. So we can certainly crank that up. We – we've been using a – a telemedicine, exercise-oriented person to work with our patients to get people moving online via Zoom, etc. in terms of having exercise classes. That's been very helpful. A personal trainer is the word I was looking for. So, I think this slide has a lot of wisdom. Be specific. Be numeric. You know, give the patient a goal. You know, let's cut down the drinking every day to drinking once or twice a week, for example. I think that is – is much more clinically useful.

Third, in terms of our treatment of hypertriglyceridemia, we're gonna use medical therapy. We're gonna optimize statins first. We're gonna think about icosapent ethyl, which we'll spend a lot more time on. If we're gonna move in the direction of LDL-lowering, we've got ezetimibe, we've got our PCSK9 inhibitors, we've got bempedoic acid, and we've got inclisiran, which is now out there. So we have a lot of tools in our shed to treat these conditions medically.

We're gonna give you a patient case. Here's the first visit – a 60-year-old man, post-MI, history of PAD, he's had a right fem pop bypass, he's got hypertension, he's treated. His BMI is 29, so he's overweight but not obese, and he's a smoker. And this is rhetorical question, we'll show you the answer in the next slide. I – I don't think there's an audience response here, unless I'm wrong. What is his yearly risk of hard cardiovascular events?

If you see if he has zero risk indicators, the risk is 3.5% at three years. If he has three risk indicators, which this patient has – he has smoking, hypertension and PAD – his risk is 14.5% at three years, and these are hard events – we're talking cardiovascular death, MI or ischemic stroke. So you can see how the number of these risk indicators drives up the risk dramatically a – and a lot of this risk occurs in the very first year.

So, our patient – back to him – here is his lipid panel, pre-treatment. You can see – I always look at the trigs first, force of habit, and I think a good habit. Trigs are 280. Probably no one's happy with that. LDL cholesterol is 170. Likely no one's happy with that. We've got a non-HDL, total cholesterol minus HDL cholesterol – sort of the poor man's ApoB, as it's been said, of 226. So, most of these parameters

are nowhere near guidelines. And remember, we no longer try to raise HDL cholesterol. We've been there, done that, didn't work, so we're focusing on reducing the atherogenic lipoproteins. That's the way to go. That's where the evidence leads.

So in summary, our assessment of ASCVD risk includes the use of the calculator – if you don't have it, download it for your smart phone, it's free. It works on iPhones and Android. You can use judicious use of coronary artery calcium testing. Remember you don't want to use this – this testing if people have known disease 'cause it's – it's doesn't add any information. You wanna use it in intermediate risk patients. You wanna identify these risk-enhancing factors, and you wanna identify who the very high-risk groups area. And that – and those groups are gonna treat LDL first. We're gonna talk about residual triglyceride risk, which is indicated by hypertriglyceridemia – that's our biomarker for the presence of triglyceride-rich lipoproteins. We know that these triglyceride-rich lipoproteins are quite atherogenic. We know there's a lot of patients in the United States who have a – a burden of hypertriglyceridemia, and we know that the guidelines are evolving to reflect these shifts.

So with that, I will turn it over to Karol. Thanks.

Dr. Watson:
Wow. Thank you, sir. (applause) Hi. Thanks so much. This is a great setup, 'cause now we can talk about REDUCE-IT clinical trials and Omega-3 fatty acids for atherosclerotic cardiovascular disease risk reduction. So, it's a statin world. The most abundant evidence we have, in terms of lipid modification for reducing hard cardiovascular outcomes, is with statins. I was a member of the 2013 Cholesterol Guidelines writing committee, and we said that. Statin, statin, statin. And at the time, we looked at a lot of non-statin data, to see if there was any additional risk reduction on top of statins, and there was none. But since that time, data has come out to show additional risk reduction, adding ezetimibe to statins, adding evolocumab to statins, and adding alirocumab to statins. So using those non-stating therapies, in addition to statin, makes sense.

There's a number of other studies, particularly with fenofibrates and niacin – two drugs that happen to lower triglycerides – not showing any benefit. You see ACCORD there, FIELD, AIM-HIGH, and HPS2-THRIVE. So we did not recommend both therapies in our guidelines, and in the updated guidelines of 2018, they're not recommended as well. What we do recommend is statin, statin, statin. If the LDL remains elevated, add ezetimibe and/or, plus or minus PCSK9 inhibitors.

What about Omega-3 fatty acids? Well, it's such a fascinating story. If you look in – in the grocery store, you will see Omega-3 fatty acids added to everything. Orange juice or butter or margarine – whatever. And we've always thought of them as always being the same. But this kind of complicated slide shows you that they're not all the same. At the very top, you see alpha-linolenic acid – ALA. It is the only non-marine source of Omega-3 fatty acids. It's found in chia seeds, flax seeds, walnuts, some of the vegetable oils that we have, and it is a shorter chain Omega-3 fatty acid, which has not been studied much. It is converted via enzymatic relationship to longer-chain Omega-3 fatty acids – the DHA - docosahexaenoic acid, and the EPA – the eicosapentaenoic acid. But that conversion is really, really, really indeficient in humans. Less than 5% for EPA, and less than 1% for DHA. So essentially, you have to get both long-chain Omega-3 fatty acids from fish. That's where we get it. And what we know is there's a lot of beneficial effects, and that we think can reduce cardiovascular disease. That's why you see them fortifying all these food stuffs.

What we've done forever is to treat the two long-chain me - Omega-3 fatty acids as though the – they were the same. You know – Omega 3's. It's fine. They're all the same. When you look at a metanalysis of clinical outcome trials, looking at Omega-3 fatty acids and cardiovascular risk reduction, you see this fore spot right here. If you look at the line of unity, right in the middle, that means there's no difference between the two therapies. If you look to the left, it means the active therapy is beneficial Omega-3. To the right, it's harmful. But what we see is, it's pretty much right down the line of unity – not much effect at all, except this one trial here, which is just to the left of the line of unity. That means that trial showed benefit. Huh, that's weird – what's different about that trial? It happens to be the only trial that used pure EPA in that metanalysis.

Okay. This is looking at those trials again, in more depth, over on the left. What did they all use? Well, you see the top three just used dietary supplement fish oil. And when you get dietary supplement fish oil over the counter, it's a combination of DHA and EPA, and it's only about 30-50% Omega-3. The rest is filler. It's usually a corn oil filler. If you get the fancy kind, it might be olive oil, but it's usually like corn oil. You see there's one that used a margarine with dietary supplement, so again, some of those things you see in the grocery store today. And then at the bottom, you see prescription Omega-3 fatty acid, but in all of those trials, the bottom, they used prescription Omega-3 fatty acid that was a combination of EPA and DHA. And if you look over to the right, none of those showed benefit – not for coronary heart disease, not for stroke, not for revascularization.

More recently, though, we've seen some newer trials. One was the VITAL trial, one was ASCEND, and one was REDUCE-IT. VITAL and ASCEND, again, used prescription combination of EPA plus DHA, while REDUCE-IT did something different. It used prescription EPA – icosapent ethyl.

So, what's the big deal? Aren't they all the same? No, they really aren't. They look alike, and that's why I think a lot of us thought they were the same. We treated them the same. You can see eicosapentaenoic acid – EPA – on the top, and DHA - docosahexaenoic acid on the bottom. You just have a couple of additional carbons on DHA, and we just thought they were all just Omega-3 fatty acids. But, just because they look alike, they have very different biologic properties, and we're gonna talk about some of those later on. But think about it. We have other examples of molecules that look a lot alike but have very different properties. Testosterone and estrogen – they look a lot alike, but it's essentially the difference between a man and a woman.

So, coming back to the EPA and DHA. The JELIS trial – what did it show? Remember, that was the only Omega-3 fatty acid trial in that first metanalysis that showed benefit. Well, this little study done in Japan, it was an interesting study. So they – in the Japanese population, they took people who were considered higher risk primary prevention – about 80% of them are primary prevention, or secondary prevention – 20% were that. They randomized them to statin alone, or statin plus EPA, and it was a probe study design, so it was open label. Everybody knew what they were getting, but all of the endpoint adjudication was blinded. What they di – saw was that if you got both the statin and the EPA, you had a 19% relative risk reduction in hard cardiovascular outcomes. Major cardiovascular benefits.

When you look at the secondary prevention cohort – remember that was about 20% of the group in JELIS, versus the primary prevention cohort – the risk reduction appeared to be about the same. And again, the parent trial, over there to the left, showing the 19% cardiovascular event reduction. If you looked at the higher risk group, with ha – which had that dyslipidemia that Greg just told you about, the high triglycerides and the low HDL, they had gangbuster outcome and outsized benefit – a 53% relative risk reduction.

So that made everyone think, well, maybe there's something special about EPA. And that brought us to the REDUCE-IT trial. Really smart people said, "Let's do a clinical trial, just with EPA only, and see if we can see the cardiovascular benefits that were seen in JELIS." So they took individuals, men and women over the age of 45. Everybody got a statin. That was very important. They had both a secondary prevention cohort and a primary prevention cohort. For the secondary prevention cohort, you had to have established cardiovascular disease. For the primary prevention cohort, you had to have diabetes plus at least one other risk factor. They all had triglycerides between 150 and 500, and their LDLs were well-controlled, between 40 and 100. So they got a lead-in phase, where they all had statin stabilization. They had any other medications washed out, and then they had their lipids remeasured to make sure they qualified. If they did, then they could be randomized on the one-to-one basis.

Everybody continued their statin, so randomized to icosapent ethyl, four grams daily, or a placebo. And then they followed them up to see who had the primary outcome of the time to first cardiovascular event. It was a composite – cardiovascular death, nonfatal MI, nonfatal stroke, or a vascularization, urgent angina requiring hospitalization.

So what did they find? Well first, let me tell you. Why did they give icosapent ethyl? What the heck is that? Well, icosapent ethyl is an esterified form of EPA. It's just a way getting EPA into you. So when you – the icosapent ethyl hits your gut, it gets cleaved to – and when – I'm sorry. Yeah, when the icosapent ethyl hits your gut, it gets cleaved to EPA plus an ethyl group via the enzyme lipase. So, it's a way to get EPA into you.

And these are the outcomes. They – in the primary outcome, remember that composite as you see there. There is a 25 relative risk reduction in those who were randomized to icosapent ethyl. They then looked at a key secondary outcome – that's the big three, the three we really care about. Cardiovascular death, nonfatal MI, or nonfatal stroke. There was a 26% relative risk reduction. So really, game-buster response, like we just haven't seen in a while.

Now remember, the primary outcome was the time to first event. But as many of us know, our patients often don't just have one event. So the green parts of those columns are the first event. And again, you see the 25% relative risk reduction. But if you look at all events – first event, second event, third event and beyond – you see even greater risk reduction. So in terms of reducing second events, there was a 32% risk reduction. In terms of reducing third events, there was a 30% risk reduction. Reducing four or more events – there was over a 50% relative risk reduction.

Okay, that's the benefit. What were the side effects? Well, it was pretty safe overall. If you look at the treatment emergent adverse events, overall, in the icosapent ethyl group or the placebo group, it's about the same. No difference. No difference in serious adverse events as well. But there were two adverse events where – which were significantly increased in the icosapent ethyl group. One was bleeding. Remember, Omega-3 fatty acids have a little bit of an anti-platelet effect. So the thought were all along, like there could be a little more bleeding when you give higher doses of Omega-3s. And they did see that. They saw some more bleeding, a little bit more bleeding overall, but serious bleeding – like intracerebral hemorrhage or hemorrhagic stroke – they didn't see. But there was more nuisance bleeding, it sounds like.

The other thing they saw more of was atrial flutter. It's funny, the first time we saw that was in the REDUCE-IT trial. But since then,

others have come along and done reanalysis of other Omega-3 fatty acid trials, and they saw increased atrial fibrillation as well. We don't really know why that happened, but they did see it.

So in terms of atrial fibrillation, or flutter, requiring hospitalization for more than 24 hours, that was an adjudicated endpoint and they did see higher rate – statistically significantly – in the osc - icosapent ethyl group. A lot of people looking at that in the mechanisms. We don't really know why now, but that was seen.

But when you put all of the data together for REDUCE-IT, we see a 12% reduction in cardiovascular death, 42% reduction in fatal or nonfatal MI, 14% reduction in – in fatal or nonfatal stroke, 76% reduction in coronary revascularization, 16% reduction in hospitalization for unstable angina, and a huge reduction in the composite endpoint, for…

Okay. Now, what is the predictor of who's gonna benefit from this therapy. Well, is it triglyceride levels? That would be a – a smart thing to think about, but it looks like if you were in this trial, and your triglycerides were either above or below 150, it doesn't matter. You still had benefit. So triglycerides didn't seem to be the differentiator.

This is showing you the same thing. If you look at the event curves, they look the same for those whose triglycerides were above 150, and those whose triglycerides were below 150. No difference, still with benefit.

What did seem to make a difference was the EPA – serum EPA level. So remember, when you give icosapent ethyl, it gets cleaved to EPA, that gets intercul – collated and gets into your serum, and you can measure it. And it seemed that if you got your EPA serum level higher, that was associated with it – with more benefit. You can see the median EPA level in the placebo group is pretty low. Most people don't eat a lot of EPA. But if you were on the four grams daily, you had a significant increased EPA level, and the higher that got, the lower your events were.

So you could see that for every outcome for the primary endpoint. The higher your serum EPA level was, on the x-axis, the lower your clinical event was. Same was true for the key secondary endpoint – the big three: nonfatal MI, nonfatal stroke and cardiovascular death. Same was true for cardiovascular death and total mortality.

Okay. Around the same time as the REDUCE-IT trial was coming out, another trial was coming out – a trial called the STRENGTH trial. This was another large, randomized control trial, and it was meant to again test the hypothesis that Omega-3 fatty acids could reduce major adverse cardiovascular events. This study used a combination of EPA plus DHA, and mean – midway through the trial, it was stopped by the DSMB, for futility. They said, we see no difference in the outcomes, and we could carry this study out for as long as it's supposed to go, we're still not gonna see a difference. So it was stopped.

You see these curves. They could not be more superimposed. Same primary outcome, a composite of cardiovascular death, MI, stroke coronary revascularization or hospitalization for unstable angina. So what was the difference? Well, the big difference was EPA level. Remember in the JELIS trial and the REDUCE-IT trial, they used EPA only. In the STRENGTH trial, they used a combination of DHA plus EPA. When – when – I just showed you that the serum – the achieved serum EPA levels were strongly correlated with benefit. You can see in the STRENGTH trial this achieved EPA level was lower than that was seen in JELIS or in the REDUCE-IT trial.

But there was something also a little weird about STRENGTH, because if you have gotten EPA up that high, you'd think you'd still maybe not see as much benefit as you saw with the REDUCE-IT, but you should have seen something, right? But they didn't. So the thought was, maybe the addition of DHA also had some of a – ne - negative effect. So it wasn't just that you didn't get your EPA levels high enough, but also the addition of DHA may have negated some of the beneficial effects. It's not known for sure.

But again, if you – this is looking at the STRENGTH data, if you would have expected that with those EPA levels you would have gotten some benefit, but we didn't. So again, it's the thought that the DHA may have had some adverse event that negated some of the benefit.

Okay. But what we know is that if you get your EPA level higher, as was done in REDUCE-IT and STRENGTH, they showed benefit. In – I'm sorry, in REDUCE-IT and JELIS, they showed benefit. In STRENGTH, the EPA levels were not as high, and they did not see benefit.

Okay, there was a more recent metanalysis of Omega-3 fatty acid trials that was published just last year. And they used – looked at 38 different trials. Four of them used EPA only versus control. 34 used EPA plus DHA versus control. Most of them were primary prevention. The dose of Omega-3 ranged from 0.4 to 5.5 grams daily, so you can see a big range – from very low dose to high dose EPA and DHA. In the EPA trials the dose ranged from 1.8 grams daily to 4 grams daily. In the combination EPA plus DHA trials, from 0.4 to 5.5 milligrams daily. So what did they see? Again, looking at the force plot, to the left of the line of unity is benefit. You see a lot more benefit in the trials that studied EPA, compared – that's the blue circles and bars, compared to the trials that studied a combination of EPA plus DHA – the red bars.

So what have we learned? It looks like the trials that showed us benefit – REDUCE-IT, JELIS, two others that I didn't talk about, CHERRY and EVAPORATE – they all studied EPA only. The trials that didn't show benefit – they studied a combination of EPA and DHA, as shown on the bottom.

So what we know is what matters in terms of Omega-3 fatty acids is this specific drug, and it looks like the molecule that has the most benefit is EPA – but also the dose. It looks like the higher the dose you get, the more benefit, so many other Omega-3 fatty acid trials studied really low doses, as I just showed you, but it looks like that 4 grams per day was necessary to se – achieve the benefit.

So, substantial anti-CVD risk, once we get everyone on a statin and we get their LDLs way down, there's still a lot of risk that stays. Part of that risk is probably carried in elevated, triglyceride-rich lipoproteins. We know that statins are our mainstay. We've tried to attack triglycerides with statin plus fibrates, or statin plus niacin – neither of them showed benefit in risk reduction. The REDUCE-IT trial was the first trial specifically targeting triglycerides that showed benefit, and it showed it with 4 grams daily of icosapent ethyl, that was added on top of maximal statin therapy, and that becomes now one of the ways we can further reduce risk in our patients.

Thank you so much. I think we're gonna turn it over to a panel discussion now.

(applause)

Dr. Ballantyne:
And also, if there's anybody has questions if you wanna just – you can stand up, and I don't know if we have a microphone for questions, but if th – are there any questions from the audience? (pause) Yes, let's go ahead and there's a question over here.

Audience voice:
Is there anything short of dietary that would even come close to getting high EPA levels in the bloodstream?

Dr. Ballantyne:
So excellent question. Karol if you were gonna be eating cold water fish or something, or Joe (45:45) Joe you haven't took it out, your – they'll get it, look to your copy, but if you were gonna be eating cold water fish or – what else could you do to try to get your EPA levels up? How much would you have to eat toda – in a day?

Dr. Saseen:
I – oh, I think that…

Dr. Watson:
Y – you…

Dr. Saseen:
Go ahead.

Dr. Watson:
Yeah, you'd have to eat so much that I'd start to worry about your mercury levels.

Dr. Saseen:
I agree, I think – I think it'll be very difficult dietary – from a dietary pathway to get very high EPA levels. I – I would venture to say that it's probably eating fatty fish for every meal, to get to the level that we're seeing in the…

Dr. Ballantyne:
Correct, yeah. I – I've seen the – the thing for total mixture of EPA/DHA, but it's very large quantities, but it – to get – first of all, it wouldn't be pure EPA, but it – to get to the concentrations that Karol was talking about, you'd basically be eating the same thing all day long, right? I mean, I…

Dr. Watson:
Y – yeah.

Dr. Pokrywka:
Yeah.

Dr. Watson:
Again, I'd worry about your mercury levels.

Dr. Saseen:
And another thing that – and we'll cover this a little bit later, too, is when you get fat from fish, you do get crude fat, which isn't all EPA

and DHA.

Dr. Pokrywka:
Correct. Correct.

Dr. Saseen:
Even though we get these prescription Omega-3 fatty acids from fish sources, they have to be purified…

Dr. Watson:
Yeah.

Dr. Saseen:
…pull out some of the other remnant oils. So if you do eat – I mean it's – I think it's rec – it's recommended to eat fish, especially cold water fish because of more fat content, but I – y – you get a whole bunch of other things that might not be worth it.

Dr. Watson:
And that's the other thing I worried about, 'cause they are now making over-the-counter EPA only fish oils, which are being sold, but again, they don't have the same standardization and not FDA approval that we do for other…

Dr. Saseen:
Right. And I think you'll talk some more about supplements versus, right.

Dr. Pokrywka:
Yes. I'll definitely cover that.

Dr. Ballantyne:
Right. 'Cause it – dietary supplements are very different in terms of their regulatory process and the quality standards that come up with this. It's a – it's – it's a very good question, though, in terms of can we do it? Now, you mentioned flax seed and ALA. So if you eat – and we – and we do see there could be health benefits for this, right? And – there may be other health benefits and there's some evidence that this – but what about the ef – impact of flax seed on triglycerides? Is there – is there any real benefit for flax seed on triglycerides?

Dr. Watson:
So – yeah, there's that data. So the data is really good for the long chain Omega-3s – EPA plus DHA – and essentially, for every full gram of either of those that you get into someone, up to four daily, you get about a 10% triglyceride-lowering.

Dr. Ballantyne:
So – so flax seed may be beneficial for other health aspects, but it's not gonna lower your triglycerides. So – that's really gonna – as Karol pointed out, that's EPA and DHA.

Dr. Pokrywka:
And flax seed has never been shown to reduce cardiovascular events either, I don't think.

Dr. Watson:
No. We have one trial that has shown that with Omega-3s and that's the REDUCE-IT trial.

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
Yeah. Now there was…

Dr. Watson:
And JELIS.

Dr. Ballantyne:
There was a dietary study where they had an added – additional ALA that did have some transferred cardiovascular benefits, but that was not a lipid it – effect. Now, you do bring up a little bit – and we'll talk some more about this, but you know, the triglyceride changes, Karol, I mean that doesn't necessarily p – it does lower triglycerides but is that the benefit…

Dr. Watson:
Right. It – it does – well, again, we don't know all of the mechanisms. But it doesn't appear, 'cause again, if your triglycerides were above 150, it showed benefit. If they were below 150, they showed benefit. So it appears to be something else.

Dr. Ballantyne:
And if you – anyone has other questions, just put your hand up and I'll get the mic over there for it.

Dr. Saseen:
And another thing about the ALA too.

Dr. Watson:
I think we have another question.

Dr. Ballantyne:
Yes, there's another question there. Yes.

Audience voice:
…do you need your triglycerides to be?

Dr. Ballantyne:
So that's a great question – is how low should your triglycerides be? So, Karol showed a slide on the epidemiology. In – in terms of basically epidemiologically, what's the optimal triglyceride, Karol?

Dr. Watson:
I – I – well, I can tell you what we think is truly normal, and it's nowhere near 150. It's kind of like glucose. We don't think of glucose of 100 really as normal. That is the threshold we use, but I think most normal, healthy, cholester – sorry, carbohydrate metabolism people have a fasting glucose that's lower than 100. I think that's the same that's true for triglycerides.

Dr. Ballantyne:
So yeah, I think – you know, less than 100, but you could call that normal at less than 100. Clearly over 150 is high, and over 200 we would consider to be – two to five hundred we would consider to be in a zone where that's really increased triglycerides. Over 500, we call very high, and then your risk for pancreatitis whenever you see over 500, we start to worry. Over 1,000's where you really start to see the pancreatitis risk. Now Karol, this – a question that comes up is, why in our guidelines do we say over 500, rather than over 1,000?

Dr. Watson:
So I can tell you, it's really unusual to see de novo pancreatitis if your triglycerides are under 1,000. But once you've had pancreatitis once, I see it as low as 300. So, 500 is probably overall, we – below that, you rarely see pancreatitis, but in general, most people who've never had pancreatitis before will not get it until their triglycerides get above 1,000.

Dr. Pokrywka:
I – I think the other is up – since triglycerides are usually measured fasting, I mean, if you're walking around with fasting triglycerides of five or six hundred, I always tell patients, "You're one six-pack of beer away from gettin' up to a thousand."

Dr. Watson:
Exactly.

Dr. Pokrywka:
So that's – that's the reason, I think, why we make that…

Dr. Ballantyne:
Yeah, so it's – when I was – Scott Grundy was the first to – it's been that number for all the guidelines, but it would – he'd explain to me, 'cause I – he was a mentor of mine at – when I was a resident at Southwestern – that, you know, we measure this in the fasting state, and if someone's running 600 – and you've seen this in your clinic – they may be 600, but they have one bad weekend, and they c – may come in 1,200 or 1,500.

Dr. Pokrywka:
Right.

Dr. Ballantyne:
And remember, you measure this fasting. Now we do a lot of post-prandial studies, where we give people a fat load. But if someone has a fasting triglyceride of around 200, and you give them a fatty meal, you'll see those people going up to four to six hundred, and what ends up happening – if someone with his – heart disease and diabetes, they go up higher and they stay up longer.

And so the peak is around six hours, so after you eat a fatty breakfast, what happens five hours later? Lunch. Then after lunch, what happens six hours later? Dinner. So, you know, so what ends up is that you were – just like you were saying, and if you wanna really get the triglycerides up, throw some alcohol in there. We've done those studies, too. If you take alcohol with a fatty meal – interesting, alcohol with a very healthy meal, lowfat meal, didn't do that much. But it - the two together – so in Houston that experiment gets done every Friday night… (laughter) Mexican restaurant, you know, chips.

Dr. Watson:
That's – I – I tell all my patients, I want you to come in and get your blood drawn. I don't – you don't have to be fasting. I wanna know what you were walking around with, 'cause literally, we're fasting for maybe a five-hour period while we're asleep, and then we're eating the rest of the day, all day long.

Dr. Ballantyne:
Okay. It – we – are there any more questions? I – I see.

Dr. Saseen:
There is – there's one from the virtual audience.

Various:
Okay. Okay.

Dr. Pokrywka:
Is flax seed puf-3 or puf-9?

Dr. Watson:
Fo – Omega-3.

Dr. Ballantyne:
So it's – yeah, it is an Omega-3. I think it's 18, right Karol?

Dr. Pokrywka:
Yeah.

Dr. Watson:
It's 18, EPA is 20, DHA is 22.

Dr. Ballantyne:
And then, it – it ends up having three unsaturated carbons in there, with it. So it is – it's poly…

Dr. Watson:
Oh, it's – it's an Omega-3.

Dr. Ballantyne:
It's an Omega-3, we got three of them.

Dr. Saseen:
And this is where – where patients can get very confused. It is true, there are three Omega-3 fatty acids. There's EPA, DHA, and ALA - alpha-linolenic acid. But alpha-linolenic acid, as stated, doesn't lower your triglycerides. There's a chemical difference in the structures, sometimes…

Dr. Ballantyne:
I think he was asking which carbon bonds were – was it. If he was asking…

Dr. Pokrywka:
It's the third carbon bond. That's…

Dr. Ballantyne:
Yeah.

Dr. Watson:
Oh, were you asking exactly which carbon?

Dr. Ballantyne:

Yeah, there's three different – if three – there's three, you know, that are in there in Omega-3.

Dr. Watson:
Right, it's a – it's a – it's three, not nine.

Dr. Ballantyne:
It's wha – just which positions are – I don't remember off the top of my head. Well – now I say that we had a break scheduled in here. If someone wants to do a quick bio-break or just stand up and stretch your legs, or…

Dr. Pokrywka:
I want to go take a quick break.

Dr. Ballantyne:
Yeah, so we'll do a – we'll do a five-minute bio-break, and people can sit – stand up and stretch. And then we'll – we'll get going. Okay?

Dr. Saseen:
We'll be right back after this break. Thank you.

Dr. Ballantyne:
We'll go ahead and get started. And we're gonna kick it off again with recent evidence from some of the REDUCE-IT substudies, with Karol Watson.

Dr. Watson:
And this is actually just gonna be more of the same, drilling down on the REDUCE-IT trial. So, as you guys know, the – certain patients are higher risk, so if you have certain comorbidities, there's certain patient characteristics with higher risk. So, let's look at the REDUCE-IT CABG substudy. Remember in REDUCE-IT, the overall trial, for the primary outcome we saw 24% relative risk reduction? We saw the same thing in the REDUCE-IT CABG trial. So these are individuals who had prior CABG. And if you look at them in terms of the key secondary outcome, it's even better. It's a 31% relative risk reduction.

And again, people who have one event tend to have another event, and another event. So you can see, the first event there was a 24% relative risk reduction, the second event it was a 33 relative risk reduction, and then they didn't have as many cases have further events, probably because people, unfortunately, end up dying.

REDUCE-IT renal. So individuals who have renal dysfunction. If you look at those subgroups, it didn't matter if you were severe ki – chronic kidney disease, moderate chronic kidney disease or normal renal function, you had the same relative benefits. And again, looking at the key secondary endpoint, you see the same kind of benefits regardless of your renal function. You actually see the people who had the worst renal function having the greatest relative benefit, over there on the left.

Peripheral arterial disease. Those are some of our highest-risk patients. And when they looked at the subgroup of patients in REDUCE-IT who had peripheral arterial disease, you can see a significant risk reduction, over there on the right compared to the overall population, so even greater risk reduction in the higher risk groups. And that's that common thing we see in a number of lipid trials. The higher the risk you start with, the greater the benefit you may obtain.

Prior MI – high-risk group. And again, the higher the risks you start with, the greater the risk reduction. So you can see the composite risk reduction in individuals who had prior MI. So really they were at 35%. If you look at the key secondary endpoint, again, it's over there at – at 32%.

And, this is something interesting, and I think we're gonna hear a little bit more about this. If you look at cardiac arrest or sudden death in people with prior MI – that's one of the major ways they die – in the icosapent ethyl group, they had a significantly lower rate of cardiovascular death, sudden death, and cardiac arrest.

So that makes you think – is the icosapent ethyl somehow stabilizing membranes? And I think we're gonna hear about that in a second. And again, you can see here the icosapent ethyl group had much lower rates of sudden cardiac death and cardiac arrest, as you see there.

Now, it's a statin world, I just said. Everyone had to be on a statin, and does that somehow attenuate the benefits of icosapent ethyl? Doesn't look like it at all. Looks like all of the different statins, whether it's in primary prevention or secondary prevention, whichever statin is was – whether it was lipophilic or hydrophilic – it really looks like they all should benefit by getting icosapent ethyl on top of it.

Alright, now, I'm gonna send it back to Greg, who's gonna tell you about some of those cool biologic effects we just mentioned.

Dr. Pokrywka:

Thanks, Karol (applause) So you know, I think one of the main take-home messages from this whole symposium tonight should be reframing the way you think about IPE, and thinking of it as an event-reducing drug, as opposed to a triglyceride-reducing drug. I know a couple of you asked me during the break, you know, how much do you have to reduce the triglycerides with IPE to get an effect and such. Well Karol showed you some of the data from REDUCE-IT, that it – it – it appears that the reduction in clinical events is uncoupled from the degree of triglyceride lowering. So, you know, we docs are – are mostly skeptics, and there was a lot of skepticism when these fantastic results that Karol showed you from REDUCE-IT came out. So if it's not the trig lowering, what is it? Well, the short answer is we don't know for sure, but we can see that the physiologic effects that EPA has on a number of biomarkers, that we're gonna summarize here fairly briefly. I don't wanna bowl you over with a lot of pathophysiology, but the other key thing in this next section of the talk is the difference between EPA and DHA. They are dramatically different, and that's what I'm gonna show you in the next couple slides.

So, we got a polling question first. So what percent of patients seen by you for the first time, will state, "We're taking fish oil," when asked about their medication history. What do you guys think? (pause) Shouldn't we have some music here, guys, or some – some Jeopardy, or something? (music)There we go. Alright, the data is rolling in. So, most of you are saying that a fairly small percentage – well, it just went up there. Let's see. My gut feeling is that most patients are – are not identify – actually, the British use fish oil supplements a lot more than Americans do, for whatever reason. But, there's still a lot of use of fish oils. So, let's go…

Now, what percent of your patients taking any type of Omega-3 are actually taking a prescription-grade version? What do you guys think of that? (music) So it looks like our consensus so far is that (laughs), that percentage of patients taking a prescription-grade version is – is pretty low, and I – I think most of us have seen that in our practices. So Karol already showed you this slide, but just to emphasize again, we're gonna focus on the marine long-chain Omega-3s and we're gonna take a look at the biological differences, mainly between EPA and DHA.

As Karol said, showed us this slide before, a tiny little difference can make in terms of biochemical structure can make a huge difference in terms of the physiologic effects, as we see differences between estrogen and testosterone. So, there's a lot of potential mechanisms by which Omega-3s can reduce cardiovascular events. They lower triglycerides, they have anti-thrombotic effects, they stabilize membranes – and we'll show you the data, the EPA is much better at this than DHA. There are antiarrhythmic actions – Karol showed you that pretty astonishing data about reduction in sudden cardiac death – arrhythmogenic death. Altered prostaglandin synthesis, augmented specialized pro-resolving mediators, known as resolvins, and any anti-inflammatory actions.

So, EPA distributes itself evenly in the, in membranes, so it – it prevents the formation of – of cholesterol grafts. That's the main take-home message from here. What we see with DHA is – is in – enables the aggregation of cholesterol, and that's where you get the formation of – of these cholesterol domains and rafts that potentially are – are much more atherogenic.

There's actually some data out there – some early data that if you have patients with ApoE4 abnormalities, and have increased risk of Alzheimer's dementia, if you give them DHA, there appears to be some preliminary evidence – and these studies are just starting – that you can potentially slow the progression from mild cognitive impairment through to Alzheimer's dementia. So we tend to think of DHA in the central nervous system, whereas we tend to think of EPA having its main effects in the endothelial cells that control the – the health of our peripheral blood vessels. As we see again, we're g – we're promoting with EPA membrane fluidity and we're promoting a more even cholesterol distribution, so you don't get the formation of these rafts that are highly atherogenic.

So again, the – it – and all this boils down to biochemical structure. There's no magic here. EPA just interpolates itself better into the – into the phospholipid membranes, as you can see on the EPA part of the slide, whereas DHA has kind of little more of a hook to it. So it doesn't – i – in terms of its structure, so it doesn't interpolate as well, into the bilayer membranes. So, again, we're gonna get differential effects in terms of membrane fluidity and anti-atherogenetic potential.

So, very different, difference very significant differences between EPA and DHA, in terms of membrane stabilization a – and – and fluidity. The resolvins are one of the mechanisms by which, we get the biologic effects of Omega-3s, and – and – and we're affecting different resolvins with EPA than we affect with DHA. The effect the activity on oxidized LDL-C is different, as we'll see in a minute, and we see differential effects on anti-inflammatory biomarkers, such as hsCRP, which many of us track.

If we look at this – this table, summarizing the – the comparative effects between Omega-3 fatty acids and other agents that lower triglycerides – someone just asked me a few minutes ago, "Should we throw the fibrates and niacin out the window?" Well, niacin, I would definitely say yes. I don't think there much of a – a – a role for niacin anymore, and I haven't started a new patient in years.

Fibrates, for people with severe hypertriglyceridemia, you're worried about pancreatitis, etc. That's – that's where we're gonna use fibrates, and there's some evidence that fibrates reduce cardiovascular events, in sub-analyses of certain clinical trials, but really, it's – we're talking about EPA here, and here's all the reasons that you can see EPA,is – should be favored in terms of reducing clinical events. It doesn't raise the LDL cholesterol that should be in patients with high trigs. It reduces hsCRP in patients with high trigs. It

maintains an even membrane cholesterol distribution, preventing the formation of those dangerous cholesterol rafts. And we talked about membrane stability, inhibits the cholesterol domains, it enhances endothelial function, on top of a statin. We all know statins – one of their mechanisms action, one of the pleotropic mechanisms of action is they improved endothelial function. This is enhanced by the addition of EPA.

We're – we're gonna inhibit the oxidation of these beta lipoproteins. These – these are the bad guys, and when they're oxidized, they're more readily taken up by macrophages to promote plaque formation and hence various inflammatory bad things happen, and we're gonna inhibit that with EPA. And then we're gonna enhance cholesterol efflux with EPA, as compared to DHA, where you don't get that effect.

So what effects do Omega-3s have on oxidation of the membrane, leading to cholesterol crystals? So, the formation of these cholesterol crystals trigger the formation of interleukin 1-beta. And – and this is very proinflammatory. I'm not gonna go through every little bit of the of the mechanism of action here, but – but certainly, inhibiting, the – the inflammation induced by interleukins it – is definitely a good thing, and one of the ways that EPA differs from DHA.

This is a slide – sometimes I wonder if I – I should put this on the wall in my patient exam rooms for patients who are reluctant to take lipid-lowering drugs, because these – these certainly – these cholesterol crystals look pretty pretty nasty.

They're almost like little swords inside of the membranes. So definitely, we wanna inhibit the formation o – of these cholesterol crystals.

Now, oxidative stress is caused by most of the classic risk factors that we look at when we look at a – ASCVD – things like dyslipidemia, cigarette smoking, hypertension, diabetes – all these things promote oxidative stress. You get lipid peroxidation, you get inflammation, you're gonna get increased cardiovascular events. So what effects do Omega-3 fatty acids have on this macrophage activation? We know macrophages play a key role i – in – in both the initiation and the progression of atherosclerotic plaque. We'll just skip over that one.

Now here's a clinical trial, where if you look at lipopolysaccharide, which is a very potent stimulator of macrophage activation, EPA but not DHA will reduce this macrophage activation. So here we have a head-to-head study, looking at differential effects of these two long-chain marine Omega-3s.

What effects do Omega-3 fatty acids have on endothelial function? And then, enhance, en – enhanced protein expression? Well, we know that nitrous oxide is a good guy. Right? It – it inhibits the platelet aggregation, it improves endothelial dilation. It's gonna improve relaxation. It's gonna cause the formation of vascular smooth muscle cells. It's gonna put them in a more relaxed state. So we want to have more nitrous oxide.

So the effects of EPA is added to the effects of statin. When you have oxidized LDL present, as you see in – in all of the bars here other than the than the placebo vehicle. If we add EPA, you could see we get a positive effect. If we add the metabolite of atorvastatin, we get a positive effect. These two are additives. So only EPA adds to the to the endothelial function enhancing effect of the statin. We don't see this effect with DHA, and we don't have that data right in front of us here.

Heme oxygenase-1 expression, w – which is cytoprotective. EPA increases the expression of – of heme oxygenase expression. It's not a topic that I know a lot about personally, but again, this is another biomarker, where EPA differs from DHA. You don't get the same effects with DHA.

Now, we're gonna finish up, I think my section by looking at some a – actual, imaging-type studies, in which we're gonna look at the effects of EPA when added to a statin, in terms of imaging. And this is Matt Budoff's study called the EVAPORATE trial, where we're gonna add IPE, 4 grams per day, standard dose, as an adjunct to diet and statin therapy, and we're gonna actually look at plaque volume, using a – a relatively new technique called multi-detector computed, tomography, against placebo.

So here's what we see. These are – are the interim results. I think they're at nine months. The low attenuation plaque is what we consider fatty plaque. It's more bioactive plaque. You can see, at nine months, there wasn't much effect. However, on fibrous calcified plaque, non-calcified plaque, and total plaque – you can see what look like pretty clinically significant reductions in terms of plaque volume. And if you look at the final results of this study, you can see their wide-ranging effects, across the board in – in – including the low attenuation plaque, which is now statistically significant, the fibro fatty plaque, the fibrous plaque – basically, all different plaque types. Their volume was reduced by adding icosapentyl ethyl to a statin, versus placebo added to a statin. So we can see part of the mechanism of action here. It's not just a triglyceride-lowering. It – it's – it's it's a – it – it – the end effect is gonna be reduction of plaque volume. Less plaque you're gonna have fewer clinical events. That makes sense, I think, to all of us here.

So, finally, summarizing again, EPA interferes with the cardiovascular disease continuum at multiple points. It's gonna reduce lipid oxidation. It's gonna reduce lipoprotein oxidation, that is. It's gonna improve endothelial fun dysfunction by inc – improving nitrous oxide.

We're gonna reduce inflammation. You can measure that with hsCRP, which drops dramatically with EPA. We're gonna get the formation of fewer cholesterol crystals, we're gonna stabilize membranes, we're gonna stabilize plaque, and eventually, that's all gonna lead to the kind of effects that Karol showed us, in terms of reduction of clinical events.

So I think that might be it for me, and now we're gonna – finally – we've been saving the best for last, here. Saving Joe for last our – our pharmacist perspective here. So, thanks Joe. (applause)

Dr. Saseen:
Well, thank you very much, Greg. A nice introduction. I've known Greg for a while. As part of the National Lipid Association, I'm very glad to be here. I serve a few different roles. Currently I am president of the National Lipid Association, very proud to be leader of that organization, and I think – I just wanna emphasize, I'm not a physician. I'm a pharmacist, and a lot of what I'm gonna talk about is sort of the interplay between other health care professionals to improve cardiovascular risk reduction, since that's where I fit in. To give you a little step, I guess, in the past, on the role of what a pharmacist can do and has done in the past, for those of you who know a pharmacist, you may know that the field has changed quite a bit. When I first became a pharmacist, in the very early '90's, I was Bachelor-trained. That's a BS pharmacist, it was a five-year degree program, and I became a pharmacist. I worked in an outpatient pharmacy for a period of time. I worked in other settings too, in the hospital, but I decided to go back and get my graduate degree, which was a doctorate degree, or a PharmD degree, to know a little bit more about how to use medicines and how to manage them.

And I even chose thereafter to do post-graduate training to learn how to do research, and it led me to the spot where I'm at right now. I'm a faculty member at the University of Colorado. Promoting clinical pharmacy's part of my job. It's something that I have a passion for, and it really has changed, so I guess that vision of the pharmacist in the white coat that Seinfeld made fun of standing up, you know, ten feet up in the air, is not really all pharmacists. We have a great deal of pharmacists who are clinical pharmacists, who manage patients' medication regimens, and I think that's one area that I do wanna focus in on – the role of the clinical pharmacist. I do think any pharmacist that deals with patients can be called a clinical pharmacist. What I'm really getting it is that sort of advanced trained pharmacist who participates directly in patient care.

There was a great summary that was sponsored by ACC – the American College of Cardiology, that was published now about seven years ago, but outlined the role of the cardiovascular team, which includes pharmacists, nurses, PA's and dietitians working alongside with medical providers to reduce cardiovascular disease. And when we laser focus in on what clinical pharmacists do, we do sort of three big buckets of different things. One is patient-specific services, and we also have facility-specific services, and then global services. The global services may be your pharmacist who works in a public health initiatives, working for the state or working in organizations. The facility-specific services of a clinical pharmacist may be that pharmacist who's working to support formularies, within a health system, and helping to develop guidelines for appropriate use.

But I think for the world of direct patient care, we're really talking about the pharmacists that provide patient-specific services. This is something that most states do allow. They allow appropriately-trained pharmacists, which usually is more than just having a PharmD degree – having some additional training; can collaborate in drug therapy management – collaborative drug therapy management protocols. These are also called scope of practice, depending on where you work, where pharmacists have the authority to, upon a diagnosis – they don't diagnose; we don't diagnose, but we do modify drug therapy. If we have these arrangements, we can initiate therapy, titrate therapy, modify therapy, monitor therapy – with the real goal to actually improve patient care, since there is really a gap where patients may be treated, yet not at their therapeutic goal, and that's called clinical inertia. Other things that come with that terrier – tory is providing drug information, counseling patients, screening for drug interactions, and using cost-effective therapy.

To break it down a little bit for cardiovascular disease, if we just use example of patients with established clinical ASCVD, which is a high-risk population that we've – that we all know about, that should be managed with statin-based therapy. I love the term "this is a statin world," or "we live in a statin world," because it's the truth.

So we know that maximally tolerated statin therapy and antiplatelet therapy is the cornerstone of treatment for established clinical ASCVD, with other more specific therapies, depending on the form of clinical ASCVD. But we can't just treat in isolation. There also is management of diabetes, which really has turned into a cardiovascular disease, ever since rosiglitazone actually had an increased risk of cardiovascular events. The FDA's mandate to study diabetes drugs more extensively and look at cardiovascular outcomes has led us to the point where treating diabetes is concurrent with treating cardi – underlying cardiovascular disease. There's targeting inflammation, there is additional thrombotic risk factors that we do modify, and – and getting more to our dyslipidemia and we do focus quite a bit on either reducing LDL cholesterol the most, with medication management, and sometimes targeting elevated triglycerides.

The statin story – the statin world we live in – is that statins are underutilized. If they're not started, that's a problem, but when they're started, sometimes they're not dosed appropriately, for a variety of different reasons, but we know that we should be living, for most of our patients, especially our highest risk patients, at the high intensity end of things.

When we heard about the REDUCE-IT trial, and other cardiovascular outcome trials, the foundation of treatment is maximally tolerated statin therapy. And, we – we know that there are reasons not to use the highest dose of a statin, but we often don't always try it, or patients stop their therapy for other reasons, too. So being able to navigate the high intensity options and the moderate intensity options, and doing it appropriately, is something that falls in the wheelhouse of a clinical pharmacist.

Now, being on a statin alone is not good enough, and I think it was a misinterpretation in 2013, with cholesterol guidelines, that there was a mis, interpretation that patients just needed to be on a certain dose of a statin, and then call it a day. Very much wrong interpretation of guideline recommendations. The reason why it's really important to actually look at somebody's response, is just what we see with drugs – there is a variability. The data that I have here is from the JUPITER trial, which is a very large, cardiovascular outcome trial, that looked at patients who are primary prevention patients, randomized to either placebo or rosuvastatin, 20 milligrams – which is, by definition, a high intensity statin, the dose of a statin that cuts your LDL by 50%. Only atorvastatin and rosuvastatin are in that category.

But if you look at the waterfall plot on the left here, we see just by patient count, that only 50% of patients actually get that 50% reduction. We see that on the – on the right with the dark teal color. We see a large number of people actually in the lighter, bluish color, that get less than a 50% response. And even some people in pink, that have actually no response or an increase – perhaps they're not taking their medicine.

But this highlights that it's not good enough just to put people on the right medicines. We have to measure the response, and that's where a clinical pharmacist may have the role of doing that deep dive in – in managing the day-to-day titrations that are needed.

It is important to get the achieved response – the desired response – and with high intensity statin therapy, it is really cutting down LDL by 50%. If you correlate over the risk of cardiovascular events from this JUPITER trial, which overall showed that statin therapy reduces events, if you cut apart the data, the people that drove the results were the people who had the most LDL-lowering. So, if you don't monitor, and look for a desire – not just the, you know, the desired response, but the recommended response, and make sure your patients achieve that, we will leave residual risk for cardiovascular disease on the table.

And we know from the Cholesterol Treatment Trialists' Collaboration, which is a – metanalysis group that looks at all the statin data and puts it together, to give us interpretable messages. One message, which we have on the left, is the amount of cardiovascular risk reduction you get is really dependent on how much LDL-lowering is seen in those clinical trials. We have several clinical trials on the left, that used statins, and actually even the PCSK9 monoclonal antibodies, and ezetimibe, so that the demonstrated reduction events really parallels, and it's predicted based on how much LDL-lowering you get. We also see a phenomenon on the right, that the longer people are on st – on LDL-lowering therapy, whether it's with statins or statin plus other drugs, the longer you're on therapy, the more benefit you get, and we interpret that based on the slopes of these particular graphs on the right – the different data points, where the shorter term trials, we have a more shallow relationship between the reduction in cardiovascular events with a reduction in LDL. But as we go up top, we see longer studies, that treated patients for more years, on lipid-lowering therapy. And to get the steepest slope, which means the biggest bang for your buck, the most reduction in cardiovascular events for LDL-lowering, is on patients who are on these drugs for multiple years. Why is this important? Well, it's not just good enough to be on the drug. It's not ju – just good enough to get the – the desired response, but you have to be persistent with therapy, which is what's implied with that graph on the right.

Adherence – I think it was C. Everett Koop said – remember C. Everett Koop? One of our Surgeon Generals – said that medications don't work in people who don't take them. And that's really getting at the fact that if our patients are not adherent with good therapy, they're not gonna reap the benefits. We do know that statins, in general, are well-tolerated medicines. There's been a recent metanalysis that estimated the prevalence of statin intolerance to be less than 10%, so it is not something that ev – that, you know, I guess it's conflated that patients cannot tolerate statin therapy. When you really look at the data, many patients do.

There are side effects that happen with statin therapy. I would never say that there are not. But really, the risk of serious adverse effects really are considered very low, and this is when you're looking at severe forms of statin-associated muscle symptoms, such as rhabdomyolysis, occurring less than 0.1% of the time. There is an increased risk of new onset diabetes, which has gotten an awful lot of attention. The FDA even puts this warning in the product labeling. But the risk is small compared to the benefit that is achieved, when you look at cardiovascular risk reduction – still that something for fair balance that has to be part of the discussion with a patient, perhaps leaving them to interpret the overall benefit the wrong way. The overall benefit is that you get more cardiovascular risk reduction than you get risk of increased new-onset diabetes, or significant adverse effects related to muscle symptoms.

A few other things about just statin adherence. I think there's – we've gotten a lot of attention – has anybody heard of the nocebo effect? The nocebo effect's got an awful lot of attention, and it's really this phenomenon where patients are sort of engineered to believe that drugs will cause harm. If you're interested in learning about that, what we know is that there's been N of one studies. One's called the SAMSON trial, which actually randomized patients to take either one of three different treatments, multiple times over a period of a year.

And each treatment was bundled in a monthly bottle, so patients got one month of atorvastatin, one month of a placebo capsule, one month of nothing. And when I say nothing, it's an open bottle that had no pills in it. And it was scattered out, there was 12 different bottles that were given to patients, with each of these three different regimens, and what was assessed were muscle symptoms. And using systematic ways of assessing muscle symptoms, what was seen is that the incidence of muscle complaints were pretty comparable between the placebo capsule and atorvastatin – numerically it was a little bit more with – with the statin, but not a whole bunch more. But what was a whole bunch less were the – the open bottles that had no drug in it at all. So people had more side effects with the placebo capsule than no treatment at all. And that was very interesting – this got to the concept of the nocebo effect, which can is estimated to contribute to about 90% of the symptoms that patients have. And I say that – I go a little bit further with that, because that's something that we need to be aware of, and wh – as providers. Maybe we need our pharmacists to actually help explain to patients the real world experiences of tolerability with statin therapy.

Getting a little bit down and dirty with statin therapy and what a clinical pharmacist or a provider should do, we've seen this graph before, and, you know, once you've optimized statin therapy, which is a very important step – you can go down LDL-lowering or down triglyceride-lowering as far as a treatment pathway. And we know that ezetimibe and alirocumab or evolocumab are proven LDL-lowering therapies that reduced cardiovascular events. We have bempedoic acid and inclisiran, but they're still unproven in their ability to reduce cardiovascular events long-term. We'll know about that in – over the next couple years.

But there is – what we've heard about, you know, many patients who have optimized statin therapy, to use icosapent ethyl, which is EPA-only containing Omega-3 fatty acids as eloquently described by Dr. Watson – all the ins and outs of the data supporting the use of icosapent ethyl. Knowing what our options are, and using them appropriately – sometimes it may be shared decision making on which end you go. Maybe you have gotten a desired LDL-lowering. Some people would like to go further with LDL-lowering, but you may have the option in a given patient to target triglycerides. And we do have data to support that.

One thing that any pharmacist will tell you is that yes, Omega-3 fatty acids first were introduced to the FDA market as triglyceride-lowering drugs. And they still are triglyceride-lowering drugs. FDA indicated, treat with levels of 500 or higher. But, one product in particular has the FDA endorsement, which is icosapent ethyl, for cardiovascular event lowering, in patients on max – maximally tolerated statin therapy that achieves an LDL that is consider acceptable, between – if you look at the studies, between 41 and 100, but if patients still have remnant elevated triglycerides, considered 150 or higher, we have the option and FDA indication to use icosapent ethyl. This is something that is only – and it's exclusive only for the EPA-containing product. It doesn't cross over to over-the-counter treatments, or the other prescription Omega-3 fatty acids.

The data from REDUCE-IT were robust enough that FDA gave that indication, but multiple medical societies have gone on record to endorse the use of icosapent ethyl as it was studied and proven to be beneficial in the REDUCE-IT trial. This is where, I know a pharmacist – I guess we tend to call ourselves anal people – we follow data, we like to live by rules, we look at product insert recommendations. This is one where the FDA label lines up with the evidence and the medical society endorsements also line up, mostly with – with all – with how the data has demonstrated efficacy.

A few other things, just that I wanna bring to light, is there's a lot of, I guess, also, purported benefits and concerns about using over-the-counter fish oils and Omega-3 fatty acids. If you look just at the prescription Omega-3 fatty acids products, a lot of the things that we've observed with over-the-counter fish oils have sort of tainted the soil with the Omega-3 fatty acids. So the American Heart Association published an AHA Sus – Science Advisory, to talk about safety and tolerability of the prescription Omega-3 fatty acid products. They looked at safety data, and overall generally viewed that tolerability with these products is pretty good, and that drug discontinuation rates in clinical trials was very small, endorsing good tolerability. They talked about bleeding, which was addressed and – and noticed in the REDUCE-IT trial, that there are some known antiplatelet effects, and perhaps FDA suggests periodic monitoring, but overall, the significant increased risk of serious bleeding really is not concernable. It's – it's lower levels of bleeding risk that is increased.

A few other things about gastrointestinal side effects, you can read about on this slide. One I want to really call out is the fear that patients with fish allergies can't use prescription Omega-3 fatty acid products, because they're from fish. Now, interestingly enough, most people when they have an allergy to a food, it's from a protein, not from not from an oil, or not from an amino acid. So based on this AHA statement, they actually stated that the prescription products are highly purified, to the point where fish allergies should not preclude use. There may be caution that is applied, but we – we should feel comfortable that our expert recommendation is that patients with a seafood allergy don't have to avoid the use of prescription Omega-3 fatty acids.

I do wanna talk about the difference between supplements and prescription products. We've heard a lot about it already. And I can go ver – yeah, I can probably talk about this for an hour. I can get very bullish about it, but over-the-counter fish oil supplements are not drugs. They are not approved by the FDA to treat diseases. They are really dietary supplements. They are endorsed, or labeled – quote, "labeled" – to support a physiologic function, whether that's brain function, weight, vision, and we see the lot of ninet – lot of Americans –

19 million – are taking a daily fish oil, which is about 8% of the U.S. population are taking a fish oil supplement. So this has a high uptake from the public.

There's been a recent publication from Dan Hillman, just a couple years ago, and he looked at actually crude fish oil, and other prescription products for Omega-3 fatty acids. And if you look at crude fish oil, which is the pie graph on the left, this is basically what you get if you crush fish, and just extract the oil. You'll actually have about 30%, up to 50%, depending on which, I guess, which supplement you use. Eight – the 18 and 12 add up to 30 – that's the good stuff, I call it – the EPA and the DHA that lowers triglycerides, where 70% is really just other oils. And we see if we break it apart, a lot of 'em are undisclosed oils from the crude extraction of fish oil. And I'll go a little bit further, 'cause some of them have saturated fat, and actually, I – I give you – I'll give you a visual that actually highlights that. You look at the prescription products – we have the mixed EPA and DHA product, which is mostly EPA and DHA. Only 6% of that product actually is – are other oils. They may be Omega-3s, just haven't been clearly identified. But with icosapent ethyl, it purely is 100% EPA.

So, if you also dive deeper into over-the-counter fish oils, you'll see that approximately 36% – just based on looking at average fish oil products, which are the supplements, over the counter, is saturated fat. And we can see that based in the visual on the right, where the dietary supplement is a solid fat at room temperature. When you open it out of the capsule – you can do that and you can observe that, and the only kind of fats that are solids are trans fats or saturated fats. So these have been identified as being saturated fat, where the prescription Omega-3 fatty acid actually is purified. It doesn't solidify, which endorses that it is actually purified forms of crude fish oil.

A few things that I like to bring up when patients, or some providers say, oh, if my patient can't afford a prescription Omega-3 fatty acids, just use fish oil, just use a higher amount. You know, you have to use a higher amount to get the good stuff. Just recognize that the FDA does not endorse these drugs – these products as drugs. They are considered a medical food, and there's not that required FDA oversight or the te – the rigorous testing. It is true that some supplement companies do internal testing to look fo – a – a – good manufacturing processes to see that they have what they say they have in them. But even under the best of situations, they are not considered a drug, and they are not approved to treat a medical indication.

I do think, also, just sort of wrapping things up a bit that a – some of the domains of a clinical pharmacist is to do that monitoring, and something that gets forgotten is that it's not an aim and shoot approach with lipid management, even if we get to im – a – Omega-3 fatty acid products, or statin therapy, is that our guidelines are very staunch that whenever you start a drug, or you modify a dose of a drug, to check your response in 4-12 weeks. And once you've achieved your therapic outcome, to not call it a day, but to repeat that assessment every 3-12 months. That is a way that you may actually assess adherence in your patient, using objective data, rather than asking open-ended questions and looking at refill histories.

Some counseling tips, I guess, that I like to advocate for, is that over-the-counter prescription medications are not equal to – excuse me. Prescription medications, being Omega-3 fatty acids, are not equal to the over-the-counter fish oil capsules. They are different products. We're looking at medical food versus a real drug. For some patients that need to actually use over-the-counter quote, "fish oils" to get triglyceride-lowering, they would have to use a large amount of capsules to get to that five – that four grams a day to reduce triglycerides significantly.

Another thing that I guess patients are not aware of, or they are aware of and they think of it the wrong way, is the fish eructions that occur with, fish oils. That really is because of the crude oil. So, the over-the-counter fish oil supplements – some patients may have the fish burps – the fish eructions, where the prescription products are purified, and there's no need to freeze them, like we might do with over-the-counter fish oils. But that highlights also, to me, that there's a big difference between a prescription product and an over-the-counter fish oil.

And lastly, when you see a yellow fish oil, that means it's been oxidized. We d – usually don't like oxidizing the medicines or the foods that we ingest. When you look at something that is a clear fish oil, that means there is not that oxidation, and the only product that is clear is the icosapent ethyl.

The last slide I have for you is sort of the bane of my existence, which is brand name drugs sometimes are not always easily approved by insurance companies, and they require prior authorizations. This is something that can be extremely frustrating. I have a personal philosophy that y – if your documentation is clear and comprehensive, and you actually attack all the criteria that are recommended to – for approval, that you have a good chance of being approved, which means that you're actually asking for a drug that is in line with the criteria that's outlined by your insurance company. But I'll tell you this, I have many instances where patients meet criteria, and it's rejected with the first submission, and I think that happens sometimes as a gut reaction. Sometimes people that make decisions, on the other end of these prior authorizations, may not be fully medically trained so with that in mind, I always say, if your patient needs the medicine and they fit the criteria and it gets rejected, submit again. Ask for a peer-to-peer assessment, so don't give up once after one submission because I think persistence may pay off here, if the medication is indicated for your patient.

And with that, I thank you for your attention, and I'll join the faculty discussion.

Dr. Ballantyne:
Thank you. (applause)

Dr. Ballantyne:
Couple of really key points in here. Maybe we get up to the first one. There's a lot of misperception, Karol, about the 2013 guidelines. They focused on statins, but that's – let me set the record straight – there was never that you don't have to check lipids afterwards, right?

Dr. Watson:
Nnnot ever. It says in about five different places, check at four weeks, and – and every four to eight weeks thereafter, until you're confident that the levels you expect to have been achieved are achieved, and to ensure adherence.

Dr. Ballantyne:
So we – in all of the guidelines, in 2013, 2018 – in fact, if it is a 1A recommendation, is that you must repeat a lipid panel after you've started therapy, to assess the efficacy of your treatment. And then, it should be also done yearly, because as was pointed out, adherence is probably the biggest challenge in prevention. How do you know if someone's taking their medication, if you don't check their lipids? I mean, you know, it – we obviously always check blood pressure to make sure someone's taking their blood pressure medicine. And for their diabetes mekins – medicines, we check hemoglobin A1C. So, if someone is on lipid-lowering therapy, you really cannot be doing your job unless you measure it afterwards. So that's the first point you very both, you know? Number one, you gotta check it.

Now there was some wording, in terms of the prior authorization. You did mention some magical words Greg, you just – I think this – this wording of maximally tolerated statin, right? What e – what exactly does that mean.

Dr. Pokrywka:
Yeah, it – it's – it's defined by the – by the patient and the physician together. So there's some patients, their maximally tolerated statin is gonna be 80 milligrams of atorvastatin. Other patients, it's gonna be no milligrams of atorvastatin. So it – it's really defined by that physician/patient interaction.

Dr. Ballantyne:
Yeah, but those are the – you know, the issue that comes up is maximally tolerated statin. And then you – if you've got that lipid panel that you checked, that's within a month, you've said that – and then you can point out the patient continues to have, you know, LDL above threshold, or their triglycerides are elevated. But this is the number one reason why they're x'd. You know, the other thing you mentioned, though, was also in terms of – the indication in terms of disease status, so you – just clarify – in terms of which – what is the indication if you're gonna use either a PCSK9, or bempedoic acid – but also, what is it for icosapent ethyl? Does anyone – who wants to take that one?

Dr. Saseen:
Yeah, I mean, I think when you look at some of the indications for the PCSK9 inhibitors, bempedoic acid, or even inclisiran, they have sort of a core indication for two big populations – for clinical ASCVD, or for patients with severe primary hypercholesterolemia, which is basically an LDL of 190 or higher at baseline. So those populations, but they – they both have the language, after maximally tolerated statin therapy. Sometimes they'll say full statin therapy, uwhen you need additional LDL-lowering, despite that. So I think they're sorta lining up with what you're saying, and they're carving out those two populations. There are some other nuances of – of how you might use, you know, the PCSK9 inhibitors. There's some language that people maybe interpret that you don't have to have those two indications, but really is those core two indications, with statin therapy. And – and if you think that's – that's pretty logical, because I almost think that – the analogy I have is with diabetes. Type 2 diabetes, and metformin. Every major outcomes trial has used metformin as sort of the foundation, right? And that's the same story with statin therapy.

Dr. Ballantyne:
So – and so now, what about icosapent ethyl? Where does that stand?

Dr. Saseen:
Ico – yeah. Icosapent ethyl, I mean, the way that I read it, is a different – two different populations, 'cause it's really diabetes or clinical ASCVD. We don't talk about the very high LDL pa – population there, so clinical ASCVD or diabetes.

But on top of that, if – if – I'm really a believer of following the data, and we have a prior auth criteria for state Medicaid in Colorado, and I was wai – I was asked, you know, what's the criteria B? I went to the REDUCE-IT study, and we used the inclusion/exclusion criteria.

So, those two diseases, while on statin therapy…

Dr. Ballantyne:
Right.

Dr. Saseen:
…to get an LDL between 41 and 100. That's what the study said.

Dr. Ballantyne:
Right.

Dr. Saseen:
For patients with triglycerides, we made a little compromise here and said 150 or higher, where the study actually went down to 135, because of plus or minus 10%. But I think it re – it implies treat the LDL first, right? In those high-risk populations, you gotta get the LDL managed. I personally, you know, don't love having patients with clinical ASCVD at the high end of the LDL range. I really would prefer that it'd be to – to the lower end of – maybe 41-70 would make me happier, than being at 70-100.

Dr. Ballantyne:
So that same language, you can say patients on maximally tolerated statin therapy has ASCVD, or could be has diabetes, and has persistent elevation of triglycerides, and th – that's the magical words for this. And so, it – you know, it's – is it frustrating? Yes, it's all frustrating, 'cause it gets rejected sometimes, but we have seen that with the persistence – of course, we're a lipid clinic that – that I work in, and so – and we've got some really good help in terms of someone who will bird-dog the prior auths when they come back. But we've had – we get very high success rates. You know, Greg, here's the other one that comes up. And so, this is – what do you do if someone's got a calcium score of 800? Hasn't had an event yet. How do you – do you call that patient that they've got significant…

Dr. Pokrywka:
Yeah, I – I was just gonna clarify because – because I think we need to expand on that, what the definition of the ASCVD is. So, significant subclinical ASCVD – you know, you – you can rank that by percentile, based upon a patient's age, you could look at the – at the MESA score, you could – I – I think the wording, and somebody correct me if I'm wrong, the European guidelines, s – which are a little bit of a step ahead of us in America; they're more current – say that if you have substantial subclinical atherosclerosis, you should be treated as if you've already had an event. So the same targets, the same thresholds, etc. That's my reading of it.

Dr. Ballantyne:
Well, it's been interesting. It goes, you know.

Dr. Watson:
It's deba – I think it's a – people debate back and forth…

Dr. Pokrywka:
Right.

Dr. Watson:
…about what is meant, and I don't think you're wrong, because if you have a big calcium burden, that's atherosclerosis, so…

Dr. Ballantyne:
So it's – it's – there – there's gonna be a new ACC pathway that'll focus a bit more on this, in terms of, you know, what do you do with calcium scores, in terms of some of our therapies?

Dr. Pokrywka:
What's the timeline on that, Christie? I mean, you say there's gonna be – you mean it's – it's…

Dr. Ballantyne:
I think it's gonna be…

Dr. Pokrywka:
Soon, or?

Dr. Ballantyne:
Yeah, maybe May? Might – might be the end of April. But whether it'll be…

Dr. Pokrywka:
This year?

Dr. Ballantyne:
This year, yeah.

Dr. Pokrywka:
Oh. Okay.

Dr. Ballantyne:
I'm an author on it, so…

Dr. Saseen:
It's a coronary calcium?

Dr. Ballantyne:
No, no. It's about – it's about – it's the update of the basically non-statin. It'll include some thoughts on inclisiran and bempedoic acid, but…

Dr. Saseen:
And that – that's actually be – yeah, it's been, it was up for public comment, I believe, right?

Dr. Ballantyne:
It's out – it's been out two months…

Dr. Saseen:
And I think that window closed for the comments, so…

Dr. Ballantyne:
Yes. Yeah. So I think there was 400 comments. (laughter)

Dr. Pokrywka:
Wow.

Dr. Ballantyne:
That's being worked on. Well you know, there's something that you brought up. I don't know, it – anybody getting any genetic testing? But you know that – we talk about precision medicine, and we've done a couple projects where we're doing a – you know, polygenic risk wars and then sequencing lots of genes. But the other part that comes up is pharmacogenomics. And one of the ones that came up right now is we – we're – we're doing well with – we're doing whole genome sequencing, in very large project in south Texas, but this is a challenge 'cause now you're generating – there may be somewhat uncommon variance, but they're pretty important for some drugs. So this is the difficulty, you know, if you don't have a integrated health care system, we've recommended, you know, that basically, you know, if I see a patient and they're on 12 drugs, and then I get this testing 'cause I'm interested about cardiovascular disease, but they're on antidepressants, and many other drugs, and something comes back which is interacting with one of those agents, I don't know that the physicians – I mean, the same thing for those of you who are, you know, very frequently you're seeing patients, but they're followed by other pa – physicians. It's really hard for us to start changing drugs that we didn't write and getting in the middle of that. So I don't know how this is gonna work out unless you're part of a system where you've got a clinical PharmD who's gonna specialize in some of this information in terms of they would – they'd be the one that would be contacting the physicians and the patients. What are your thoughts on this? I mean, have you thought about it? Is this coming up with your…

Dr. Saseen:
Yeah. This is something we have – so at the University of Colorado, we have personalized medicine clinic, we have two pharmacists – two clinical pharmacists that work in that space.

Dr. Ballantyne:
Yeah.

Dr. Saseen:
I – I started off by saying pharmacogenomics is evolving, and I think it has evolved. I do – I – and I – I don't wanna say it's ready for prime time in every patient.

Dr. Ballantyne:
Right.

Dr. Saseen:

However, I think that we're gonna – we are seeing patients already have their genome types, and they know exactly, you know, if they have this – this allele, if they have a mutation in their LDL receptor or a PCSK9 mutant mutation…

Dr. Ballantyne:
Right.

Dr. Saseen:
…also. I think though, that pharmacogenomic testing may be very helpful in patients that have I guess, a history of multiple intolerances, or – or maybe they have, you know, you see that list of – you've been on five different statins and you have side effects to all of them. Maybe they have some genetic make-up that is making them predisposed to that. There are other patients that have a lack of response, despite proven adherence.

Dr. Ballantyne:
Yeah…

Dr. Saseen:
That maybe they have a genetic mutation that would guide therapy in one way or another. I think – I think it still is evolving.

Dr. Ballantyne:
So for cardiovascular, the only two that we're really look – this SLB1 was… But it's really for simvastatin, which we don't use much anymore.

Dr. Saseen:
It's for simvastatin. SBL1…

Dr. Pokrywka:
Right.

Dr. Ballantyne:
And the – and the other one was, you know, warfarin.

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
Which we don't use that much anymore either because of the – the – now I still use sometimes, though, but – and then, and then – so it's interesting…

Dr. Saseen:
And I think in – I think, yeah, in cardiology, you're right. Oncology and – and psychiatric illness that's – there's a little bit more…

Dr. Ballantyne:
But there is – well, then there's some things…

Dr. Saseen:
…useful information, I think.

Dr. Ballantyne:
…there was, you know, not in – G6BD to patients. There's a few other ones that are in there that are – that are, I think, as you get broader. But it's an interesting area – you know, most of this do – unfortunately and th – this will need to change. Even though when we're in health care systems, we don't always have PharmD's well-integrated, except in – you know, the transplant team tends to have that, or sometimes critical care, but it's not necessarily in the – in the general cardiology practice, or internal medicine practice, where you have this ability. But I do think it's gonna be a bigger role in the future, as we get into precision medicine, 'cause if there are people who have somewhat unusual variants that might make a big impact on certain drugs, and rather than having a side effect, you could alert them. Well…

Dr. Saseen:
Yeah, a – and as far as the clinical pharmacist, too, it – it – some institutions are like that, where they're all in the specialty clinics. At the Univ – in Colorado, it seems, we have more clinical pharmacists in primary care than we do in some of the specialty areas, because of the…

Dr. Pokrywka:

Wow.

Dr. Saseen:
…paucity of primary care providers, to do some of the chronic disease state titration.

Dr. Ballantyne:
Okay. Alright, so we're gonna go through some patients, and so we're gonna go back here. I think you had already started with this case, right…

Dr. Pokrywka:
Right.

Dr. Ballantyne:
…Greg? And we were talking about his yearly heart attack risk for this person. So let's go back – remember, take this slide back here. Can you go back one slide? I'm not – it's not working for some reason. So, PAD, right fem pop, 60 years old, hypertension, 29 BMI, smoker with a – had pretty bad lipid profile. But basically, you – this – this – remember, polyvascular – very high risk patient population. And the annual risk – annual risk, about 5% for this.

Dr. Pokrywka:
Wow.

Dr. Ballantyne:
So the – I think the lipids was a 170 LDL, 280 triglyceride, HDL of 34, non-HDL of 226. And I – I – I – you know, we had started out – what was our first thing that we were gonna do with this person? For the audience, if you see this profile, what's the first lipid agent you're gonna put them on? (pause)

Dr. Watson:
I heard someone say it.

Dr. Saseen:
I hears someone say it too.

Dr. Ballantyne:
High intensity statin. That…

Dr. Watson:
I heard it. Someone said it over there, right?

Dr. Ballantyne:
Okay. Alright. So that's exactly right. High intensity statin. Why? Well, this was discussed. You know, we – this person's got an LDL of 170. If you could reduce it 50%, that's almost 80 milligrams, so that would be a – quite a nice risk reduction. This was already discussed.

In terms of you know, so you talked about this. Just – there's just two statins to remember for high intensity. Atorv and resuva. Both generic agents. Both relatively inexpensive. With a – and, you mentioned this issue of the diabetes risk, which is actually very low, if you look at it. And those patients who had impaired fasting glucose, with a slight increase – what happened in terms of their events? Did it go up or were they still – had benefit?

Dr. Watson:
Had a ton of benefit.

Dr. Ballantyne:
They had a ton of benefit, right? So, the – just because there's a little increase in the number, I mean, you know, it – 124-128 now, you have diabetes, right.

Dr. Watson:
Statins don't cause diabetes. They unmask your diabetes. You're sitting there teetering right on the edge. You tip over, but you were gonna get it anyhow, whether you started your statin or not. But now you're on a lifesaving drug, in addition.

Dr. Saseen:
Yeah, and that's a really good point, because the people that get the new onset diabetes are not people that have no risk factors for diabetes.

Dr. Pokrywka:
Right.

Dr. Watson:
They're teetering…

Dr. Pokrywka:
There's always people that are on that brink, right?

Dr. Pokrywka:
I've never heard that phrase – unmasked. That's really useful, because I get at least one patient a week, says I don't wanna take these statins, because I heard they cause diabetes.

Dr. Ballantyne:
So – so…

Dr. Pokrywka:
Unmasked – that's a great…

Dr. Ballantyne:
What I use is this is a time to point out to the patient that, listen, yes there is a slight risk for this. Now, statin's gonna be done to do what? Reduce heart attack and stroke, reduce your LDL. See, but we also know that, you know, these are people, particularly who are at risk for prediabetes, that if you were to walk, at least 30 minutes, five or six times a week, lose five to seven percent of body weight, we saw on the DPP program, you – the – what was the impact on new onset diabetes? A reduction? By almost two-thirds, right?

Dr. Pokrywka:
Yeah. Like 70%.

Dr. Ballantyne:
So, you know, and I think – what I've seen is when people are told that, they say, well I could do that. A 70% reduction in diabetes, 'cause the two things you're worried about – you don't wanna have heart disease, you don't wanna get diabetes either for it. So, and the – and this is really – in terms of exercise, if the – the people who did more and lost more weight, had a greater reduction in the onset of diabetes. Okay, so, the – the – he got treated with a high intensity statin, got exactly a 50% LDL reduction. So that's gonna be a nice, you know, capillary reduction in terms of MACE. Triglycerides did go down some. They're at 238. So, what do we do now in this? His LDLs – Karol, do you like his LDL, or you still would like to get that lower?

Dr. Watson:
Do I like which LDL? The 85?

Dr. Ballantyne:
The 85 – the second one.

Dr. Watson:
I – I hate the first one. I don't really like the second one. I'd rather it be much lower.

Dr. Ballantyne:
Okay. Anybody disagree with that? So it's – it's good. It – we've made progress, but…

Dr. Watson:
It's not good, it's…

Dr. Ballantyne:
We're not – we're not – what I'm saying is…

Dr. Pokrywka:
It's better.

Dr. Ballantyne:
It's good that we made progress.

Dr. Saseen:
And it's good that he's got – this man's probably taking his statin.

Dr. Ballantyne:
He's taking his statin, because he didn't…

Dr. Pokrywka:
He's still above the threshold.

Dr. Ballantyne:
…it didn't go down 50%, but he's still above that. So, in this case, the discussion was about options for it, and in terms of that, to get a little further reduction here, there with the addition of an inexpensive generic agent, ezetimibe. That's also mentioned in the guideline. In terms of cost, it's a reasonable choice. And he got further reduction. He's at 72. So, you know, that gave him some – some – some further benefit. Now you mentioned this bridging point. in terms of what are we gonna go here, now, he's got an LDL of 72, it's got a triglyceride of 214. And so, you know, I think, Greg, you'd – you talked about this, and Karol – I'll – I like to talk about this. What are your thoughts right now, in terms of this particular patient? Yeah.

Dr. Pokrywka:
Well, you know, we – we believe that if we lower the LDL cholesterol further, that we're gonna get more reduction in clinical events. So we have evidence to support that. But we really know (laughs) without a doubt, from the REDUCE-IT trial, that we're gonna get very significant reductions if we add IPE to this patient. So that's where I – that's what I would go with.

Dr. Ballantyne:
So, two – two approaches on this one, Karol, what are your thoughts?

Dr. Watson:
I mean, I would do both.

Dr. Pokrywka:
Right.

Dr. Watson:
I – I would like to think…

Dr. Pokrywka:
But you're forced to do one. I mean, maybe that's the intellectual question.

Dr. Watson:
I would fight…I'm joking.

(laughter)

Dr. Saseen:
That's the intellectual question here. Or maybe that's where you – you use shared decision making, right? We have two proven options. We can go down the triglyceride route with an oral medicine, or we can use a PCSK9 monoclonal antibody to go with the proven drugs and – and there's pros and cons to both, right?

Dr. Ballantyne:
Yeah, feel free, if you have any questions, to – someone watch with a microphone. Yeah. There's a – there's a question over here.

Audience voice:
Yes, is it important to take (1:54:06)

Dr. Watson:
So – oh, okay. So I always make sure my patients understand, there's drugs that are meant to make you feel better, and there's drugs meant to make you live longer and prevent bad stuff from happening. And I let 'em know their statin is meant to prevent bad stuff from happening, and hopefully they can live longer. But it may give 'em muscle aches. And CoQ10 may help them feel better. There's a bunch of small studies, none of which showed benefits, but when – and metanalysis, when you put 'em all together, it showed a little bit of benefit, in terms of muscle aches and pains. So I tell them, this a feel drug – feel better drug. It's safe. You take it if it makes you feel better. You get to decide.

Dr. Saseen:
Yeah, and I agree with that approach, in – in that I don't – I don't believe it really works all that well. I don't think it hurts, though. So if it's what keeps…

Dr. Watson:
But if they think it works, it's…

Dr. Saseen:
Yeah, if it's what keeps them on a drug, it…

Dr. Pokrywka:
If it improves the patient's adherence.

Dr. Saseen:
So, yeah.

Audience voice:
Do you have to use it, though? You don't – it's not a standard of care, and it's not recommended to…

Dr. Ballantyne:
You mentioned the nocebo effect – but don't forget there's also – just the way it's harmful, there's a beneficial placebo effect, that's also very strong, so, you know, whether it's the CoQ10, or just the thought of taking the CoQ10, I've had patients feel better on CoQ10.

Dr. Watson:
I have a lot of patients who feel better on CoQ10.

Dr. Ballantyne:
Yeah. So if they do it, that means if they take their statin, I'm happy with that.

Dr. Watson:
Totally happy.

Dr. Ballantyne:
Now, one thing I would recommend though, is that, you know, we – we just finished telling somebody we're gonna put you on a statin. I want you to start walking at least 30 minutes, five or six days a week. I want you to start exercising. I want you to lose weight. How many of you exercise? Let's see a show of hands. Okay, and how many ever get sore after you exercise? All the same hands going up. Gee, how is that? You know…

Dr. Watson:
I – I can tell you, the minute you give a preventive therapy to some of your patients, that's the second they start plotting how to get off of it. And that means they're gonna go out and start jogging, they're gonna go on a low-fat diet, they're gonna do all these things, any of which can cause some side effects.

Dr. Ballantyne:
So – so, it's great that you're exercising, but it's an interesting thing that does come up, is so I have a very bad family history for diabetes and heart disease, and then also I got lymphoma many years ago, and I asked the oncologist, what might help get a recurrence – I don't know why I got it in the first place. He said, the people who exercise a lot seem to have a better immune system.

So I thought, well I'm gonna really get after it. So I do a lot of exercise. That's – I try to get seven to ten hours a week, and not 30 minutes, five or six days a week. And I get a lot of soreness, but one thing that does come up, I notice, is that, you know, people – you have to warm up and then stretching. So the whole issue – the concept of stretching – it – it's very important. You know, most of the people that we're treating are not 20 and 25 years old. They're getting older, and as you get older, you have more stiffness and musculoskeletal – so, this whole issue of – of a intelligent workout, where you have a warmup, you do intensity, and then also there's some warm-down, and particularly some stretching, flexibility, balance for those things. Okay. So, what are the options here? Let's kinda go through this. Do we need more LDL lowering? So, one thought would be PCSK9 inhibitor. So, here's adding a PCSK9 inhibitor – get down to 29. And that would reduce L – another, you know, we drop the – a little bit for the reduction in MACE. You mentioned, though, another option, and this was the option of the LDL pathway or the triglyceride pathway. And what would that end up doing here? You mentioned it, about a, you know 26% reduction in MACE might be seen by adding the – the – this, adding EPA. So it's – it's – it's – there's – that's in that pathway, where we can go and Karol, you mentioned doing both. That's another option for it. But it is something, and dis – one of the things that does come up, I think that's really important, is this concept of shared decision making. So, you know, it's a little different. If someone's having – you know, unstable angina, or particularly if they're having a STEMI, you know, there's not a whole lot of – there is not much shared decision making. They're just gonna go on the lab, and you're gonna open that up.

When someone has to take a medication, really, in – for the rest of their life, usually there is a different process here in terms of, you

know, what's going on. And they're not having any symptoms. They're not in that same urgent and feeling bad. It's not like you're treating arthritis where if you don't take your medications… So, there really has to be this decision process, and this is, I think, you know, you mentioned where PharmD's play a very critical role. And unfortunately, 'cause if they don't take the medicines, they don't get any benefit, you know?

Dr. Saseen:
And if you – if you – I know shared decision making seems daunting, 'cause you have a limited amount of time. But if it's a treatment that your patient's gonna take for a long period of time, if they're not bought into it…

Dr. Pokrywka:
Right.

Dr. Saseen:
The chance of them actually being persistent with therapy, which is being adherent year after year, goes down if they're not bought into it, and sort of comfortable with it in the – from the up front.

Dr. Ballantyne:
Yeah. A – any – how do you do this (1:59:35), you got a busy practice. How do you try to do this in a – in a concise way with a patient?

Dr. Pokrywka:
I – I – well, I spend a lot of time with the patients. I – I try to really emphasize the clinical trial data as much as I can. I – I – I'd try to give them the opportunity to express why they're afraid of the medi – because there's a lot of – it seems like a lot of fear among our patients as to why they're – we talk about the diabetes issue. We talk about issue of muscle aches and pains, so I just…

Dr. Ballantyne:
Karol? Any…

Dr. Pokrywka:
…give 'em the opportunity.

Dr. Watson:
I – I – I say to everyone, I say I'm – I'm an expert in cardiology. You're an expert in you, so we have to work together and figure out what works for your life. I'm gonna tell you what the best medical evidence is. You tell me what you think about that, how it will fit in with your life, what you're willing to do.

Dr. Pokrywka:
That's great.

Dr. Ballantyne:
So it – it's, you know, I try to present really quickly. You know, it – you've got a couple of choices. Here's basically – because people wanna know, well, what's the side effect? And then also what's the benefit? So in – in a quick way…

Dr. Pokrywka:
And what's the cost?

Dr. Ballantyne:
…in a lot of people, it's interesting, is that the thing – the first thing they're worried about is what's the side effect? And – and – and we…

Dr. Pokrywka:
It's amazing.

Dr. Ballantyne:
Now, if you were gonna answer that question, PCSK9, what's the side effect?

Dr. Watson:
I say it has the same potential side effect profile as statins, but it happens about one-third as often.

Dr. Ballantyne:
And it's – you get the injection site reaction, which was in the trials – was one to – one to three percent. Usually self-limiting, not a big deal. What about icosapent ethyl? What's the side effect?

Dr. Pokrywka:

Well, we got some potential for bleeding, but mainly that's in patients that are on, other agents that can cause bleeding, as…

Dr. Ballantyne:
And the – and the reassuring part of that that I tell people is, no increase in what? They didn't have an inc – a UHMA, if they control that.

Dr. Pokrywka:
Great.

Dr. Watson:
No intravertebral – no scary bleeding.

Dr. Ballantyne:
The scary bleeding…

Dr. Watson:
It's the nuisance bleeding.

Dr. Pokrywka:
Right.

Dr. Ballantyne:
Right. And which – which, to put it in perspective, when you take an aspirin a day, you do have an increase in that.

Dr. Watson:
That's when you get the strokes.

Dr. Ballantyne:
Right. And so…

Dr. Pokrywka:
And the other potential problem with diabetes, the Afib, the…

Dr. Ballantyne:
So the Afib, which is also was usually showing up in people who at least might have had some bout of Afib before, and most – if we looked at the data – if it's – well, it was in there for it. So, those are some just discussions that are taking with the patient. Okay, and it was early benefit. Okay, we go through a case here, and we'll finish up here.

So Katherine is a 61-year-old female. She's had a history of bypass in 2003. Dyslipidemia, hypertension, Type 2 diabetes, and obesity. Lives in Houston, south like. She presented in 2014 with a abnormal coronary CT angiogram. This was many years after her bypass. More recent, left superficial femoral artery angioplasty and stent placement with good pedal pulses. She is here for the results of her nuclear stress in December. She was having some recurrent angina with exertion. She is on a number of medications. In regards to her lipids, she is taking rosuvastatin, a high intensity statin, 20 milligrams daily. She is on ezetimibe, 10 milligrams daily. She is on clopidogrel for anti-platelet. She is on metformin. She is on semaglutide, amlodipine and carvedilol for blood pressure, and on losartan, too. Three medicines for blood pressure, two medicines for lipids, and she's on two medications for diabetes, and one antiplatelet. Pretty typical. This is one reason why we have our PharmD's trying to keep straight, when they start throwing in too many medications, where you might get interactions.

Alright, how's her labs? LDL is 82, triglycerides 227, her LP(a) 118 – this is milligrams per deciliter, so that's high for a – for that assay. Her blood pressure, 134/77, BMI is 37.

Dr. Pokrywka:
Hmm.

Dr. Ballantyne:
What d'ya think? If we just – first assessment here, at this point.

Dr. Pokrywka:
Well, I don't like the LDL parameters. I mean, number one in terms of the LDL cholesterol being ele – being above the – above the threshold for action. So, every guideline says we need to do something here. And you have the LP(a), which is elevated, which points me kind of in the direction of something like evolocumab, because there's preliminary evidence that you can both lower definitely lower LDL…

Dr. Ballantyne:
Not going to answer this question right now.

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
What would be the best next step for her LDL? ‘Cause you mentioned LDL first.

Dr. Pokrywka:
I’m voting for evolocumab.

Dr. Ballantyne:
Okay. Her lipid management – yeah. (pause)

Looks like everybody’s agreeing with you.

Dr. Pokrywka:
Sorry, I didn’t realize there was a question.

Dr. Ballantyne:
Okay. Keep going. So let – let’s – let’s see, so it was added here. Let me kind of go back, just a - go back to when you first showed her…’cause we didn’t talk about a couple of other things there. Karol, what about her blood pressure?

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
137.

Dr. Watson:
Yeah, and I – well, it’s not good enough. And I also need to see her A1C.

Dr. Pokrywka:
Right.

Dr. Ballantyne:
And we don’t have an A1C here. Now, she is on semaglutide, and that’s – that’s a med – good medication in terms of cardiovascular event reduction. We don’t have her creatinine proteinuria. So there’s a few things we wanna know about her…

Dr. Watson:
She…

Dr. Ballantyne:
What’s her renal function? What’s her A1C?

Dr. Watson:
Overwhelming that her A1C is high.

Dr. Pokrywka:
Yeah.

Dr. Watson:
That’s driving her triglycerides.

Dr. Ballantyne:
Probably.

Dr. Saseen:
With her triglycerides, yeah.

Dr. Pokrywka:
She is very overweight, and increasing the semaglutide would help…

Dr. Ballantyne:
And then BMI was 37. Now she being treated with an agent that helps with weight loss. Alright, so… Evolocumab was added. And they listened to Greg, and so about her triglyceride levels now? We're still concerned. And let's go to the next slide. What would be an appropriate next step to manage her mixed dyslipidemia – fenofibrate? I guess that would be fenofibric acid at 120 milligrams daily. Icosapent ethyl 2 grams, twice daily. Omega-3 acid ethyl esters,4 grams daily, or a fish oil supplement, 1,000 milligrams daily.

Looks like – looks like our audience was listening here.

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
With such clear presentation for it. Okay. So, yes. The other ones that were on there, unfortunately, the fibrates on top of statins, but we didn't get benefit. There's one trial ongoing, but we didn't see positive results overall in this study. A subgroup showed some trends, who had high TGs, low HDL.

Dr. Watson:
Well, studies also showed that for women, that combination was worse than…

Dr. Ballantyne:
Yeah.

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
And – and – and it – it's one that you know, we'll have another trial coming out, but I think you have to go with a – the data that there's been a couple of trials, and we just have not shown benefits of that combination therapy. Alright. So, icosapent ethyl was added here. And what we end up seeing is the – in follow-up, the triglycerides are 112. Now, as mentioned, it's probably not so much the triglyceride level afterwards, the – but it – she did have a drop on this with it. Okay. Looks like she's been working a little bit more. Her BMI went down to 36, so she got…

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
…lost a little bit more weight. Her blood pressure has improved, some so that's also a little bit better here. Okay. Well, listen, I – I think we've gone through a lot, and what I would like to do now. We have any questions from the audience? Yes. Microphone – we have a couple questions. Let's do some questions now.

Audience voice:
In your patients, do you have – do you ever do these serial, follow-up coronary artery angiograms, to see any go – any regression in the plaque formation?

Dr. Watson:
No.

Dr. Ballantyne:
So, that's – that's a really good question. You know, with the advent, I don't get serial coronary angiography although – 'cause I know – you mentioned CT surgery at Baylor, and I know our back in the day, that used to get cath every year, to check the graphs and everything else. So we don't – we don't do that. Now, with CTA as a noninvasive test, it's expensive. I don't do it, and it's not reimbursed right now, unless you have symptoms of angina.

Dr. Watson:
Yes. And it's the only indication. It's only actually been shown to be predictive if you have symptoms.

Dr. Ballantyne:
Right. So it's – it's used if you have symptoms. As a research question, you're asking a great question, and there'll be studies that'll be setting up right now, but it's kind of beyond where we have any evidence, and that they're very expensive, you know, if you – I remember the first time, so one of my patients, we were ordering a – just a calcium score, and, you know, they ended up getting a CTA somehow with a $3,000 bill. And so there was a lot of upset about that.

Dr. Watson:
And – and the other thing is, we are interested in plaque stabilization, and you can't really see that on the angiogram. You don't know which plaques are vulnerable and stable, so…

Dr. Ballantyne:
Yeah.

Dr. Pokrywka:
Right.

Dr. Ballantyne:
CTA may actually be better for the angiograms for that is…

Dr. Watson:
Probably.

Dr. Ballantyne:
It's not my aspect, but it – it's still we're not quite there yet. So it's a great question. I think in the future, maybe we'll be there, but we…

Audience voice:
It's really relatively simple. The – the angiogram, now they do it through your wrist, so it's not a big deal…

Dr. Ballantyne:
Yeah, you know, it – but, what you get is the luminogram, and so, we – we've done this before. We – I – we did – we did a large trial of beta called the LCAS study. And it was 429 patients, and we looked over two and a half years at over 1,300 lesions. Guess what the median change was? Of a – of a – of a lesion? Zero. That's in the placebo group, too. So what ends up – you know, it's not that it's not an – bad test, it just hasn't been ever shown doing – you know, frequent caths to improve any outcome in the patients.

Dr. Saseen:
Except that – it's – it's more of a research study right now.

Dr. Ballantyne:
And as mentioned, we – you really just see stabilization, not regression, for the most part. You see small changes. There is a question over here. I think we had another question, yeah.

Audience voice:
I've had a few cases where I had a patient on the pure EPA, and then I got a kickback from the insurance company saying, well they – their approved drug is the combination EPA/DHA, and so what – what do you say that in your appeal to try to get that covered?

Dr. Ballantyne:
That's – so that's a great question. The question was, he's had patients where he wrote pure – for pure EPA, and the insurance company kicked it back using basically the generic for EPA/DHA. Do you wanna start with that? You talked about…

Dr. Saseen:
I think – I – I would – I would assume if that's evidence-based, as a reasonable option it would only be for people with triglycerides of 500 or greater. There's no reason that – and there's no evidence that would support an interchange of EPA only with mixed EPA and DHA, for the cardiovascular indication with triglycerides between 150 and 499. Ma – sometimes I – sometimes criteria is written that way, and who interprets it is a technician, who may not actually get things correct. So that's why I think it's reasonable to push back. So that would be an incidence where, if it were triglycerides of 500 or greater, then, I can see why that might occur.

Dr. Ballantyne:
So I think that would be… Yeah, go ahead.

Dr. Watson:
I'm sorry. I – I'm – this is my dot phrase, that I put into EPIC: "In closing, let me add this. This is a life-sustaining intervention and you are directly interfering with the health and wellbeing of my patient. Thank you very much." So that's a little fill-in which I put in my prior auth…

Dr. Pokrywka:
I have something very similar. (laughter)

Dr. Ballantyne:

You know, and I – I – I…

Dr. Watson:
Good job, right?

Dr. Ballantyne:
The other one is the clarification is that this is being prescribed not to lower triglycerides, it's being prescribed for cardiovascular event reduction, which is only indicated for EPA. So I think that kind of language, and then with that final conclusion, that Karol put in there…

Dr. Watson:
I'll send you my doc. (laughs)

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
Yeah, so it is – it is the issue of if it's for very high triglycerides, then you're having a losing argument. And I've got people where, you know, they've had very high triglycerides. They don't have (2:12:48) or diabetes. And they've got to switch. I don't have an argument. In fact, the EPA/DHA is effective for that, but usually, it's – if it's, you know, the indication we're talking about, you're the one with all the signs and all the data, and it's just a matter of coming back at 'em hard. Yes, question over here?

Audience voice:
Have you looked into how EPA, here affects inflammatory markers like C-reactive protein, and have you looked at other inflammatory markers at all in these studies – myeloperoxidase, is that something you check, or other – other markers?

Dr. Ballantyne:
So, it's been looked at and I think – Greg, you showed a slide on this.

Dr. Pokrywka:
Yeah, we did – I don't think we showed the differential effects of EPA and DHA, but I believe EPA is better at lowering hsCRP, and – and I look at – anecdotally, I see a lot of drops in Lp-PLA2, and I think there's data showing that. But in terms of reducing oxidation of lipoproteins they've done head-to-head studies with EPA versus fibrates and niacin, for example, and the EPA is far superior, and had that…

Dr. Ballantyne:
And there was some data published – on lipid studies they were doing an anchor, which I was involved with, in the MARINE study. But basically, there was – looking at Lp-PLA2 and some other inflammatory markers. There was a placebo subtracted difference in those studies. I think there was another question at this table, too. Or was there not? Yes, another question over here.

Audience voice:
A lot of my cardiology friends, they have (inaudible, 2:14:30)

Dr. Ballantyne:
So, that – this – let me put – this clarif – for clarification, where – you know, we – we always use the generic, but you wanna just clarify the question on that?

Dr. Pokrywka:
I'm not sure that I heard the question.

Dr. Ballantyne:
Is cardiology using the Vascepa?

Dr. Watson:
What – which is…

Dr. Ballantyne:
Which is the…

Dr. Watson:
Icosapent ethyl.

Dr. Ballantyne:

Yeah, that is...

Dr. Pokrywka:
Right.

Dr. Ballantyne:
Icosapent ethyl.

Dr. Pokrywka:
Right.

Dr. Ballantyne:
That's pure EPA.

Dr. Pokrywka:
That is IPE.

Dr. Ballantyne:
That's IPE. When he's saying IPE, it – that they – the branded version of that, the trade name…

Dr. Pokrywka:
Right.

Dr. Ballantyne:
…of that is Vascepa.

Dr. Pokrywka:
I see what they – okay. There is a generic IPE out there, which is – does not have the same clinical indications of reduced cardiovascular events.

(audience question – inaudible, 2:15:10)

Dr. Ballantyne:
So – so krill was looked at in a study, and it didn't – basically they failed their primary endpoint. It was a – they did not lower tri – they lowered triglycerides, but the placebo group also went down. And, you know, it didn't make that…

Dr. Pokrywka:
It's also the capsules are really small. You have to take a ton of those capsules.

Dr. Ballantyne:
…Yeah, this was a – this was a – they were trying to make it pharmaceutical grade. They were gonna pursue…

Dr. Pokrywka:
Yeah.

Dr. Ballantyne:
…for it, and then the amount in the capsules is a small amount…

Dr. Pokrywka:
Yeah, there was a company that was after this.

Dr. Ballantyne:
So we don't have the evidence for krill oil. Either for being as effective for triglycerides, and there's none for event reduction. Were there any other questions? Okay, so why don't we just finish up – if each person wants to give a take-home, key point for our audience tonight.

Dr. Saseen:
Yeah, I – I mean – I – I think I'm gonna beat on the same thing that I've said before. Adherence, and it's not good enough just to have your patients be on a medicine. We have to help them. Adherence coaching to actually assure that they not only st – take their medicines regularly, but stay on them persistently, to get those long-term benefits.

And there's a lot of tools that you can use – simplifying your regimen promoting shared decision making, have your patients know the truth about their medicines – but I guess the biggest thing that you can do is look for adherence. Don't ask – don't necessarily only ask

whether patients are taking their medicines. Look at their refill pattern, if you have access in your electronic health record, to track their filling history. Those are all tools that you can use to empower your decisions.

Dr. Watson:
I would just say, we are getting more and more tools in our armamentarium to help our patients, and we should use each and every one of them, in their appropriate context. And I think this is really exciting, 'cause we've never had a therapy that lowers triglycerides, and also directly lowers events.

Dr. Pokrywka:
I would say that I would use the triglyceride level to identify the type of patient – the type of high-risk patient – who is going to benefit from being on IPE. The goal is not to lower the triglycerides. The goal is to improve the patient's health and reduce events, and that's where the triglycerides identify the type of patient, where we know from the REDUCE-IT trial that we can reduce risk dramatically, on top of a statin.

Dr. Ballantyne:
So, let me just kinda finish up the – the concept – these guidelines change all the time. They – the – it's hard to remember them all, but the concept of the intensity of therapy is related to the risk of the patient. That concept has never changed in any of the guidelines. And what has changed is we have a lot of things we can do now to address risk, as Karol mentioned. So we have new tools for the person with high LDL. We mentioned that the person who has a residual high triglyceride – they're a high-risk individual. We've got something for that, where there's got – we've got more work in the pipeline. We've got some things we didn't focus on tonight, like that last case. The person with diabetes. We've got a couple of – couple of new tools that are really effective in that area, and CKD's involved with that. Some – some – and great things for heart failure, so – and – and also inflammation is an area that's really exciting in terms of these – you know, this issue of precision medicine, or personalized medicine. It is a little more demanding that you have to look at each patient, and – and look very carefully as what's driving their risk. But it's an exciting time but I do wanna – as a final comment, is that lifestyle – so diet and exercise – is still the foundational therapy, and we could do a lot better ourselves and for our patients with that. I wanna thank everybody for coming tonight. We may have had a – a small group, but we had a great questions and great participation, that's here, and some online, so thank you very much. Don't forget to take your post-test. You'll receive an email with a link to the post-test tomorrow. And, any more slides here? I think that's our last slide. Okay, thank you very much.

Dr. Watson:
Alright, thank you.

Dr. Pokrywka:
Thank you for sharing your time with us.

(music starts)

Announcer:
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