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Adopting the New Therapeutic “Lineup” to Manage ASCVD - East

Dr. Miller:
Good day, everyone. It's really a pleasure to be here for this exciting conference this morning. I’m Mike Miller, just moving from Baltimore to Philadelphia, where I’m at the Michael Crescenz VA MC, Medical Center. And I have to say it's - this meeting is both live, as well as broadcast remotely from across - through across the country. So I think you'll - you'll get a lot of great information today. And it's the first live meeting that - that I've been to since February of 2020. So it’s good to be back and my colleagues who are with me today, I'm sure will – will - are also excited to be here.

I think it's fair to say that we are in a new era of atherosclerotic cardiovascular disease prevention, especially as it relates to lipid management. These are just some of the recent studies and guidelines that have come out over the last several years. I think we don't have too much more information between 2018, 2020. Everything has been kind of in a black hole for the last 2 years. But I think we'll get right back to it. So a lot of great information that has advanced the field.

Faculty include, both myself and Dr. Cheeley, who's a clinical pharmacist specialist in primary care at Grady Health System in Atlanta. And - and our faculty include my good coll - good friends and colleagues, Dr. Aruna Pradhan, who's associate professor of medicine at Harvard Medical School, associate physician and scientific director of the Preventive Medicine Cohorts Repository and the Division of Preventive Medicine at Brigham and Women's Hospital. And Dr. Jamie Underberg, lipidology and cardiovascular disease prevention. He's a diplomat of the American Board of Clinical Lipidology, and actually has headed that group, Clinical Assistant Professor of Medicine at NYU Medical School, and the Langone, I guess it's called NYU Langone, director of Bellevue Hospital Lipid Clinic, and past president of the National Lipid Association. And as I mentioned, president at the American Board of Clinical Lipidology.

So we have several learning objectives today. First is to apply some of the main findings of recent omega-3 ,fatty acid clinical trials as it relates to clinical practice with our objective really to reduce cardiovascular events. We’ll also apply recent clinical trial evidence of icosapent – pentanoic acid to the care of patients with established CBD who are also on statins and may pose additional risk of cardiovascular events. And finally, to identify some of the barriers to implementing some of these long-term strategies in managing many of our patients that have chronic disease.

Here is our agenda. Today we'll talk about the burden of - of heart disease. Today we'll elaborate upon atherogenic dyslipidemia. We’ll, of course, discuss the REDUCE-IT clinical trials and omega-3 fatty acids, which is near and dear to my heart since I was involved in this study. We'll discuss some of the recent evidence from the REDUCE-IT sub studies, discuss some of the biological effects of omega-3 fatty acids. Dr. Cheeley will discuss the role of the pharmacist in lipid medication access and usage. And finally, we’ll have some case discussions along with my - with my colleagues, Dr. Pradhan and Dr. Underberg. So we hope this is - will be a very instructive and a fun meeting – this - over the course of the next few hours.

And with that, let me introduce again my colleague, Dr. Jaime Underberg, who will talk about the burden of heart disease today.

Dr. Underberg:
Lots of applause. Lots of applause. Okay, good morning, everyone. We're going to start off with just a quick overview of why we're here. Why are we concerned about that beautiful, wonderful agenda that - that Dr. Miller elaborated for us. And it's because of this burden of

heart disease. But we'll start off with a polling question. After an ACS event, what percent of your patients have optimized lipid management after one year?

Okay, so we've got a really aggressive group who's convinced 100%. Super. Alright, so let's go on.

So when it comes to atherosclerosis or atherothrombosis, depending on how you want to refer to it, you know, we tend to think of the heart. And certainly, cardiovascular disease is part of this constellation of concern. But I don't want people to forget about all of the other ways that cardiovascular disease and atherosclerosis can present. And even those of us who do this all the time, can miss stuff, if you don't constantly remind yourself of it.

Recently, I had a patient in my office, and we were deciding on whether to be more aggressive about lipid management. And it just came up in discussion that she had had an event 10 years earlier that was probably a TIA that I didn't know about that she hadn't mentioned to me. And it dramatically changed the way I thought about her risk and the way we managed her.

And so again, whether it's the brain, whether it's the peripheral vasculature, whether it's the cardiovascular system, whether it's the presence of a stent, or a intervention to improve vascular flow, all of this is the type of thing that we need to consider. And - and when it comes to coronary heart disease and its prevalence in the United States, this obviously is a significant issue. I love the term massive, maybe we could use huge, I don't know.

But - but the bottom line from this graphic is to not look at the percentages, but look at the absolute values, right? We're talking millions of patients, and now this is a little older data 2011 to 2014. But - but when it comes to new and recurrent MI just in patients over the age of 35, getting close to a million. So again, this clearly remains an issue. And heart disease is the number one cause of death in the United States. Stroke is number five. And again, not trying to list all of the numbers, but pick out those that I think are significant. The estimated annual incidence of myocardial infarction is over 600,000 new attacks and 200,000 recurrent events.

And I want to really focus on those recurrent events for – for a bit because many of those recurrent events occur fairly rapidly after the first event. And we're talking about lipid management today. And lipid management, for some reason seems to be this kind of sleek, be casual, relaxed approach. We're going to follow your lipids over time, we'll add risk-reducing agents as needed. And I want to remind everyone, that's not the case. There's an urgency to managing lipids aggressively in the high-risk population. And the reason why is because things happen faster than you think. The average age of the first MRI in the U.S. for men is 65, 72 for females, 25% of these happen with no symptoms.

And despite the presence of the overwhelming cloud of COVID for the past several years, heart disease still remains the number one cause of death in the United States, actually followed by cancer death. And as we know, because of the recent pandemic, much prevention around things like cancer prevention, and of course, heart disease prevention, has fallen by the wayside as people have not followed up with routine care. I'm always amazed when I get a call from a patient and they have a question and I look back and I see I haven't seen them in two years. These are people that normally I would see every six months. And so again, I think it's important to remember that this still remains an important cause.

And globally. Again, this is not just a U.S. problem. Cardiovascular disease affects 4% of the global population, over 500 million persons, almost 18 per - 18 million people died from cardiovascular disease in 2019, representing 32% of all global deaths, 85% from MI or stroke.

Now, this is older data. It's a registry called the REACH registry. Deepak Bhatt was the primary author on this paper, who obviously was also the lead investigator in the REDUCE-IT study. And what they did here was they looked at a cohort of patients who either had atherosclerosis, cardiovascular disease, coronary artery disease, or peripheral artery disease, or patients who had risk factors. And the risk factors are the typical risk factors that we know, diabetes, hypertension, smoking, obesity, etc.

And the first thing you see is that there's a tremendous overlap between these atherosclerotic disease states; that if someone has one, they may have another, right? Peripheral vascular disease is the always the one that I think that we miss the boat on often. And I'm completely convinced that patients with peripheral vascular disease who haven't had a heart attack or stroke are actually undermanaged. Often, they don't get to the right person soon enough. And they're at very high risk for having a heart attack or a stroke.

But what they also were able to show here is that, when it comes to patients, even those with significant risk factors without a history of event, their likelihood of having an event going forward over the next 4 years, is extremely high. And this is the 4-year CV event data from REACH. And you can see that if you look at a prior ischemic event or stable atherosclerotic cardiovascular disease, the incidence of MI stroke, or death, cardiovascular death, it's not insignificant. Now, this is 4-year data. However, I mentioned earlier, the urgency of lipid management is really what's driving a lot of the things we're going to talk about today.

And when we look at real-world data, and this is very recent data, alright, you can see here looking at another cohort of patients, and

following the risk of MI stroke or cardiovascular death, following the first year, or the first year after that initial index MI, there is a significant risk early on.

And so if you think about the typical time course of what happens, someone's in the hospital, they have an event, they get sent home, follow up with your cardiologist, go back and see your internist. Well, I don't know about your institution, but at my institution, they don't make the appointment for you in the hospital, and you go online and try and make it. And if it's January, they're going to tell you it's May before you can see a patient. And so there is often a lapse in follow-up. And if someone gets discharged, say on a high-intensity statin, when's the next time they're going to have their labs done? Are they going to stay on it? Do they follow up and fill it? And it's so important to make sure that early on in its immediate time period after an event, we actually follow them.

And what's key here is that if you look at the elderly population, those here over age 74, who are at high risk one-third, one-third of these patients will have an occurrent - recurrent event within the first year after their acute coronary syndrome. One-third of the patients. So again, this is an urgent story, one that needs to be addressed in a rapid fashion.

And the last piece of the puzzle is that it's not just all about how low do you make LDL cholesterol. This is one of my favorite slides. I show it to our house staff and fellows all the time to remind them that yes, we have all these great tools now, tools that I didn't have when I was an intern and resident. And we can make the cholesterol really, really low. This is data from the FOURIER trial looking at evolocumab in patients, many of whom who actually started with LDL cholesterol levels less than 70 milligrams per deciliter when they entered the trial. And you can see here patients got to LDLs below 20 milligrams per deciliter. And if you look at LDL at 4 weeks, obviously there's a stratification of risk, right. The ones who came in with the higher LDLs did not do as well as the ones with the lower LDLs. But even if you got your LDL cholesterol level below 70, there's still a significant, what we describe residual risk. People continue to have events. And so the patient with high risk for recurrent events with well controlled LDL, still has wiggle room to be managed more aggressively.

So when you think about your patients with atherosclerotic cardiovascular disease, the first is how many of your patients actually have it? You're probably underestimating it, right? We tend to underestimate anything bad. I call it the American Express Theory, right? When your American Express bill comes in the mail or comes online now, you have in your head an idea of what it's going to be. And when you open it up, how often is it less than you think it's going to be? It's never, right? It's always more. We underestimate risk. We underestimate the severity of the disease, right? I'm not an interventional cardiologist, but my colleagues go in and do a CAT, they always find more than they were looking for.

How do your patients respond when you tell them they have ASCVD? How concerned are your patients about having an event? What level of difficulty do you have in managing these patients? And what do you need to better manage them. So these are all things that we're going to discuss today. And hopefully, by the end of the day, we'll have a better understanding of how we can utilize some of these newer tools. Thank you very much.

Dr. Pradhan:
Thank you, Jamie. That was wonderful. As always, I love your color and flavor as you inject that into your talks. My name is Aruna Pradhan, I'm a cardiologist and clinical trial assistant, and an epidemiologist at the Brigham in Boston. And what I wanted to do with you over the next 30 minutes or so is share with you the contemporary approach to risk assessment and cardiovascular disease, and then also how we integrate atherogenic dyslipidemia as an emerging concept. It hasn't really been the focus so much of our contemporary guidelines, but I think it's a time when we need to integrate more carefully.

Alright, so we are in a very exciting phase of cardiovascular medicine. We have many, many pathways that may mediate the risk that Dr. Underberg had mentioned to you. That residual risk after cholesterol lowering can be related to a number of factors that we now have therapeutics that may actually address those issues, whether it's LDL, this has been the primary target for so many years now. But we have emerging targets with regard to inflammation, thrombosis, triglycerides. We are going to talk about that quite a bit during the course of this symposium. LP little a is on the horizon. And then the diabetes risk that now is being mitigated by some of our blockbuster diabetes drugs. So it can be confusing, it can be challenging. Where do you go first? Well, certainly we need to go where the data tells us and what clinical trials have told us work in application of these various approaches.

So today, we're going to talk first about LDL, why we focus on LDL and then transition to what triglycerides tell us about these patients and mitigating their risk.

Alright, so the first thing that you do in common practice, when you see a patient, you're trying to determine what the next step is to lower that burden that Dr. Underberg told you is as an urgent matter, is to look at the guideline. And the joint guidelines from the AHA and the American College of Cardiology are probably the first place to go. It's where primary care physicians, cardiologists go when they're looking at these patients.

And so the first step is to use a risk assessment tool to assign your patient a category of risk. And the tools that are out there now, they're constantly being updated, you can access them online. And the slide shows you the links to the same calculator, both at the Heart Association and the College. You use that risk calculator to divide patients into 1 of 4 categories, less than 5% being low risk, 5 to 7.5% being borderline risk, 7.5 to 20% being intermediate risk, and greater than 20% being very high risk. And this is the 10-year projection of their risk. So it's a discrete number that resonates with patients. These risk calculators tell you what your chances over a 10-year period for developing either a non-fatal myocardial infarction, death from heart disease or stroke, so the hard cardiovascular endpoints. And they also provide you an estimate of lifetime risk. So that patients who may be low risk for the short-term 10-year period, get an assessment of what their 30-year and 40-year projected risk over their lifetime.

Now they're intended to - the number you get is intended to facilitate a patient-provider discussion about this and discuss this best strategies to reduce risk. So remember, you're in control with your patient. The number that you get back from these risk calculators provide you with an algorithm to guide which steps you might take. But it really - and the recent - most recent iterations of these guidelines really emphasize that when your patient doesn't look like they match one of these risk categories, look at other factors that may enhance risk. And we'll go through that in particular.

Just to mention that 7.5% is traditionally accepted as the threshold for initiating statin therapy. It's not a mandatory prescription. Again, these are guidelines. But that's where most would say, ‘Hey, this is where we need to add a new medication.’ Remember, it's lifelong therapy, so it's an important decision.

So for those who are in a low-risk category, don't qualify. The recommendation is to repeat risk assessment every 5 to 6 years or so for those who don't - who are in the primary prevention category.

So once you get that risk, let's see what happens when you apply the primary prevention guidelines. What else is there in these big, big documents? I want to mention that in 2018-2019, that there are a set of guidelines that came out that first introduced this concept of risk-enhancing factors. And again, the emphasis here is you're in control with your patient but look at what the calculators tell you, but then also look at other factors that may either up risk or down risk your patient.

So it's generally agreed with these guidelines that you start statin therapy as the base first-line therapy for anyone with clinical cardiovascular disease, anyone with elevated LDL cholesterol over a value of 190 milligrams per deciliter, anyone with diabetes who's between the age of 40 and 75 with an LDL that's high, over 70 for that risk - for that group. And then it's this last category, the age 40 to 75 without any of the, you know, factors I mentioned previously, where you start looking at additional clinical conditions that may, again up risk or down you. And these risk-enhancing factors I want to go through in the next couple of slides.

So first, premature history of ASCVD in a family member. So for men, that's less than 55. For women, that's less than 65. It's generally a first-degree relative. History of primary hypercholesterolemia. Metabolic syndrome, this has come in and out of favor, but it definitely is a feature that is associated with risk. What to do about the syndrome is not quite clear. Presence of chronic kidney disease, chronic inflammatory conditions. In particular ,history of chronic HIV/AIDS, psoriasis, rheumatoid arthritis all up-risk a patient. And you're applying this to that intermediate group. The less than 5%, you're not so worried about. The greater than 20%, you’ve got to do something. It says, again, that intermediate-risk group that you need to start thinking about other features in your patients in front of you that may trigger a reaction or therapeutic change.

Additional factors again, for women in particular, there's been an underappreciation of pregnancy-related and gender-specific risk factors, but two that I want to mention are a history of premature menopause. So women who've had menopause before the age of 40, strong association with future cardiovascular disease, and then ask about pregnancy-related disorders or conditions that they may have experienced a decade ago, preeclampsia, for instance. High-risk ethnic groups, in particular, those with South Asian ancestry. Also Native Americans, a very important group to be more vigilant about. Persistent primary hypertriglyceridemia. And the guidelines you should threshold of 175 milligrams per deciliter optimally measured on multiple occasions, not just a single one. And then if measured, if you really want something quantitative, you're not sure, you can do 1 of the 4 things that are listed here high-sensitivity C-reactive protein, the value over 2 milligram per deciliter, lipoproteins delay with the value shown here, both in milligrams and mil - nanomolar units, apoB levels, and then also an ankle brachial index value less than 0.9, suggesting presence of peripheral artery disease. Which is an area I think, just as Dr. Underberg mentioned, is something we don't pay attention - enough attention to.

The other thing that's been recommended and really based upon a number of prospective studies that have shown the power of coronary artery calcification to really be more specific about the event risk is the is the CAC score. So in those patients who are sort of in that intermediate borderline risk, a CAC score can again help you decide, do you initiate statins? Can you wait? A value of 0 suggests that statin therapy can be withheld or postponed. A value between 1 and 99 favor statin therapy but again, you make that decision with your patient. And then a value over 100 is a threshold where you really should be thinking about initiating statins, if you haven't - you haven't gotten to that point with a risk score alone.

The MESA score - risk score is there. It gives you a quantitation of how the risk changes with the CAC score. So it's very helpful to have that but not necessary. You can just look at these values shown here.

And then finally, a really important group of patients, it's a subgroup of patients who have prior history of cardiovascular disease, are those at very high risk. So it's beyond that - they're in that 20% risk category, but you really want to be aggressive of where you take their LDL level. The major types of events, they qualify as recent ACS, acute coronary syndrome, history of myocardial infarction, history of ischemic stroke, not hemorrhagic stroke, ischemic stroke, and then history of symptomatic peripheral artery disease. There are also a number of high-risk conditions, they're all listed here. I'm not going to go through each of these in detail. But the very high-risk ASCVD patient is the one with multiple major ASCVD events, the ones I just mentioned, or they have one event plus two of these other conditions. And what do you do with that patient? Why do you want to identify them? That's the - those are the patients that you put on a statin, ezetimibe and PCSK9 inhibition to get their LDL levels less than 70 milligrams per deciliter. So be aggressive with those patients.

Okay, well, the reason that we're here today is to tell you that there - it's not just about LDL. There are other risk markers, risk indicators that you need to be aware of. And that's because the data over the past decade first from the statin trials, on the left of this slide, tell you that whether you're using a low-intensity statin, the first trials that came out all the way to the right with rosuvastatin, atorvastatin, high-intensity statins, there's a lot you're leaving behind in terms of residual risk if you just place a patient on statin.

On the right-hand side is - are the graphs that Jamie just nicely showed you. But what I've done is I converted the risk reductions, which I find are a little difficult to convey to my patients to an absolute event rate. So these are the 3-year event rates. What can you tell your patients is going to happen in 3 years if you get you're high-risk patient, according to where you get their LDL cholesterol. So take that bottom curve, even if you get their LDL to less than 20 over 3 years, 10% of them are going to have an event. Quite high. So we need to do more and be thinking about other parameters that can modulate risk in these patients.

The other thing that I think you're going to see and hear a lot about, why we're here with you today, is that it's not just about LDL and the LDL-based strategies, ignore the other lipid parameters that may be important in mediating risk. This was - the graphic on the left was taken from a really nice paper. If you're interested more about this, it's a consensus paper led by Henry Ginsberg, which shows you the types of atherogenic lipids circulating in all of us. The ones on the top are the apoB 100 related parameters that are made in the liver. On the bottom, those that come from the intestines. And LDL is in the middle, it's there. But they're also these precursors that go through a metabolic process, eventually end up in LDL, causing disease. And also we've begun to learn these larger particles also enter the vascular space and transfer cholesterol directly into the plaque that's developing in patients who have an excess of these larger particles. So you don't measure these all the time. It's not something you're going to get back in a routine lipid profile. But the clinical hallmark of that is atherogenic dyslipidemia. That's what most of us are familiar with. This high triglycerides, low HDL, and if you measure it, small dense HDL. Most of us just look at the high triglycerides, low HDL component. And that's the patient that you'll see, and you'll be able to pick up quickly in the clinic that may have these other parameters that we need to address to mitigate risk.

It's also important, we'll talk a lot about triglycerides today, but what do triglycerides tell us? This is what you're measuring in the plasma, but it's telling you about the cholesterol content that's being contained in these lipid particles. So triglycerides are a measure of all of the lip - all the triglycerides carried by these atherogenic lipids, but these particles also carry a lot of cholesterol as well. So triglycerides, cholesterol, the two major components. In fact, in most patients, these large triglycerides contain one-third of the total cholesterol circulating in plasma. So really important to recognize that the triglyceride level is just a marker of these other lipids and a risk – a really strong risk correlate of future disease.

Now, I love this slide. Michael Miller, our chair, published this quite a while ago now, but I think it's probably one of the first slides that - first studies that have told us what we're leaving on the table if we just address LDL risk. In the PROVE IT-TIMI 2022 trial, high-intensity statins were used. If you looked at where patients got - all of these patients I'm showing you on the slide had LDL levels less than 70 milligrams per deciliter, but they're stratified, separated according to where they achieved their triglyceride levels. And you can see that even if you've got your LDL cholesterol level to less than 70, on the far left of this slide, if you're on treatment, triglyceride levels was over 150 milligrams per deciliter, you had a 16% absolute risk of having a cardiovascular event. If you've got your triglycerides down, you had a 11% risk. And for those of us who follow clinical trials, that's about a 40% risk reduction. That's massive. If we could only achieve that by driving triglycerides down, we would do a great benefit to our patients. So this started really making us think about what else can we do within clinical trials to target this problem.

We also have a lot of epidemiologic data. So we're just following patients over time. And I probably 20, 30 studies that have shown this, but I like this one, which followed a large cohort of U.S. patients, both in the Fram - in the atherosclerosis, the ARIC study and the Framingham study. And what's being shown here is the predicted risk according to their triglyceride levels. And you can see that steep part of the curve goes anywhere from 50, all the way up to 200. That's where the risk increase is steepest. There's a plateau after 200. It's still there. But it tells you inversely, if you can – any change you can make in the triglyceride level, potentially below 200, even if it's

20, 50, whatever, it's going to give you a - convert into a large risk reduction potential for your patient. So that - these are important data to recognize. But again, we haven't talked anything about clinical trials that tell us whether it's the right target or not. And we'll do that today as you hear much more about the REDUCE-IT trial.

We also have an, you know, a large body of evidence now that has told us that not only from the - if you observe patients over time, but now if you do genetic studies, and you look at, you know, people who have certain genetic determinants of triglycerides, that they're causally related. Meaning that there is a real biologic link, not only with what you're measuring in plasma, and you look over time, but a real biologic link between the mechanisms driving disease. We also know that triglyceride-rich lipoproteins promote inflammation much more than LDL cholesterol. So there's another link for you. And then we know from some basic science and animal models that remnant lipoproteins, these triglyceride-rich lipoproteins accumulate in the subendothelial space. So all lines of evidence for you that maybe not be important as you're managing your patient, but certainly give you the framework and the context from which to apply the guidelines that we'll talk about to mitigate risk.

So the pathways involved are shown again, here in a different type of graphic. It's the components of triglyceride-rich lipoproteins include not only the triglycerides, apoC, but also cholesterol. They promote inflammation. There are many pathways that can be involved. And you'll hear a lot about omega-3 fatty acids today and how they might impact this pro-inflammatory component of this nexus.

So how often will you see this problem? And you all - I wish I had a polling question here for you to ask how often you see this in clinical practice. On the left-hand side, we know at least across the country, if you take a large database like NHANES, and you look at just diabetic patients who are on a statin, one-third of those patients irrespective you know, if you've got their LDL down to 70, one-third of them is - will still have a high triglyceride level. Really important to recognize that they're not completely linked. There's – there are two pathways here. And your patients may be - whether you've gotten their LDL down or not, you cannot - you have to stay vigilant about other risk markers.

On the right-hand side is another cohort of patients with established cardiovascular disease. These patients well treated with a statin, 1 in 4 still had residual high triglycerides. So it's very prevalent, the common - the abundance of this problem requires urgency to treat.

Now, we do have some guidance. This isn't a formal guideline, but it's a consensus statement. It's contemporary, and came out in 2021, I believe. And it's from the American College of Cardiology. And really, it's because there's been a lot of ambiguity about what to do, as we recognize triglycerides as a risk factor. And it's a little complicated, but I want to walk you first through the general overview, and then perhaps some of the takeaways that may be practical for your practice.

So what the this consensus statement tells us is that you can think of these patients in 1 of 4 categories, those with a fasting triglyceride over 150 or nonfasting over 175, and less than 500, you can put them into 1 of these 4 boxes. Those with established ASCVD, so high-risk patient, those with diabetes but no ASCVD on the right top, those on the left bottom without CVD or diabetes, but again, persistent hypertriglyceridemia, and those on the right bottom with values that are extremely high, over 500. And that - you will see also in the boxes, and I like the color coding here, because I think what you'll see is that there's an LDL-based pathway for medical therapy of these high-risk patients and then a triglyceride-based pathway. And the only agent that really makes it in this triglyceride pathway at this point is icosapent ethyl, which we'll talk about the reasons for that later in this in this symposium.

So the first thing common to all of these four boxes is that you have to rule out major other secondary causes. And the fact is, these patients are not going to have a monogenic disorder, for the most part. The most common reasons for having hypertriglyceridemia are conditions, medical conditions on the left, and then medications on the right. Some of these are remedial, others you can't really fix readily, but at least you recognize and can tell your patient this is why you have the problem that you have. So if for those that you can address, address those. Not the topic of this this talk today, but certainly some of these medications could be withdrawn or substituted for other agents to help address this problem.

The second thing is to optimize diet and exercise. And it's challenging, right? But it's - this is really - it's on the patient. It's certainly on you as a physician, as a nurse practitioner, as a health professional to send the message but it's up to the patient to take it up. But it's most important as you're delivering this message, to think about what the patient can do. And remember, it's a lifelong commitment. And it needs consistent, relentless messaging from you every time you see the patient. And I know many of you will only have 5 minutes with that patient. But in the next slide, I'm going to illustrate some of the talking points.

But on average, what you can expect from weight loss is up to a 70% reduction in triglycerides. So it's more than anything we've talked about so far. From dietary modification, the ceiling is about a 70%. And then from physical activity and exercise about 30%. Whether the - you know, there's an independent effect of dietary modification beyond the weight loss or an independent effect of physical activity beyond the weight loss, that's not very clear to me, but these are numbers that you can use as you talk to your patients.

On the right-hand side of things - these are sort of my commentary, I think it's very challenging in the food economy in the U.S., for many of our patients to have access to healthy foods. And the ability to pay in particular and even just in their communities have the physical – be in a physical environment where those options are available. Processed foods for women - working women become a go-to because they just don't have the time. And this is an issue worldwide as well. So that may explain some of the burden of this problem. And sometimes it's just you know, high-calorie foods that you can get to your kids on the table. So it's - these choices are difficult to make. The dietary modifications are challenging for reasons beyond, you know, that relate to economics.

But one thing you can tell them and that's cheap, everyone can do this, is exercise. And whether it's going out for a walk, just incorporating exercise into daily activities. And the rule of thumb you can tell them is that a 5 to 10% decrease in weight gets them about a 20% lowering in triglyceride. It's a pretty good message. It's a pretty good message. Avoid a drug if you can do it on your own with exercise and you don't have to pay for it.

Some key prompts and messaging regarding diet and exercise. I love this expert consensus document provided this just, so I've extracted a few. Again challenging for the busy clinician. The box on the right I want you to remember try to be specific and be numeric. That's what patients want. They want certainty. And you've got a few minutes to give them that. There are components of diet that have simple fixes, or at least little measured steps you can take. Sugar-sweetened beverages, sweets, alcohol, saturated fats, weight, and exercise. These are the topics. Maybe pick one that you're going to ask about. There's some simple questions. Let's just take the one: How often do you drink sugar-sweetened beverages? And you specifically define what it is that you're talking about. Many patients don't really understand that fruit juice or fruit drinks are a sugar-sweetened beverage. And then the clinical message might be just try sparkling water or regular water. Sparkling water may be expensive, regular water then with a lemon slice. So something specific that you can tell them that they can take home and start thinking as they reach for these unhealthy behaviors. And these slides again will be available, so you can go through the remainder of them.

The third thing to do is medical therapy. That's the other reason that we're here today. So you've done - you've addressed the reversible causes, you've addressed diet and exercise, very likely you're going to be in this box. You're going to have to do something. And so the guidelines or the consensus statement helps you organize your thoughts to go down the LDL-lowering pathway or the triglyceride risk-associated pathway. And based on which, you know, your triglyceride level and your risk factors, you may prioritize LDL lowering. But once that is done most of the pathways that I showed you, you end up with optimizing triglycerides as well once you've gotten the LDL down. And the only option we have today is icosapent ethyl. There are a few other drugs on the horizon that may emerge. Some of these will fall off and not work. But today in contemporary practice, focus on what you can do, which is adding icosapent ethyl for the reasons again that we'll talk about later today.

So I'm going to end just to keep this one thing in your mind. It's a preamble to what we're going to talk about later. So as you listen to other speakers, think about this patient that you might have in front of you. This is a high-risk patient. I'm in the VA system, is a typical patient for me. A 60-year-old man, post MI, he has had a history of PAD, he's status post fem-pop bypass, he's probably had multiple, multiple interventions and is at risk for losing his limb. He has treated hypertension, he's, you know, overweight, not quite obese yet; 30 is the - remember the criteria for obesity. He's a smoker. Think about what his yearly risk of a heart cardiovascular event. Again, heart attack, stroke, or death from cardiovascular disease. Jamie already got this correct - Dr. Underberg did earlier, but we'll - he's an expert and someone to aspire to. But for most of us to think about this, there are a few - there are only a few scores in secondary prevention. This is one of them. This is a secondary prevention patient. I'm not recommending that you use this all the time, but to illustrate and to put into context, the cases, one score that's available is the TIMI risk score, also called the TRS2P. And what you do is you add up the risk factors on the left, those are their 7 or 8 risk factors. And then once you plug those risk factors in, you can project their 10-year - their 3-year risk of cardiovascular disease. So this patient with those risk factors has a 14.5% risk at 3 years, that's about 5% per year. And we're going to discuss different approaches to getting that risk down what you can do and the choices that you'll have to make to prevent heart disease.

So I'm going to stop there and hand off to - I'm going to summarize.

So, you know, the first - LDL first. Think of that whenever you see these patients, but think about now shifting towards residual triglyceride risk as the next potential target. We're starting to get therapies that actually work on this. We do this because we know the biology is there. We also know there's burden, high burden and we have treatment options. So I'll leave you with that as a stage for the remainder of the symposium that's going to really explore the potential promise and delivery of risk reduction through use of icosapent ethyl. Alright, thank you very much.

Dr. Miller:
Thank you, Dr. Pradhan, for that wonderful lecture, I'm now going to switch gears a little bit and talk about the REDUCE-IT trial, as well as omega-3s for ASCVD risk reduction.

For those of you who've been interested in this field for a long time, you know that there have been a number of studies that have evaluated both from the standpoint of statins and then more for lowering LDL and ezetimibe for part of lowering LDL on top of a statin, and then the new PCSK9 inhibitors that now came out about almost 10 years ago, as well as some of the neutral study. So the positive studies in the more contemporary era with IMPROVE-IT showed that ezetimibe on top of a statin, which was simvastatin, did conveyed lower risks compared to a statin monotherapy. And then the PCSK9 inhibitors, the combination of either FOURIER in stable disease or ODYSSEY in patients with acute coronary syndromes led to a 15% risk reduction on top of conventional therapy. So those were the positive studies.

On the right side were the neutral studies. And they included a number of studies that were inclusive of the medications known as fibrates, or fenofibrate, specifically. Prior to fenofibrate, there was gemfibrozil, that actually was positive in patients that have a tendency of low HDL going back a number of years. But these more recent studies, ACCORD and FIELD, as well as the use of extended-release niacin AIM-HIGH, and then HPS2-THRIVE, which also use niacin in therapy, all were neutral. And so the question is why were some studies positive? Well, it appears that all the studies that had an effect on lowering LDL contributed to lower risk. And then the question on the right-hand side is, Why were those studies neutral? And then, of course, we look at the mechanism of action and the population that was being tested, I think we're contributors to this effect. I think many of us really believe that AIM-HIGH was going to be a positive study. And that was because a lot of patients were high risk by virtue of having the metabolic syndrome, tendency to low HDL. But the medication on top of statin therapy had baseline LDL levels that were fairly low. So that also likely played a role here.

Moreover, these studies did not test hypertriglyceridemic populations. And if you looked at the subgroup of patients that were hypertriglyceridemia, often with low HDL, there tended to be benefit or a trend toward benefit. So again, it raised the possibility that maybe these neutral studies would not have been neutral, had the proper population been tested. Again, we don't know because that's the - it is what it is.

The revolution in omega-3 acid research is - has been borne out for a number of years. And you know, you can go back all the way to the 1970s when Icelandic Eskimos were tested by Bang and Dyerberg and other colleagues, and they found that that the Greenlandic Eskimos were at low risk of heart disease. And in part because the Eskimos consumed a lot of fish. Whale blubber was among their favorites. And whale blubber contains a fair amount of icosapentaenoic acid.

So if we look now at the revolution of omega-3 fatty acid research, and I just have to, as my kids would say, this is a humble brag. But actually, the humble brag is that I got into this area because I was really excited about these - the Eskimo research. So when I was a fellow - when I was a resident and thinking about doing a fellowship in lipid metabolism, my mentor Peter – the late Peter ___ 49:44, said, 'Okay, write a grant.' I wrote a grant, and my grant was for natural – a National Research Service Award. My grant focused on these Greenland – well, Eskimos. And so I looked at fatty acids. And the fatty acids that chose to study where oleic acid, so a monounsaturated fat, palmitic acid, a saturated fat, and icosapentaenoic acid. So this was back in the mid 80s when I looked at this stuff. And icosapentaenoic acid behaved very differently when you looked at cellular incorporation into lipids. And so that was my first inkling. But I have to say that it all began because I was fascinated by these Greenlandic Eskimo studies. So it was pretty cool.

And now of course we have these - the sources, metabolites, you have the plant-based chia seeds and flax seeds and walnuts, linolenic acid, that doesn't really get converted to any sufficient degree into EPA or DHA. And then you have the prescription omega-3 fatty acids, as well as those derived from marine fish, some from algae, of course, which contain these omega-3s. And it's a pretty complex pattern but the two that we - that had been focused for a number of years, icosapentaenoic acid and docosahexaenoic acid, separated by 2 carbons, and some other things that - some other chemical entities that we'll talk about.

As it turns out, triglyceride-lowering and omega-3 CV outcome studies have really been nil until JELIS came out. And those studies were probably swayed in part by using low doses. So a total of a gram dose of a mixture of EPA and DHA. So that combination, I think really didn't parlay - did not translate into appreciable triglyceride lowering. If you take 1-grams' worth of an Omega-3 mixture that you can purchase at your local health food store, you're probably going to get about one-third of that, that's concentrated in EPA and DHA. So it's a very small percentage, and you just don't get a whole lot. There's a lot of contamination as well, a lot of other fatty acids thrown in there.

But the bottom line is that these studies are not translate into cardiovascular improvement except when you look at JELIS. So if you look at the major vascular events and go for 4 rows down, you see the JELIS study and that stands out, favors treatment compared to the other studies, which were neutral. So perhaps the combination of EPA and DHA did not work compared to EPA alone. And perhaps the population of patients that were studied was not beneficial. So JELIS, the only positive trial and the only pure EPA trial. And again, if you look at the question as to why JELIS worked, and the other studies did not work, probably from some of the combinations I've already mentioned, dose differences, presence of DHA, and lack of studying hypertriglyceridemic patients.

And then we get to more recent studies including VITAL and ASCEND again, using EPA/DHA in both of those trials did not work. And

then the REDUCE-IT trial with the EPA that we're going to talk about.

So EPA versus DHA, they look similar, but they're different. EPA, as I mentioned is – and DHA separated by 2 carbons, and where that double bond is. So EPA is 20 carbon and DH – and docosahexaenoic acid 22 carbon with the double bond 6 versus 5 change position here. And some might even liken that to while you have testosterone and estrogen, and they are chemically look pretty similar. There are some differences but they're - but they look - if you just looked at them, you'd say, 'Hey, they look pretty similar.' But obviously there's just a tiny bit of difference between them.

JELIS did show CV risk reduction with icosapentaenoic - with EPA icosapentaenoic acid, and it was a 19% risk reduction. But interestingly enough, the patients in this trial were not specifically hypertriglyceridemic. And as you see here, the medium triglyceride was about in the 120 to 140 range I believe in – and there was still a benefit to using this compound, both in secondary prevention as well as in primary prevention in a Japanese population that consumed a fair amount of fish to begin with. And many of us did not believe that this study was going to work for that reason. I mean, if you're eating a lot of fish, you're going to have high levels in your bloodstream, as you'll see a VPA to start off with. And then how much of a magnitude of an increase in that would be needed to show some differences between the groups.

But if you look at the hypertriglyceridemic subgroup on the right, the differences were more profound with respect to events. So while there was a 19% reduction in the total group statin versus statin EPA, those individuals stratified in a post hoc analysis to hypertriglyceridemia, had a much larger effect. And that, in turn, led to the design of the REDUCE-IT trial. And this is the design of the study. I think the study was designed now, going back about 10 years. I think we may have the anniversary – maybe it was February 4th of 2012, that was the anniversary when this actually originated, but it was around that time. And that study had - was really designed to test the hypothesis, knowing that hypertriglyceridemic patients are at increased risk, will the use of a therapy that intuitively, based on the study in Eskimos and then followed by JELIS, might that benefit if you test the proper population? And if that proper population were a high-risk group of individuals, those with established cardiovascular disease or diabetes, and at least one risk factor, those that had triglycerides of at least 150 up to 500. And patients who were well treated with LDL levels that were somewhere between 40 and 100, based on contemporary use of statin therapy. You could use ezetimibe, but again, the study was, you know, started at a time when statins were much more commonplace. PCSK9s were not in the picture at that time. Patients were randomized to icosapent ethyl or placebo, and then followed out for the primary endpoint, which is typical cardiovascular MACE, and then compositive CV death, non-fatal MI, non-fatal stroke revascularization, and stable angina that required hospitalization.

Here's just a nice demonstration of intestinal processing and absorption of icosapent ethyl, a purified EPA, so it's re-esterified in phospholipids, and triglycerides and packaged for transport in chylomicrons. So icosapent ethyl, as a protege of EPA is not readily taken up into triglycerides diverted off through the phospholipid pathway. Those are the studies that I did 30 years ago, but others have shown that as well.

So here, if you look at REDUCE-IT primary and secondary endpoints, so what I want you to look at, to what Dr. Pradhan said before, which I think is really important, look at the primary composite endpoint. Everybody looks at the difference between placebo and icosapent ethyl. I tell my residents and fellows, the first thing you should always look at is what happened in the placebo group because that will give you an idea as to the relative risk that - intrinsically in that population. And so Dr. Pradhan mentioned before that high-risk patients here, based on that TIMI score, were somewhere about 5% annual event rate. If you think about a patient that has perfectly stable angina, the annual event rate in that group of patients is only about 1.5 to 2% per year. Now, so a high-risk group would be patients maybe, if you throw in a top diabetes, medical controlled, and some of the factors. So 5% per year is pretty high. And if you look at the placebo group, that's what you're seeing, somewhere about 5, 5.5% per year. So it's a high-risk group of patients, and icosapent ethyl brings it down pretty substantially. So not only a significant relative risk of 25%, but also the absolute risk care of 5% was quite striking. And then the secondary composite endpoint of CV death, MI, and stroke also was favorably influenced in the study.

And then you could look at first and subsequent events. I think this is key because if you have an event, you're more likely to have recurrent events. In fact, if you have established coronary disease, you have upwards of an 80% likelihood of dying from a cardiovascular event. And therefore, it really behooves us to try and make every effort to reduce that risk. So looking at first placebo and icosapent ethyl, and the difference here is 30% relative risk reduction. And you look at that P value, it's more than impressive here.

Treatment emergent adverse effect events, no overall treatment differences shown between the two groups assigned to either icosapent ethyl or placebo. Bleeding events were - all bleeding events were slightly higher. Again, icosapent eth – EPA or icosapent ethyl as here, or purified EPA, affects platelet aggregability and some mild change of bleeding time, although there was no - in some of the major bleeding risk, was not different between the groups. So that's important. Afib and flutter, we don't know the mechanism yet. This has been seen in several studies now with EPA, or EPA/DHA, but there is a small increased risk of about 1% difference between the groups of afib and flutter. But fortunately, you know the big concern with afib is stroke risk. And stroke risk went down - was reduced in

REDUCE-IT. So even though there was a small increase in afib, there was - it seemingly did not translate into adverse events. But V - ventricular arrhythmias seemed to be offset. Sudden death was reduced in the REDUCE-IT trial.

So REDUCE-IT it showed a decrease in total events for every 1,000 patients on icosapent ethyl 4 grams a day for over 5 years. And you see here, you're reducing cardiovascular death by 12. And fatal and non-fatal MI and coronary revasc and primary composite endpoint. So a lot of events that are being reduced for every 1,000 patients.

So did it matter what your baseline triglyceride is? And I've already said, patients entering this study were at high risk by virtue of being hypertriglyceridemic, many of them were diabetic. Many of them had other risk factors. Of course, the majority had cardiovascular disease, so - But when you look at the use of IP and evaluate them and evaluate its effect in patients with elevated or without elevated triglycerides, patients benefited. So even though icosapent ethyl lowered triglyceride, it did not appear that the major driving effect that resulted in reduced cardiovascular events was the triglyceride per se.

And the on-treatment triglyceride did not alter cardiovascular disease risk here, as shown statin placebo and statin IP, whether or not they had a TG above or below 150. Those patients benefited, compared to a statin placebo.

And here's a primary endpoint by on-treatment serum EPA. So we believe that this was more - or a primary driver of the benefit observed. It was a serum EPA. And here's CV death, MI, stroke, coronary Revasc, unstable angina. And then the area under the curve derived daily EPA levels. And the higher the EPA - serum EPA, the lower the risk of events starting off at a baseline of about 26 micrograms per mil. If you look on this slide between the primary endpoint and then driving down to the secondary endpoint and so forth, you see, even if the trend was not statistically significant to the right, the primary endpoint was, and the trend was there in all groups looked - evaluated. So the on-treatment serum EPA did affect the outcomes in the REDUCE-IT trial.

Turning our attention now to STRENGTH. Now STRENGTH was a bit different in that both EPA and DHA were used, and EPA was half the dose. So was 2 and 2; 2 grams of EPA and 2 of DHA versus 4 VPA alone in REDUCE-IT. And also looking at hypertriglyceridemic cohort and followed by traditional MACE endpoints. And the study was - went on for somewhere again between 3 to 5 years. And no difference though, in this group here combination using EPA/DHA, versus the placebo here of a corn oil. Baseline and achieved EPA levels in omega-3, the cardiovascular outcome trials, and cross study comparison.

So let's look at this. If you look at now the baseline of STRENGTH and REDUCE-IT, they're very similar. And plasma and serum EPA are - studies have shown that they're pretty concordant. So not much of a difference here. And then if you look at the plasma, EPA of STRENGTH, you're getting to 90 micrograms per mil, which was similar to the baseline plasma EPA of JELIS. So basically, in the STRENGTH study, you gave them enough EPA that they would be similar to a Japanese population that consumes a fair amount of fish. But then when - in JELIS, of course, the plasma EPA in those that were treated at the end of study was 170. So it was quite high, much higher. And then if you look at that level in JELIS, and now you look at REDUCE-IT, so you're starting off with REDUCE-IT, as I said, at 26, and with the STRENGTH, but serum EPA levels are dramatically higher than what is seen in STRENGTH. Okay, so remember if we're trying and looking at the effect of EPA, we see that EPA levels are much higher in the REDUCE-IT trial, similar to what we're seeing in JELIS with benefit but much higher when compared to STRENGTH.

And here's ASCVD benefits follow-up on EPA levels in REDUCE-IT, pure EPA but not STRENGTH. So again, the difference here is in EPA levels that we think fundamentally affected the results of the trial. No CVD benefit in STRENGTH even in the top tertile of EPA levels. And we think here that there was also an increase in DHA. So if there is a counterbalance effect, and in this trial that may have accounted for the lack of benefit observed despite having a higher EPA levels.

Now, here's the outcome trial with the role of formulation. So we have JELIS again, REDUCE-IT, and STRENGTH. If you're looking at the formulation of a purified EPA product at a higher amount, of course, in the REDUCE-IT trial, STRENGTH having the combination of EPA/DHA so having less EPA. Baseline triglycerides were going to be high in both REDUCE-IT and STRENGTH. Baseline EPA was higher in JELIS, again, a Japanese population consume a lot of fish compared to REDUCE-IT and STRENGTH. And then you achieved EPA, high in JELIS and REDUCE-IT but less so in STRENGTH. And of course, having increase in achieved EPA levels, highest in REDUCE-IT, triglyceride-lowering similar in the – in REDUCE-IT and STRENGTH. And seeing benefits both in JELIS and REDUCE-IT, where again, the totality of evidence suggests that this was driven by EPA levels. And we see that achieved EPA level is different here. Baseline effects here in JELIS. So - and we could - you know many of us thought that we were not going to see a big difference. You know, again, Japanese consuming a fair amount of fish, would we really see a big upward swing in their levels? But there was in the JELIS trial.

And here's a metaanalysis of omega-3 trials for compared EPA versus control, 34 compared EPA/DHA, and 22 in primary prevention. And EPA levels – the EPA trials had 1.8 to 4 grams a day versus 0.4 to 5.5 grams a day. And follow-up across trials was 2 years. And you see here pure EPA shows benefit. The combination of EPA and DHA does not. And this is a review that ___ 1:10:17 did. And just

for color coding purposes, green is favorable, red is not. The green which includes angiographic studies, two angiographic – two outcome studies all show improvement with purified EPA, whereas studies using the combination of EPA and DHA did not. So it looks like a fairly consistent picture here.

So the bottom line for patients with elevated triglycerides and high risk of ASCVD, REDUCE-IT is shown that a good dose with a good drug makes a big difference. Icosapent ethyl at 4 grams indicated across a broad spectrum of ASCVD risk in patients with hypertriglyceridemia, and icosapent ethyl has unique, well-documented mechanism of action profile for benefit in ASCVD. Atherogenic, lipid-lowering, anti-inflammatory, anti-plaque, membrane stabilization, oxidation, endothelial dysfunction, are all believed to be contributors. But it starts off with the level of EPA that drives these effects.

So in summary, there's still a lot of ASCVD risk. And personally, I am concerned in the era of COVID that, you know, we had stabilized cardiovascular disease. And I kind of wonder, with all the added stress over the last 2 years, lack of socialization. I mean, it's great to be in a standing-room-only crowd here today. Thank you. But I'm concerned that the added stress over the last 2 years may have contributed. We'll have to see what the epidemiologists show in years down the line. But I'm wondering whether the last 2 years when we had done such a nice job keeping ASCVD rates down, that we may see a little bit of a spike for some of those reasons. And it's not the myocarditis from the vaccines. That's not -

Combination therapy of statins with fibrates are nice and have not shown effectiveness and are generally not recommended to reduce ASCVD event risk. But however, very important, there is an ongoing study that I'm super excited about that Dr. Pradhan is spearheading right now. And that's the PROMINENT study. So we'll stay tuned for those results with pemafibrate. And, but until then, REDUCE-IT was a landmark trial showing that icosapent ethyl 4 grams a day, in addition to maximally tolerated statin, does reduce ASCVD events significantly. Although again, hypertriglyceridemia is important. The impact on triglycerides does not appear to be the primary driver for their benefits observed.

So with that, I'm going to stop right here. And we're going to have a panel discussion. So we'll bring up doctors Underberg and Pradhan. Thank you.

Dr. Underberg:
Want to work to the left? Alright. Thank you. Take the first question.

QUESTION FEMALE 1:
I'm an oncology nurse practitioner. Several of our breast cancer patients on tamoxifen, their triglyceride levels go bananas. And as you well know, probably the overwhelming majority of those patients will probably die of heart disease and not their breast cancer at that stage. So I'm wondering, of course, when you stop the tamoxifen, the triglyceride levels go down, but if we really want - that patient really wants to be on tamoxifen, how do you treat that high triglycerides? Or do you?

Dr. Pradhan:
I think probably, again, this is one of those situations where you look at risk assessment, cardiovascular, where do they fall, in your brain and on the risk scores, in terms of their risk of cardiovascular event? And, I mean, I personally wouldn't mess with the tamoxifen, but that's just because it's not - I don't know enough about that data, to be honest. But I would probably add on therapy, depending on where they fall. If their LDLs are controlled, and they still have that triglyceride, and you're really worried they're not - you can't get them to do other things like lose weight, exercise, all of those things, and you're left with this issue and you are looking at a high-risk patient that could benefit from additional therapy.

Dr. Underberg:
You know, this is a fascinating issue for practicing lipid specialists. We often get referred patients who have secondary causes of lipid disorders, whether it's elevated cholesterol or elevated triglycerides, often caused by interventions that are required for other disease states. You mentioned tamoxifen. I recently saw someone on gabapentin who raised their LDL, oral contraceptives will increase the lipoprotein abnormalities. And I think in each case, you have to do a risk assessment and decide, should you be treating this and how should you be treating it. The other issue is, is are these interventions associated with risk related to the lipid disorder, and in many cases, we don't know. And so to add a second medicine to treat the cause of the first medicine, I'm always a little uncomfortable about it.

Dr. Miller:
I'd also want to know how the triglycerides went. So if the patients who went on tamoxifen had gone up in 4, 5, 600 range, which can happen, then I'd certainly want to treat that. And I would probably use a therapy. So a therapy like icosapent ethyl, I think would be consideration here. Even though the patients in REDUCE-IT were not breast cancer patients specifically. But we do know that we'll get at least a 20% lowering. And importantly, I'm not aware of drug-to-drug interactions, which also play a role in your decision to what

you're going to use for the therapy.

QUESTION FEMALE 1:
Thanks to just one more question, Do you - do any of you have any experience using this icosapent with patients who are being treated for cancer? Because as you know, many of our cancer patients have, you know, we cure a lot of people believe it or not, but they have clotting problems when they're on treatment, or with their cancer. And some of the side effects that you listed were like all the same side effects that could maybe be cumulative. Do you guys have any experience using that medication with any active cancer patients?

Dr. Miller:
I do. And again, as both Dr. Pradhan and Underberg stated, you really need to look at their risk. So if their triglycerides are pumped up in the - in that range 3, 4, 500, then I - you know - and they're bleeding - you know, you do have to worry about bleeding risk, obviously. But if things are pretty stable, then I'm comfortable using it.

Dr. Pradhan:
Maybe I'll ask you guys while we're waiting for other questions. What do you think about the bleeding risk? And how, you know, there has been this sort of talk about I think it's overhyped with icosapent ethyl?

Dr. Miller:
I think it's overhyped, you know, again, because there were 4 grams. Not all of our patients take 4 grams a day. Now 4 grams, of course, was used in the REDUCE-IT trial. If you're using it for a different reason that's outside of REDUCE-IT, you may use perhaps 2 grams or 3 grams. So I think, again, you have to determine what might be reasonably effective if it's not specifically for, you know, if it's more for concern about pancreatitis, for example.

Dr. Underberg:
And there's some older data looking at other preparations of prescription omega-3s in patients who undergo bypass surgery, and there's no increased risk of bleeding-related events in those patients. So while I agree that it's a known side effect of the medication, and I always hate to use anecdotal results in my practice, but I've really never seen anyone have a bleeding issue that caused them to end up in a hospital or have a bad side effect. We still do, though, if it's not something someone has to be on all the time. They're having elective surgery, I'll tell them to hold it for a couple of days before the surgery.

Dr. Miller:
Yeah, and I think that's right. I think Peter Tao, a noted electrophysiologist, was lead author of a study that was published in JAMA a number of years ago looking at the use, it was not EPA, but it was EPA/DHA combination, Lovaza, in patients with afib, who were on anticoagulants, and did not see – who did not report an elevated risk of bleeding or it was nothing substantial.

Dr. Underberg:
That's my recollection.

Dr. Pradhan:
So practically speaking, it's always this risk-benefit analysis, and you guys don't change much, you know, except for maybe periprocedural withdrawal, but that - there's no data for that either. But it's, you know, it's what makes you feel comfortable and also assessing the risk benefit-ratio long-term.

Dr. Underberg:
And also remember there are ton of patients on high-dose prescription omega-3s, EPA, in the primary prevention space who are not taking other anticoagulants or anti platelet agents. But in REDUCE-IT, there were a significant number of people because they were specifically enrolling one cohort with preexisting ASCVD. So I always remind people when they come to me, and they say, 'Oh, I read that there's an increased risk of bleeding on this drug,' I said, 'I know, but in your case, you're not taking any other things that put you at increased risk.' So I do think that it's something, while it's worth being aware of, it's not a reason not to take it.

Dr. Pradhan:
Yeah.

Dr. Miller:
I mean, the other consideration is hypertriglyceridemic patients often have - live in a prothrombotic state. It might be a mildly pro thrombotic state, but their - some of their factors are affected, and so clotting factors are affected. So you know, the likelihood of having, again, if they're living at a triglyceride of 2, 3, 400, as long as they're not taking other agents that promote or have intrinsic enhanced bleeding risk. So they should be able to tolerate it pretty well.

Dr. Underberg:

So while we're waiting, another question that comes up often is, from my perspective, in clinical practice, it's always very easy to recognize the patient who comes in who's had an event whose high risk. There's like almost the star in their chart, let's do everything we can to reduce their risk. But, you know, the data from REDUCE-IT was so compelling in the diabetic primary prevention population, and I do primary care too, and capturing that population and reminding yourself about their risk, it's not an easy thing to do. And I'm just curious what the two of you do in your practice to make sure you don't miss these patients?

Dr. Pradhan:
You know what, I honestly don't practice a lot of primary care anymore. I'm on the other spectrum where I'm so heightened to this issue. And, you know, for our veteran population, it's so rampant and we are kind of restricted, it's hard to get EPA within the veteran population. So it may actually be challenging for assessing therapies. So, I mean, in many cases, for me, it's that patient who's a diabetic, has had their event, they're on maximal statin therapy, and now I'm thinking, you know, this is a ticking time bomb, what's the next thing that's going to happen? So I am very aggressive with those patients.

Dr. Miller:
The same here, I mean, we see a lot of patients. Now, of course, I'm also at the VA, but I'll also be at the University seeing patients, and we do get a lot of patients that are coming with family histories, they may be early diabetic, as well. And - but inevitably, their risk is high. And despite all the great - here's the thing is we do have great lifestyle changes that can be made. The real issue is how do you get patients to follow those lifestyles?

Dr. Pradhan:
You've given so many talks about this, Michael. I learned much of what I know from your talks about lifestyle modification. And what do you tell your patients? What are the top three things?

Dr. Miller:
Oh, so top three. That's great. Thanks. Thanks for that lead-in. Things - so since I see a lot of hypertriglyceridemic patients, we know triglycerides are elevated after you eat a fat meal. The best triglyceride you ever have, I tell my patients, is a triglyceride you have after a long fast. And that's the truth. I mean, if you're coming in and your triglyceride fasting after a 12-hour fast is about 200, then during the course of the day, you're likely to see it jump up, not surprisingly, to 300, 400, maybe 500 depending on what you eat.

And so, the way I - what I recommend for my patients that have hypertriglyceridemia, and presuming they may be on medication, you know, if they're not they - can - some can exercise obviously, exercise would - is key because that reduces that postprandial surge if they could exercise. Unfortunately, that's aerobic activity, so walking is really not going to do a whole lot. But if they can walk and do exercise to kind of limit that triglyceride peak. Also, I recommend that they don't eat any meals that have a lot of fat. So they really keep their fat intake low. So sorry, no cheeseburger - no bacon cheeseburgers for them, and fries because that's already about 800 to 1,200 calories, and they can't tolerate it because their triglycerides may triple. And that's a problem.

And the third thing is so tell them the best triglyceride is what they come up with. And that level is going to go up. Limit the amount of high fatty meals and then - at a setting. And then the third thing is don't eat anything between for about 4 to 5 hours. And -

Dr. Pradhan:
You said something about exercising. So when would you exer - is there any data on you know, later - exercising later in the day, early in the morning.

Dr. Miller:
There's a lot of, you know, there are a lot of data not necessarily relate to triglycerides, but a lot of data with respect to, you know, maybe morning is better. But, you know, to me, if a patient could do it at any time of the day, do - what you want to do is activate lipoprotein lipase. And that helps to blunt that hypertriglyceridemic response.

And the thing too, is, you know, you don't want to go to bed - I tell my patients, the worst thing you could do is go to bed right after eating. So unless, you know, it's a special occasion, but you do want to do something. Yeah, so I tell my patients after they eat. In Florida, not a problem, may be a little different in Boston, New York, or Philadelphia this time of year, but to go for a walk. And do something after you eat not exertion, you know, but just walk in try to, you know, get your muscles activated, and just, you know, try to burn something, even if it's not a whole lot. And try not to eat a whole lot 4 to 5 hours, give your body a break.

Dr. Underberg:
That's why dog ownership is associated with improved cardiovascular, that evening walk. So I have a question for you. In REDUCE-IT, everyone was taking a statin. So a colleague recently asked me, 'What about the role of icosapent ethyl in patients who are statin

intolerant, who otherwise would meet the criteria based on the two populations that were studied? Would you use it? And do you think it matters?

Dr. Miller:
I would use it. I do think that that that combination, just like ezetimibe and statins, have a better effect on inflammatory biomarkers. I think ideally, the combination of icosapent ethyl and a statin is more optimal.

Dr. Underberg:
Right.

Dr. Miller:
But if they can take a statin and they can only take ezetimibe or PCSK9 or whatever, I don't think that rules out or precludes the use of icosapent ethyl, even though of course it was not part of the REDUCE-IT trial.

Dr. Underberg:
I feel better. That's what I said.

Dr. Pradhan:
All right, my two lipidology friends, fasting, nonfasting. What do you - what do you guys do? Do you - and this is probably a common question for our primary care colleagues, if you're going to assess their triglycerides, do you always bring them in fasting? You've gotten a random that's sort of high, do you bring them in fasting? What do you - what's your trigger for therapy?

Dr. Miller:
So in the AHA statement that came at 10, over 10 years ago now, we said you can do nonfasting. The thing is the 2018 now say 150 fasting, 175 nonfasting. So they're giving you a little bit of a leeway. I think whatever is most convenient for the patient, is what you should do. So if you've - if the patient has never had their levels drawn, and you're not making decisions based on those levels, I think it's very reasonable coming nonfasting. Nobody should ever have - so here's the thing, nobody should ever have a triglyceride of 300.

Dr. Pradhan:
Right.

Dr. Miller:
It's just not normal. Just like nobody should have a glucose of 300. You know, you give somebody, you know, a box of Hershey Kisses, it shouldn't get to 300. The same thing with triglycerides, if it's 300 nonfasting, you have a problem. But the thing is 20 years ago - this is what we used to do 20 years ago, a patient would come in, and their triglycerides would be 300. And the physician said it was nonfasting, you have nothing to worry about. That was the problem. And, of course, we know that's a problem.

Dr. Underberg:
So I have a very simple algorithm. I just go out into the waiting room, and if there's an empty pizza box there, I suggest we do the labs later. But otherwise, there is no reason not to draw lipids on someone ever. And that's what I've – and same with if you're assessing blood sugar, you do a hemoglobin A1c. So I don't let them out without labs if I think they need labs.

Dr. Pradhan:
Great.

Dr. Miller:
We're going to now proceed with the recent evidence from the REDUCE-IT sub studies. And first I'm going to talk - I'll be talking about a series of studies that have been published or presented in recent years. And I'll first discuss REDUCE-IT CABG. And the nice thing about a large study like REDUCE-IT, is that there were a lot of prespecified analyses that if the primary endpoint was met, then we would proceed. And this is from the - from looking, evaluating patients that may have proceeded with CABG, and the primary endpoint here of CV, death, MI, stroke, coronary Revasc, and, stable angina, and those with a history of CABG, was reduced. So again, 24% reduction in patients with a history of with a CABG undergoing CABG here. Secondary endpoint also reduced by over 30%. And then if we look at those with a history of CABG, first and subsequent events were substantially reduced by 36% over those that had multiple events. So again, history of CABG translate into reduced likelihood of future events. Quite nice.

REDUCE-IT RENAL, we know that many of our patients that are coming in at high risk will have, over time, chronic kidney-related diseases, especially those since many of our patients have hypertension and diabetes, or either one. And so looking at GFR at baseline, looking at, again, a prespecified primary endpoint at baseline, those that have a GFR of less than 60, between 60 and 90, and those that had levels of greater than 90, those patients benefited. So if you had a G – a class 2 to a class 3 of chronic kidney disease, then you tended to benefit with icosapent ethyl. And again, we think probably endothelial function, improvement in microvascular, and

microvascular endothelial contributed to these effects.

Here are some of the key secondary endpoint events by GFR at baseline. Again, looking to the left with levels of less than 60, and then moving to 90. There was an approximate 30% reduction in events in those that had some degree of renal impairment.

Peripheral diseases is an important marker because we know that patients that have vascular disease are at high risk of future events. And so again, the idea was in evaluating patients going into the REDUCE-IT trial to look at this. And so here are some of the benefits with that icosapent ethyl in patients with prior peripheral disease. And close to 700 patients entering into REDUCE-IT had PAD. And the primary endpoint with PAD with IP was 26% versus 32%. And also event rates with REDUCE-IT were over this period of time. Safety did not differ between the groups based on PAD history, and was consistent with the overall study. So again, we're looking at high-risk biomarkers in showing that the use of icosapent ethyl was associated with benefit in these high-risk patient groups.

Prior MI, again as was stated, if you've had a prior MI, then you're at high risk of future events. And here are first and total primary and key secondary endpoints in patients with primary MI. If you look at both - looking to the left, looking at first events, you see a 26% reduction and then total events, a 35% reduction in risk, and these are highly significant, consistent and highly significant. Secondary endpoints as well was assured benefit in those patients receiving icosapent ethyl or assigned to icosapent ethyl that had a history of a prior MI. Again, if you look at the placebo and total events, it's about 70%. So it's a very high likelihood of having an event with a prior MI over a 4-year period of time, or 5-year period of time.

We had also mentioned earlier that IP reduced cardiac death. And here's cardiac arrest and sudden cardiac death in patients with a prior MI. So they have scar, and they have an increased likelihood of having a arrhythmogenic events. And so total mortality reduced in cardiac arrest. Fortunately, event rates were low to begin with, but they were a lot lower in those assigned to icosapent ethyl compared to placebo, sudden cardiac death, reduced by 40% and arrest reduced by 56%.

This slide again shows you the difference in sudden cardiac death and cardiac arrest pictorially between icosapent ethyl and placebo, again, favoring icosapent ethyl and significant by 4 years.

Now a question comes up in regard to lipophilicity. This has been an issue that's been discussed for many years, way before REDUCE-IT was conceived. And that is are statins that enter the blood brain barrier might react a little bit different compared to those that are more hydrophilic. And - but if you look here, icosapent ethyl versus placebo, we're really not seeing a difference between lipophilicity and lipophobic use. So they're very - there's no difference here. You see that pravastatin crosses above the line, the point estimates, and that's because the number of patients on pravastatin were quite low. But again, the trend is very similar.

So bottom line here, both primary and key secondary endpoints, that when you compare icosapent ethyl, depending on what statin you used, there was benefit across the board. And with that, I am now going to turn over to Dr. Underberg, to discuss some of the differential biological effects of omega-3 fatty acids. Thank you, Jamie.

Dr. Underberg:
All right. This is going to be lots of fun, very interesting. And I remind you that some of the stuff I'm going to be showing you has been studied in vitro, not in vivo. And so we're going to try and make some assessments as to, you know, what might be the beneficial effects of omega-3 fatty acids, in particular icosapent ethyl, with regards to some of the clinical data that you've seen today.

I'm a biochemist in my background. I was going to be a research biochemist before I decided to become a clinician. And I think that's why they gave me this. But I actually think it's fascinating, and I enjoy thinking about it.

So here's the first polling question: What percent of patients seen by you for the first time will state they are taking fish oil when asked about their medication history? We'll just do the polling question? Alright.

And I'll tell you, from my perspective, it's about 80% of my practice. People come in and you're taking your medical history, and they just say, 'Oh, I'm taking a fish oil.' And then I say to them, 'Well, who prescribed it for you?' And they'll usually say, 'Oh, no, and prescribe that for me,' or 'someone just told me to take it,' and then I asked them, 'What exactly are you taking?' And most of the time, they have absolutely no idea. And when we actually do find out what they're taking, and you'll hear more of this from Dr. Cheeley later on, we find out that taking a non-prescription, which means not over the counter, because none of these are over the counter supplement, then probably has very little EPA in it, and may have a lot of other things that we don't want.

Okay, what percent of your patients are taking any type of omega-3 fatty acid preparation of those who are taking prescription grade versions? So here's the next question.

And I will tell you again, in concert with the information I gave you on the last question, I think the percentage is very low. And in fact, the disturbing thing is that even for those who are given a prescription for omega-3 fatty acids often end up not on that prescription. And

I always say that one of the issues is that on the way to the back of the pharmacy where the pharmacist stands high up on their pedestal, looming over everyone, you have to pass through all of the shelves in the pharmacy. And on the pharmacy shelves are all of these easy to grab non-prescription products that don't require you waiting on line. And so again, I tell my patients, please fill the prescription we've given you.

So Dr. Miller showed you this slide already, but I just want to again, remind you that there are differences between these long chain fatty acids. There are plant-based fatty acids. And what you're seeing here is on the top those that are sourced by things such as chia seeds, flax seeds, walnuts, otherwise known as linolenic acid ALA, not to be confused with alpha linoleic acid, which is a completely different structure. And then we have our marine source omega-3fatty acids, EPA or icosapentaenoic acid, and DHA, docosahexaenoic acid.

And again, the way to think about these is based on where the first carbon bond begins after the hydroxyl end. And so again, you see here for icosapentaenoic acid, and for docosahexaenoic acid, you count 3 carbons from the hydroxyl group. And that's where the first double bond appears. So it is an omega-3. If you counted 6 carbons, it would be omega-6. Very easy way to remember it. And then obviously, the number of bonds determines how you name the agent. So icosapentaenoic-5, docosahexaenoic-6 double bonds. So again, really easy to understand the nomenclature once you think about it.

We've talked a bit about the clinical benefit of omega-3 fatty acids. And the real question is: What's going on here? And I would tell you this is, I think, very much still up for debate. Nothing I'm telling you, is going to be an absolute or a definite, but clearly there are a lot of potential ways that these benefits may indeed be occurring. In fact, if you actually go back and just think about the triglyceride-lowering effect of high-dose prescription omega-3 fatty acids, I will tell you, there are at least 3 or 4 proposed mechanisms as to how these agents actually lower triglycerides. Which one is the one? Or are they all in concert? Which I suspect may be the case when we talk about the antiatherogenic or cardioprotective effects of these drugs, is probably similar. It's probably a collaborative effect in my mind, and not any one single thing. But certainly lowering triglyceride-rich lipoproteins with our atherogenic in nature. And you heard Dr. Pradhan talk about that earlier. Anti-inflammatory effects, antithrombotic events, impacts on certain other mediators that may indeed modulate some of these effects. The effect on the membrane, the cell membrane, and the ability of cholesterol to deposit in the cell membrane, and actually lead to the development of cholesterol crystals, may be a rather significant player in this process. There's always been talk about the antiarrhythmic effects. Going back decades now, people have been talking about this. And then other effects on things like prostaglandins and even platelet functions may play a role.

So I think one of the key and interesting things about the difference between EPA and DHA is that they have differential effects on membrane stability, and the way cholesterol distributes within the membrane. And so again, in the presence of EPA, it turns out that cholesterol is more evenly distributed throughout the membrane. Whereas cholesterol tends to segregate in larger clumps or groups in the presence of DHA. And this leads to a variability in the ability of the flexibility or the stretching capability of the membrane. And so there are these distinct membrane interactions with regards to tissue distributions of both EPA and DHA. And you can see on the right in the boxes, DHA undergoes rapid conformational changes that reduce antioxidant activity, it promotes cholesterol-rich domains, and increases membrane fluidity. And it's highly concentrated in the membranes of the brain and the retina. And there probably are some beneficial both ophthalmologic and neurologic effects. You know, I always love this concept of which is bad and which is good. It's not like, you know, it's a black and white scenario. And, you know, I always remind people that fish have both EPA and DHA, and they seem to do pretty well.

So anyway, EPA extended molecular conformation that preserves membrane fluidity, and more uniform cholesterol distribution. You can see the graphics here, they're wonderful, potent antioxidant that inhibits cholesterol crystallin domains, and we'll talk a little bit more about that. You know, as cholesterol tends to segregate, it's more likely to crystallize.

And then finally, it displaces arachidonic acid, which we know is a proinflammatory molecule, and associates with atherosclerotic plaque in the arterial intima. And so again, here is an example of what's going on contrasting these intramembrane effects of eating EPA and DHA. And again, we pulled out the boxes a little larger for you to see. But free cholesterol which finds its way in the artery - I mean in the membrane, can distribute very differently. And EPA and DHA, guide it in those different concentrations.

And so again, a variety of different things including an effect on oxidized LDL in the presence of EPA versus DHA, different effects on antiinflammatory processes, including biomarkers, which we know are just biomarkers, right? C-reactive protein is probably not causal; it's probably a marker of other things going on. But again, differential effects there are also between the two.

And this is a nice graphic, just kind of going through all of these different findings. Alright, they're findings based on the comparable effects of both EPA and DHA. And so again, one of the first I think, which is interesting is that EPA does not raise LDL in patients with very high triglycerides, where DHA and fibrates and niacin have been shown to have this effect. You know, part of this effect we always thought was based on the redistribution of the cholesterol component from LDL and VLDL are 1:46:12 back from VLDL into LDL as triglycerides came down. But there still seems to be a differential effect on this process, comparing EPA to DHA. High-sensitivity C-

reactive protein again, it's reduced in patients with EPA, not with DHA. I mentioned the membrane effect and the effect on cholesterol domains. Endothelial function - and I had asked this loaded question of Dr. Miller earlier in the presence of statins, seems to be enhanced. Meaning that there is a beneficial effect when DP - when EPA is added to statin metabolites in particular in the in vitro study I'm going to show you, showing a beneficial effect on markers of endothelial benefit or function. Oxidation. And then finally, even cholesterol efflux can be differentially affected.

And so here's the question: What effects do omega-3 fatty acids have on oxidation of the membrane leading to cholesterol crystals? And so again, why are we concerned about cholesterol crystal? What's the point? Do we care? And the answer is yes, right? That when cholesterol crystals form, they actually trigger a variety of different processes, including some inflammatory mediators, one very important one, which is IL-1beta. IL-1beta is key, because it ultimately then leads to the production of variety of other proinflammatory factors, such as IL-6, which focuses on the liver and leads to the production of high-sensitivity C-reactive protein, 1:47:47 P1 and fibrinogen, effects on vascular permeability and vascular health, etc. And then the effect on a variety of different chemokine and cytokines and adhesion molecules that affect the way macrophages actually find their way into the artery wall.

And so again, the presence of cholesterol crystals is one of the ways that this process gets started. And cholesterol crystals are associated with atherosclerosis, and cell apoptosis or cell death. And it's just an example of what they look like. It's kind of a cool electron micrograph. And it's key to remember that in the presence of oxidative stress, alright, we're more likely to see the formation of these cholesterol crystals, leading to lipid peroxidation and, no surprise, enhanced by dyslipidemia, cigarette smoking, and other risk factors such as hypertension and diabetes. And so again, while the formation of the cholesterol crystals, and the change in the membrane permeability and flexibility is an important component of what's going on, ultimately, it's the conglomeration of all of these different risk factors that promote a very proatherogenic milieu, and we're looking for ways to modulate or impact this in a beneficial fashion.

So we talked a bit about cholesterol crystals. What about macrophage activation? So this is a wonderful graphic, Kathryn Moore, who is my hero, who is a professor at NYU and knows more about anything than anyone I've ever met in my life. This is one of her graphics from a review article on macrophage function, and I really love it. It just reminds me about how these macrophages kind of roll along the artery wall almost like a beach ball that's going around in a baseball game and people are batting it. And then finally it finds its way into the outfield and settles down, and what happens here is these ultimately 1:49:52 ___ into the subendothelial space and start the process of foam cell formation and activation, proliferation leads to the development of the inflammatory fatty streak and the atherosclerotic process. So it's how these macrophages actually find their way to the wall and attach and get in, that's mediated by these chemokines and cytokines. And so that's a very important thing to look at, alright. Because it turns out that EPA, but not DHA, actually reduces activation of macrophages, which is part of this step.

And so, this was a study looking at the production of nitrite, which has been determined to be a very effective marker of macrophage activation, alright. And so, again, in vitro now, not in vito – in vivo, comparing a simple vehicle, a delivery vehicle, versus an antiinflammatory agent, a nonsteroidal antiinflammatory agent versus EPA and DHA. And you can see that EPA significantly reduces macrophage activation, as at least represented by this biomarker of nitrate production.

So what affects the omega-3 fatty acids have on endothelial function, and the expression of certain proteins that we may be concerned about? And so endothelial function obviously, is key and important. And we know that endothelial function as measured by a variety of noninvasive techniques, such as flow mediated basal dilatation is a wonderful predictor of cardiovascular risk and future events.

And if you look here, you can divide the effect of endothelial function based on the role of nitric oxide, which has been shown in the vessel lumen to have beneficial effects by inhibiting platelet aggregation. Jeff Berger, who runs our prevention group at NYU, is fascinated by this process and has published a lot on it. So I get to hear a lot about platelet inhibition in our weekly meetings. But then there's also an effect that nitric oxide had - has on the conversion of GTP to cyclic GMP, and in the process leads to a vessel wall relaxation, alright. And when we think of endothelial function, I think that's the role that a lot of people ascribe to nitric oxide. And it turns out that there are some beneficial effects when you look at the role of EPA against studied in vitro. In this case, now, looking at the production of nitric oxide and other nitric oxide metabolites, comparing oxidized LDL, which we know to be proinflammatory in a vehicle, compared to that with EPA, compared to that with a metabolite of atorvastatin, that's what ATM means here in this graphic. And then finally, the EPA with the oxidized LDL and the metabolite of atorvastatin. And the group that does the best is the group that gets both the EPA and the statin.

And so I asked that question of Dr. Miller earlier about what his thoughts were on this, and we know this to be the case, by the way, in a variety of other settings too. And so if you can get a patient on a statin, it's a good thing. But it also shows you this potential added benefit that we see at least in the test tube, so to speak, on markers of endothelial function. It turns out that EPA preserves vascular endothelial function following exposure to IL-6. IL-6 which I told you again is another inflammatory mediator. And here again, looking at

these same markers of nitric oxide and their metabolites, you can see a drop down when the cells are exposed to IL-6. The protective effect is greatest with EPA, compared to DHA and then arachidonic acid.

I mentioned some other protein expression that might be important. There were several that I thought might be worth talking about, but decided to focus on heme oxygenase-1 expression, which is fascinating. It turns out that EPA can induce the formation of heme oxidase-1 as opposed to heme oxidase-2. Why is this important? Well, it tends to have a lot of very positive effects that might impact a variety of and beneficial effects, such as basal dilatation, an antiinflammatory effect, an antiapoptotic or cell death effect, an angiogenesis, and an antithrombotic effect.

As an example, the conversion of biliverdin to bilirubin, and the conversion of the pro-oxidant iron into ferritin, which is an antioxidant. Now we know that the ferritin is also an inflammatory marker, right? I've been checking ferritin in COVID patients for the last 2 years now. But it turns out that in this setting, it may also have an antiinflammatory benefit.

So there are emerging benefits for EPA in multiple target organs and the variety of vascular beds that I alluded to in the first lecture I gave today. And again, focusing whether it's on the brain in inflammatory cytokines and heme oxygenase-1 in the vascular beds and the potential effects on inflammatory cytokines, and ACE, or ACE angiotensin converting enzyme, and finally in the pulmonary bed, too.

And so, you know, again, none of this has been shown to be the absolute causal mechanism that accounts for all of the great data that Dr. Miller has shown us from the REDUCE-IT trial and all of its sub studies, but clearly is a variety of differential effects between EPA and DHA on a host of end regulatory mechanisms that may potentially, whether either alone or all added together, contribute to the beneficial effects that we've seen.

So now I'd like to talk about a different trial. And this was a study done looking at the effects of icosapent ethyl on the progression of coronary atherosclerosis. Matt Budoff was the lead author in this study, it was called EVAPORATE. And again, what did EVAPORATE investigate? It sought to determine whether 4 grams a day of IPE as an adjunct to diet and statin therapy. So again, study very similar to the outcome study, would result in a greater change from baseline and plaque volume, measured by serial multidetector computed tomography, or MDCT, as we call it, compared to placebo. Again, the placebo group, we're statin treated patients. So here we're looking at anatomy, we're looking at atherosclerotic burden. And again, you know, we've seen these types of studies done in patients who undergo severe LDL lowering in interventional settings. But now we're looking at the role of EPA.

And so the first graphic I'm going to show you was shown early on, it was 9-month data, before the trial had actually even ended and the study had been officially published. And here you can see that low attenuation plaque, which was really the primary outcome of this trial, at that time, showed no benefit. And that was a statistical analysis. But you can see that the group in blue did better than the group in red, whereas fibrofatty streaks seem to go in the opposite direction. Calcification, you can see there was a reduction in total noncalcified plaque and total calcified plaque, total plaque.

But fast forward to the actual final publication of the study, and you can see here that the low attenuation plaque in that first graphic on the left showed a 17% reduction compared to the group in red that got placebo. So again, if you look across the board in blue, there seems to be a benefit for a variety of these endpoints. Now, if you look statistically at the P values, they're not all significant, including total plaque volume was close, it was 0.0019. But in general, at least from the primary outcome perspective, this matches the results that we saw from the improvements, excuse me, not from the improvements, from the REDUCE-IT trial. So we have anatomic correlation now with the outcome data from the EPA outcome trial. And this is very similar to what we've seen both from patients treated with statins and even patients treated with PCSK9 inhibitors. You know, people feel very comfortable when they see kind of an anatomical confirmation of plaque benefit that correlates with cardiovascular outcomes.

So when we talk about EPA and atherosclerosis, I think everything on this graphic is relevant. But I cannot tell you that any one is singularly more important than the other, right? EPA increases endothelial function or improves it, right? Nitric oxide bioavailability as measured by a variety of biomarkers seems to go up, membrane lipid stability, vasodilatation, and free radical scavenging. Alright? This all has potential beneficial effects on endothelial dysfunction and oxidative stress. EPA decreases crystallin domains, oxidized LDL, remnant lipoproteins, ICAM, adhesion of micro – monocytes, and arterial stiffness.

Again, if we look at markers of inflammation and plaque growth, we can look at things like bioactive lipid metabolites, IL-10, EPA to arachidonic acid ratio, all seems to be improved. Macrophage foam cells are diminished. IL-6, hsCRP, Lp-PLA2 very specific marker for cardiovascular risk, matrix metalloproteinases which we know are actively involved in destabilizing plaque, and apoC-III, which you saw earlier, is a biomarker that tracks very nicely with triglyceride-associated cardiovascular risk.

And then finally, with regards to the unstable plaque, thrombosis, platelet aggregation, I would actually move MMPs over to that side also for the unstable plaque. And it promotes cap thickness, lumen diameter, plaque stability, and regression of low attenuation plaque, as you saw in the EVAPORATE trial.

And so ultimately, again, we're talking about this smorgasbord of effects that gives you a continuum of protection across the spectrum of cardiovascular disease, whether it's risk factors, depending on how you like to look at them. But I would tell you that high triglycerides might be one of them. Lipoprotein oxidation and endothelial dysfunction, markers of inflammation, cholesterol crystals or membrane instability, plaque instability, ischemic end organ damage, and then finally cardiovascular death, all potentially impact in a variety of different ways by these agents.

You know, it's a fascinating discourse. And I wish I could give you a concrete answer. As I said earlier, I'm not even completely sure I understand how these drugs lower triglycerides, which is why we do the clinical trials, right? And which is why we do the clinical trials to also understand that there are variable differences between drugs within a class quote 2:01:37. And for that reason, I think the clinical data, as supported by now the basic science data, clearly reminds us that there is a differential effect of these agents. And I think it's important when prescribing these drugs, to make sure that you get the right thing into the hands of the patient. And I think that's why I think it's so important not to let people wander into the supplement aisle, not to be taking combination DHA and EPA if you're trying to reduce cardiovascular event rates.

So I think I've come to the end of the road here. I finished a little early. And I think our next presentation is from Dr. Cheeley, right? Thank you very much.

Dr. Miller:
That was outstanding. And now we're going to turn to Dr. Mary Katherine Cheeley, who I introduced earlier, and she's going to discuss the role of the pharmacist and lipid medication access and usage. Thank you, Dr. Cheeley.

Dr. Cheeley:
Thank you so much, Dr. Miller. I hate that I am not there with you guys today. But I'm really excited that in the age of technology, I still get to talk to you and we still get to do a little bit more information to close out the day. So let's go ahead and get started.

My name is Mary Katherine Cheeley. I am a Clinical Pharmacist at Grady Health System. And I'm not sure how many of you have seen a clinical pharmacist in the wild. So I wanted to kind of start off by saying a little bit about what we do. There are a lot of clinical pharmacists in all different facets of healthcare. But today we're going to focus mainly on drug and disease state management, as well as drug therapy management. But I know if you guys have done a prior authorization, you have also seen a clinical pharmacist in the pharmacy benefit manager world or insurance company world. So they're the ones that kind of review the prior authorizations. We do a lot of different things in a lot of different settings, both inpatient and outpatient. So if I was there with you today, I would ask you: Have any of you guys ever worked with a clinical pharmacist? Did you ever train with one of us? But I'm really excited to be here with you today. So let's kind of jump right in and get started.

So the first thing that we're going to talk through is different therapeutic approaches to cardiovascular risk reduction. I know we spend a lot of time on this today, but I want to make sure that I go through and talk about the fact that statins are the backbone of what we do. And ideally, it would be those high-intensity statins. So your rosuvastatin 40 or 80, or your sorry – your atorvastatin 40 or 80, or your rosuvastatin 20 or 40. But we know that not all patients are going to get the same response from those. So in JUPITER, it was published that some patients had, you know, a less than 50% response, some had more than 50% response. But what we do know is that the more LDL lowering that you get, the better your reduction in hard cardiovascular endpoints. And that was seen in the cholesterol treatment trial list and in this conglomeration of trials that you'll see on the slide in front of you. So every 40 milligrams per deciliter reduction in LDL that you get, is about a 25% reduction in hard cardiovascular endpoints. So as we get more reduction and go further to the right on the X-axis, we actually get more reduction in cardiovascular events. And that was seen in the IMPROVE-IT study with ezetimibe, FOURIER with evolocumab, and ODYSSEY outcomes with alirocumab. So that's our kind of LDL-lowering arm.

But until recently, we had all these neutral studies that didn't really do much for us in the triglyceride-lowering arm. That was the ACCORD and the FIELD study with fenofibrate. And then both AIM-HIGH and HPS2-THRIVE were stopped early because they didn't show a difference in lowering triglycerides in patients who already had an LDL-C at goal.

So current guidelines is that we have statin fibrates not really recommended, and statin niacins not recommended either because not only are they not helpful, but they may actually increase some adverse effects for patients. But if you have a patient with diabetes and ASCVD secondary prevention, and they still have an LDL cholesterol that's above 70, or equal to 70, then we need to do something else. And naturally, we would consider adding additional LDL lowering with ezetimibe or PCSK9 inhibitors.

So we have all the statins, and they're super important to take, and they're super well tolerated, but they're not something that everyone can tolerate. And that's okay. We know that they're super effective. We know that they have rates - with super low rates of adverse events, with rhabdomyolysis and hepatotoxicity. But in the usage study, it was seen that about 50% of patients will stop taking their statin at one year. That means if I'm seeing 12 patients in my morning clinic, then 6 of them may not be taking their statin within the next

year. And we know that that makes a difference with their cardiovascular risk reduction. That could be because they just don't want to take a medicine for the rest of their life. Or it could be because they have some kind of adverse effect, or they have the nocebo effect. So this thought that something is going to hurt me. 'My best friend's sister's daughter's niece's dog had a problem with their statin, and that means that I'm going to have a problem too.' And they're fearful of taking it. So the slightest little twinge or the weirdest piece of hair that falls out, they're going to stop taking their statin. But that doesn't necessarily mean that they have to continue to stop taking their statin.

So we published a paper - a survey in 2019, called the Statin Adverse Treatment Effect Survey, which looked at 1,500 patients who had had issues with their statin therapy, they reported at least one adverse effect. And we showed that a large majority of them actually could tolerate something. So it may not be those high-intensity statins that we want to do for our patients, but something is better than nothing. And that's where you can either do a lower dose of the same statin or change to a different statin or do alternate daily dosing. But just because a patient can't tolerate one statin, doesn't mean that we lost the entire class for them. And that's what it means by optimized statin therapy.

So we've talked about ezetimibe and alirocumab, we talked about icosapent ethyl today, as we've gone through the triglyceride pathway. We're not quite sure where bempedoic acid and glycerin can fit in yet, because we don't have the results of their outcome studies. But we know that we have different ways to reduce cardiovascular disease. We've got the LDL pathway, which remember, as you decrease LDL by about 40 milligrams per deciliter, you get further risk reduction. And now with icosapent ethyl, we have this triglyceride-related pathway for patients who have stable ASCVD, or diabetes plus two or more additional risk factors. And that was updated in the FDA label in December of 2019. So it's an adjunct to maximally tolerated statin therapy. Remember, that may not be an all or nothing kind of thing. But it's to reduce those major cardiovascular events in patients who have an elevated triglyceride of 150 or more. And it still maintains that same, you know, place in therapy that we've always had for severe hypertriglyceridemia.

One thing that's really important, and again, this is me putting my pharmacist hat on, the daily dose is 4 grams per day. So in the study, it was 2 grams twice a day with food. And we're going to come back to that, but that's a really important counseling point for a patient. So not only is icosapent ethyl now FDA approved, but it's also recommended by 19 different medical associations throughout the world to reduce cardiovascular disease for patients.

Now, of course, every drug is going to have some warning that comes with it. And it's my place as a pharmacist to make sure that patients are the right patients to get these medications as well. We're kind of the last line of defense before the patient gets it in their hand.

So we think about atrial fibrillation or atrial flutter. Icosapent ethyl was associated with an increased risk of afib requiring hospitalization but mainly seen in patients who had a previous history of afib. So not necessarily new onset afib would then require hospitalization, but patients who already had afib.

We don't really know about this shellfish or fish allergy, but it is something that I get asked a lot as a pharmacist. So we know that icosapent ethyl is omega-3 fatty acid, which is EPA. And it is obtained from fish. But we don't know if this highly purified omega-3 will actually cause some type of allergic reaction in people who have a shellfish allergy. It's something certainly to talk to your patients about. But it's not necessarily this definite, 'Oh my goodness,' I certainly would talk a little bit more to a patient.

There was also seen an increased risk of bleeding. So we know that omega-3 fatty acids kind of have this antithrombotic effect to them as well. And so it was - an instance of bleeding was seen more so in patients taking icosapent ethyl, especially if they were on other antithrombotic medications. So your pharmacist at your regular retail store may know that the patient's also getting aspirin, or also taking some other anticoagulant from some other provider. So it's important that they kind of keep an eye on those, and they'll certainly reach out to you if they have a concern.

Here's where I want to spend a little bit of time, because this I feel like is definitely something that me as a pharmacist has a big say in. And this is fish oil dietary supplements. So we all know that dietary supplements are everywhere that you try to look for them. They are on the shelf at your regular retail store. They're in grocery stores. They're in health food stores. So they're very readily accessible to patients. We also know that there are other prescription combination omega-3 fatty acid products, but there is only one EPA-only prescription product. So let's take a little bit of a deeper dive into that dietary supplement.

So we used to joke in pharmacy school, that I could go out in the yard, get some grass, pack it in a capsule in my bathtub and sell it as a dietary supplement. And that's because they are so poorly regulated by the FDA. They're seen as a food. They're not seen as a drug or some type of medication. So the amount of oversight is minimal. And that's something really to keep in mind when you have patients taking these and thinking that they're doing something helpful for their health. Now, there's certainly different accrediting agencies that can go through and make sure that what's in the capsule is actually what is stated to be in the capsule based on the label. However, that

doesn't necessarily tell us that they are helpful to treat diseases. Dietary supplements make all kinds of claims, and about 19 million people in the United States take some type of dietary supplement of fish oil. That's a lot of people. And it's something that we as providers need to make sure that we're asking our patients about.

The last point that I'll make is that they're really expensive. So if you think about the amount of fish oil, and we'll get to this later, that you would have to take it's multiple bottles of these dietary supplements every month.

One thing I think a picture tells 1,000 words. And you can see from this picture, that this dietary supplement is not something that I would want to inject. If I knew that that is what was in the capsule, I can promise you, I would put it back in the bottle and not take it. And that's because there's so much saturated fat in the dietary supplements omega-3, or fish oil products. So oftentimes, the amount that's on the front of the bottle will say 1,000 milligrams of fish oil, but it's not actually 1,000 milligrams of fish oil, and said it's a combination of EPA and DHA. And it's about 500 milligrams per capsule. So remember, if we go back, it's 4 grams per day that you need to take. And now we're telling you that the combination of the two is only 500 milligrams. So these patients are having to swallow 8 of those giant capsules, which also have saturated fat, which we know is not helpful for your cardiovascular health. In contrast, you have the prescription omega-3 on the right side of the picture, which looks much cleaner, it is a more purified substance. And certainly, from the EPA side of it, that is even more pure than the combination prescription product.

So it's really important not just to get people on the right medicines and not just to have them take the prescription products versus the OTC or the dietary supplement products, but making sure that we're monitoring how these drugs are doing for patients.

It's important that I always tell my patients, 'Hey, look, I'm not just going to put you on this medicine and let it ride. We've got to know how it's affecting you, but also how you're tolerating it, and what it's doing to your cholesterol.' So we want to make sure that you're rechecking lipid measurements. Most people do it in about three months. There are instances where you could do it sooner or even later if the patient's stable in therapy. But we need to make sure that patients understand that there's the lifestyle component and the medication component. And those together will show you what your reduction in LDL cholesterol or your non-HDL cholesterol, if we're talking about icosapent ethyl would be.

I always like to make sure that I tie it to something for our patients that hits home for them. So in motivational interviewing, we always talk about making it personal to the patient, trying to figure out why they want to take this medicine, what would be the benefit from that. 'Oh, Miss Jones, I really want you to be able to see your grandchild's graduation. And the best way that I can do that as your provider is make sure that you don't have another heart attack or a stroke. So these are the medicines that I think will get us there. Your job, Miss Jones, is to take them.' I always try to tell people that drugs only work if we actually take them. And that's me prescribing the right ones, and the patient's swallowing them, not just having them in their hand, not just putting it in their pillbox, but actually swallowing them.

So I try to make sure that patients understand that dietary supplements are not the same as prescription omega-3 products, specifically, icosapent ethyl. That is - you cannot replicate that with an over-the-counter dietary supplement-type product. And even there, all prescription omega-3s are not considered equal either. So when the - there are large trials, which I know that we talked about today, where DHA and EPA combinations are not seen as helpful, they're neutral; however, icosapent ethyl in the REDUCE-IT trial really did show a pretty substantial benefit for patients. And then we come back to this 2 grams twice a day with food. Again, 2 capsules twice a day with food.

I have a lot of patients - I work in indigent health care, and I have a lot of patients that either try to stretch their medicines because they can't afford them, next, which we'll get to in a minute. Or they just don't understand 2 grams twice a day. And they think, 'Oh, I just take one out of each bottle.' So it's really important that I write it in a way in the sig on a prescription that patients are going to understand it, but also that I take the time when I'm counseling them to tell them 2 grams twice a day with food.

If I have patients who have some of those safety concerns, for instance, atrial fibrillation, or they're also taking aspirin or a dolac, then I want to make sure that I go over that with a patient before they get to the pharmacy. And I go over it every time with them when they're in the office, as well. How are you feeling? Have you had any bleeding? All of those different things are really important every single time the patient is in the office. Because again, remember, if you can't take your – and 50% of patients are going to stop taking their statin at the first - at the 1-year mark, then that's something that we also need to take into account with any and all of our other medicines. Continually going over how to take it, how they're tolerating it, that is the key to success for adherence.

And I'll go back to my last point that I made that I tell all of my patients, drugs only work if you can take them. And it's not just me prescribing the medicine, it's the patient actually being able to get it in hand. And that's where affordability comes in. That's where prior authorization through the formulary come in. So most commonly, insurance will have at least one drug per class on a formulary. So they may not have both evolocumab and alirocumab, but they'll have one or the other. And they still may require prior authorization. Same thing, they may have both the omega-3 ethyl esters products as well as icosapent ethyl, they may have one or the other. But it's

important that you can do the prior authorization and be successful.

So I have learned to play their game a little bit. And I'll kind of let you in on the things that I've learned. Most of them - most insurance companies have their algorithm. So it goes through a pharmacy technician first. Sometimes it's even an automatic process. So CoverMyMeds. We actually have that integrated into our health system, we use Epic, we have an integrated in where we can submit CoverMyMeds claims through the actual Hyperspace application. And oftentimes, you know when you get those responses back super fast, within 15 or 20 seconds or a couple of minutes, that's because it's an electronic process. If you know how to answer the questions, then it will automatically approve. Things that can take a couple of days are reviewed first by a pharmacy technician. And then if it needs to go for further review, then it's tended for further review with a clinical pharmacist.

So we have to make sure that we understand the utilization management or UM criteria for all of these different drugs. And that mostly commonly comes from the FDA-approved indication. So if you go back and you remember FDA-approved indication, it is maximally tolerated statin. So you have to make sure that in your claim, you are telling them this patient has had previous intolerance, and can only tolerate atorvastatin 20 milligrams once a day. Or great, they're on atorvastatin 80 milligrams, or they're on rosuva 40, and you can check that box and move on.

Some things that I have learned from prior authorizations. So we started to get a lot of denials in our practice, from one particular PDM. And we started to look through those denials and realize that the denial criteria was, this is a good one. 'You didn't tell me that they were on diet and lifestyle modification.' Okay, you didn't ask me if they were on diet and lifestyle, I would have told you that they are. So now in my progress note and in all of the different - so again, since we're integrated with Epic and CoverMyMeds, I have doc phrases that I can use. So I put that at the bottom of all of my prior authorizations that says patient is adherent to diet and lifestyle modifications, or patient is counseled on diet and lifestyle modification.

Once you kind of get the hang of that a couple of times, it's easy to reproduce. Now, you'll still have some that come back with no's, you'll still have some that come back denied. But don't take no for an answer. There's always an additional level of appeal that you can go through. And some of that goes to a peer-to-peer. Sometimes I just skip the appeals altogether and go straight to a peer-to-peer if it's a really challenging case that I think it's going to be difficult to get through in a letter of appeal. And insurance companies, they'll have you get on the phone with a physician or a pharmacist, sometimes the medical director themselves will get on the phone, and you get to plead your case and explain this is a patient that I'm seeing in front of me, and this is why I think this is the treatment decision that's the best.

Once you get the process down, it's easier to replicate over and over. And it is - certainly there's consistencies between different prior authorizations and different pharmacy benefit managers. But the more you do it, the more you get, the more you understand about it.

Thank you guys so much for spending some time with me today. I really enjoyed it. Again, I hate that I am not there with you. But I hope you learned that drugs only work if you take them. It's our responsibility as providers to give patients the necessary information to help them be successful with their therapy. And I hope to see you guys again soon.

Dr. Miller:
Thank you, Dr. Cheeley. We miss you. We're going to go up for another panel discussion here. I guess we'll see if first if there are any questions from the audience. No oncology questions?

HOST:
There was one from the live broadcast. So let me read it out. From a Mark Carmen. With such compelling data from RI, there's an obvious broad patient population that could benefit from IPE. From a practical sense beyond elevated triglycerides, which factors should we be looking at to identify patients that should be on IPE?

Dr. Underberg:
So I would say, let's start with the patients studied in REDUCE-IT. And I think that's a great way to find patients who would benefit starting with those who fell into the category of underlying ASCVD who are on optimal statin therapy. And then the diabetic population with multiple risk factors.

And you know, it's interesting, the diabetic population, a lot of people tend to lump them together as a increased risk group that needs to be on moderate statin therapy. But everyone forgets that the guidelines actually allow us to further risk stratify diabetic patients for more intensive lipid-lowering therapy. So we're already risk stratifying our diabetic patients and should be. And once you find those diabetic patients with additional risk factors, that's the other group that you need to think about with regards to IPE. Any other thoughts?

Dr. Miller:
No, I mean, I agree with what you said - I'm - and as Dr. Cheeley pointed out, there were a number of societies, I think she said 17

around the world, that have approved it. And you know, the - whether you're diabetic, you know, even mild hypertriglyceridemia of 150 is quite common. Probably about 1 out of every 4 adults in this - worldwide has some degree of mild elevation in triglyceride. So I don't think we're really pigeonholed in terms of its use, because it's pretty applicable to pretty sizable proportion of high-risk patients.

Dr. Pradhan:
Yeah, I think I would just add that I mean, before initiating drug therapy, I think you still do have to attempt diet and exercise and those types of things. Give that a try before you add another drug to their already complex combination or regimen. The likelihood is that it won't work in the vast majority of patients, so you're going to get there anyway, but at least you will have given them one trial of nonpharmacologic therapy to get to their goal before initiating a drug.

Dr. Miller:
Okay, how long do you, you know, give them?

Dr. Pradhan:
Yeah, I would generally give them three months. But it may take longer than that. I mean, I, you know, it's a case-by-case situation. You know, some people just don't want to take another drug. But the key is to keep following them, don't leave those levels elevate for long periods of time.

Dr. Underberg:
Do you give your patients a follow-up appointment for three months later when you have that discussion?

Dr. Pradhan:
Yeah, pretty much. Yeah, you got to get them in the books to come back. There's - they have to have a deadline. It's either they make that - those changes by that time, or you have another, I mean, you can have another intensive conversation. But yeah. What do you guys do?

Dr. Miller:
Well, you know, and I try to change the mindset, because some of our patients believe in these, you know, supplements and vitamins, which don't work.

Dr. Pradhan:
Yeah.

Dr. Miller:
And I basically tell them, you know, 'Most of the stuff you're buying over the, you know, as dietary supplements, have not been proven to be effective. But if you think that vitamins are really good for you, then consider medications your vitamins.' So I turn it around. These, these are your vitamins, except they really do work.

Dr. Pradhan:
Yeah.

Dr. Miller:
And you know, you give them the mindset that these are effective, and to stay away from things that are not proven.

Dr. Pradhan:
Right.

Dr. Miller:
Whether or not they, you know - some do buy into it.

Dr. Pradhan:
Right.

Dr. Miller:
Others don't.

Dr. Pradhan:
the fact that you have a marker now, triglyceride levels that, you know, you can show them, it's not budging. It's beyond just the LDL, it's something else. I think people like numbers and something that they can, if they don't reach a target, then -

Dr. Underberg:
I will say that in my patients with elevated triglycerides, so many of them are still consuming alcohol regularly. And they've often been

referred to me by people knowing they were consuming alcohol regularly. And I generally tell them, 'You need to stop drinking,' because I found counseling to moderate alcohol consumption leads to no change at all.

Dr. Miller:
Do use a certain level for that? I mean, clearly, if they have –

Dr. Underberg:
Yeah, these are my patients with very high triglycerides, right.

Dr. Miller:
Okay.

Dr. Underberg:
But in the patients with mild to moderate hypertriglyceridemia, it's hard to tell someone to never consume alcohol anymore, especially people where it's part of their lifestyle, going out, etc. And so it becomes an issue because I believe it still does contribute to what's going on. It's - I always say to my patients, it's like lighter fluid for triglyceride metabolites and alcohol. And so it's a tough one. And it's, you know, people can exercise and do all the right things, and then you find out they're going and having wine five days a week. And that could be an issue.

Dr. Miller:
But it's also the quantity because there's a direct correlation between the quantity of alcohol in some individuals, and the increase in triglycerides. So if you're keeping it, you know, in truth, what we've learned in - over the - over time is that one drink or 1 ounce of alcohol, which would be the equivalent of you know, a shot.

Dr. Underberg:
Yeah, a shot, or bottle of beer or something.

Dr. Miller:
But women it's probably half that.

Dr. Pradhan:
Right.

Dr. Miller:
To give you the cardiovascular benefit.

Dr. Pradhan:
Right.

Dr. Miller:
And so if their triglycerides are mildly elevated, you know, 150, 200, 250, I think I'm okay with them having, you know, the cardioprotective effects of alcohol, but it's probably not every day, it's probably only about 3 to 4 days a week that you still get the protective effect.

Dr. Pradhan:
Yeah.

Dr. Underberg/MILLER?:
So it doesn't have to be every night.

Dr. Pradhan:
Are there any other questions from the audience?

Dr. Miller:
Somebody all the way down here in centerfield.

Dr. Underberg:
So I have a question. Are either the two of you routinely measuring EPA levels on your patients based on that fascinating data you showed us including the - I thought was great, that analysis looking at the levels from both STRENGTH and JELIS, two and where they started from in JELIS, which were much higher levels because they were consuming a Japanese diet?

Dr. Miller:

That's a great question. My answer is no, I haven't. I'm not sure how well it's standardized and how expensive it is and how often it's being done. So I think if we had a really good well standardized assay that was, you know, reasonably priced or covered by insurers –

Dr. Pradhan:
Yeah.

Dr. Miller:
Then I could see doing it.

Dr. Pradhan:
I don't even know how to –

Dr. Underberg:
I've had patients bring it to me having had it done at a lab.

Dr. Pradhan:
Yeah.

Dr. Underberg:
Often it's with a host of other biomarkers that I have no interest in knowing about.

Dr. Pradhan:
Right.

Dr. Underberg:
But, you know, while the data was certainly informative, it was not used as the way to decide who got the drug. And that's what I try to tell people.

Dr. Pradhan:
Yeah, and you don't want to, I think, give the message that you have a nonresponder if they don't get their levels at high. So I do worry a little bit about the measured level. You know, the drug, yes, may have had some enhanced benefit at higher levels, but there is some benefit throughout the range. So I guess I would hesitate to use that level to identify a nonresponder to the drug, for instance.

One thing I had, if I can ask you guys, so I've been really curious - and Jamie, your talk really emphasized the importance of plaque delipidation potentially from EVAPORATE. How important - so we've talked about inflammation, endothelial dysfunction, these other things, but you've got now a measure where the plaque actually regresses, right? You can see that in that study. And I think I'm getting a lot of feedback. So I don't know what to do about that. What do you think about that as being the dominant, maybe the predominant mechanism of benefit? Do we just have that study or anything else that could be?

Dr. Underberg:
So I've always felt that while markers of plaque regression or delayed progression seem to correlate with interventions that reduce risk. I still believe that it's probably plaque stabilization that has the beneficial effect on the outcomes we see. And, you know, I try not to put too much weight in changing plaque size, because there are so many aspects of the stability of that plaque that I think probably are more likely to predict events. And we know that if you look at studies, albeit with statins, that in folks who just simply don't progress, they seem to do as well as those who regress. And so I think it's more confirming than guiding from my perspective, but I'm curious what you think.

Dr. Miller:
No, I think that that's reasonable. Because we don't - I don't think we have the - certainly the wealth of data for this. I mean, we have the CHERRY study too that was similar along those lines, but we don't have the kind of data that we have in the clinical outcome studies. And so I use CHERRY and EVAPORATE as guiding, or clinical outcome studies more so.

Dr. Pradhan:
Okay. Alright.

Dr. Miller:
So, but it's reasonable. It's a reasonable mechanism.

Dr. Pradhan:
So let me push you a little bit, though, because it takes about 1.5 to 2 years to get a benefit, right? So you know, you need to use this drug lifelong. We're saying sort of a lifelong therapy. And so that benefit emerges, may correlate with the time it takes to deal with the

plaque, right? You've got the early benefit from, you know, from stabilization of the plaque and maybe less plaque rupture, but the benefit you see 3, 4, or 5 years into the trial may actually be due to regression, more than the immediate effects on membrane stability. That's how - I mean, maybe I'm going beyond. I like poring over numbers. I like poring over clinical trial datasets. So I'm maybe going beyond the reach of what the data and the curves show us. But that's been on my mind since I've seen these results.

Dr. Underberg:
Yeah, but I think vascular function, as Jamie also talked about, effects on the endothelial appear pretty early. And well below - well before a year and a half. So I think that those are probably going to interplay as well.

Dr. Pradhan:
As well, yeah.

Dr. Miller:
And maybe even higher prioritization in terms of the big picture.

Dr. Underberg:
The other way to look at this is that the anatomical changes that you measure may be just a simple marker of plaque stabilization. And that's how long it takes to get to the point where you've actually changed the quality of the type of plaque. And that seems to correlate with what we know about the landmark effect in these trials that the initial benefit is not as great as the 1-year or 1.5-years on. And maybe that's because you've now done something to the plaque that has more of a permanent effect long-term.

Dr. Pradhan:
Yeah.

Dr. Underberg:
Potentially.

Dr. Miller:
Well, right. And we do know that in a number of studies that have shown benefit. You have the so-called legacy effect.

Dr. Pradhan:
Yeah.

Dr. Miller:
That even after patients have stopped the medication, the benefit still appears to have been there for a period of time.

HOST:
We have another question. Could you comment on triglycerides as a marker of high risk?

Dr. Miller:
Yes.

Dr. Underberg:
Yes.

Dr. Pradhan:
Unanimous yes.

Dr. Miller:
Right. So I think it's fair to say when we think about triglycerides, but you know, how they enter into this to the overall scheme of atherosclerosis, because triglycerides are really a source of energy in mammalian cells. So mammalian cells will deposit that or use it – muscle-based energy derived sources and activities. But triglycerides in of themselves don't appear to be atherogenic. However, free fatty acids may be arrhythmogenic. So if you're breaking down lots of free fatty acids, they – you know, if have a lot of circulating fatty acids that may trigger an arrhythmogenic event.

And at least that's been postulated to why some people experience sudden cardiac death, like James Gandolfini. If – as just one example, the night that he died, he had eaten - he was in Italy, and he had this incredible meal, super fat meal. I mean, I think he probably consumed about 8,000 calories. So and a lot of it was fat.

And you kind of wonder whether driving that process early on – that's one of the things that I ask my patients who've had a cardiac event is what did they eat that the - preceding the event, because I think that can give you some insight into what might have triggered it. Because we know there are triggers.

Dr. Pradhan:
Right.

Dr. Miller:
You know, there are a bunch of triggers. So from the standpoint of triglycerides, even though triglycerides per se, do not enter into the atherosclerotic plaque as cholesterol, when triglyceride-rich lipoproteins are hydrolyze, free fatty acids go out, they go into fat or muscle, and the byproduct of course, is a cholesterol-enriched remnant particle. And those cholesterol-enriched remnants are atherogenic. But a high triglyceride serves as a marker of having more of these circulating remnants, which can be taken up by macrophages in an unregulated manner. So the difference between - if you think about remnants versus LDL, LDL needs to be modified to some degree, remnants do not, to be taken up by macrophages in this unregulated fashion.

Dr. Underberg:
You know, it also seems to me that if I think about the recent iteration of our guidelines, which is now a couple of years old, and you really did a wonderful job kind of going through those, in my mind, two of the major paradigm shifts that occurred from that document was, one, the idea of thresholds for intervention, which focuses on absolute change in LDL as opposed to passing a magical number or goal. But the other is the identification of elevated triglycerides as a risk factor, independent of whatever else is going on. And if you recall, we used to say that if you had lowered non-HDL or apoB, and the triglycerides were still moderately elevated, but not severely elevated, there was nothing more to do.

Dr. Pradhan:
Ignore them. Right. Yeah.

Dr. Underberg:
Now maybe that was because there wasn't any more to do, but now we do have an intervention, and we've understood the risk now associated with moderate hypertriglyceridemia even in the setting of low LDL, apoB, and non-HDL cholesterol. I mean, you saw that data from FOURIER. And so that, to me is huge. I mean, just that triglyceride staring out there. You know as well as I do, people still ignore that. Like if the LDL was okay, they say, 'Oh, the triglycerides are 200, no big deal.' And it is. So that that to me, is this is one of the helpful components of the guidelines.

Dr. Miller:
Right, you could think of it you know, if you think about, as was already amply stated, if you think it's somebody who has again as a biomarker of risk, a high

triglyceride means that person has some degree of endothelial dysfunction, has some degree of dysregulation in lipid metabolism and, some degree of clotting that may be potentiated. So for all those reasons, a high triglyceride tells you that they're - you're a - it's a great biomarker of enhanced risk.

Dr. Pradhan:
Yeah, I think the nuance behind that question may have been: Is it a marker or maker? And I think you guys answered that nicely. You know, right now it seems the weight of evidence is that it's a marker and it doesn't really - wow, I apologize. Are you guys hearing this? Or is it just – yeah.

Dr. Miller:
Well, I would say it's directly a marker, indirectly a maker.

Dr. Pradhan:
Okay.

Dr. Miller:
Because of the downstream effects.

Dr. Pradhan:
Yes. Okay. Alright.

Dr. Miller:
Alright, with that I think we're going to move on. And the next order of business is, and I'll man this here, is clinical approaches to personalizing medical management of ASCVD risk factors. So we're going to do a case discussion. And I believe this patient was –

Dr. Pradhan:
I can walk through this. Yeah.

Dr. Miller:
You want to walk through this?

Dr. Pradhan:
Sure. Okay. Alright, just to keep you on your toes, we're going back to that patient that I introduced earlier this morning. This is a patient with, you know, polyvascular disease, peripheral artery disease, coronary disease, lots of risk factors. And when we calculate his risk score using the TIMI score – TIMI secondary prevention score, we get about a 5% per year annual risk of cardiovascular disease.

So let's go to what we do next. So his - and this is a 3-point major adverse cardiovascular event, those hard endpoints is about 5% or so. And then this is his lipid profile. So his pretreatment triglyceride values before - so naive – drug naive 260 for total cholesterol, 170 for an LDL. Just imagine this patient having all this disease and not being treated, but this is where we start. I's really just to illustrate the progressive risk reduction you get with adding therapies. Triglycerides are 280, his HDL is 34, and his non-HDL is 226.

So I think, should I walk through this and just keep going?

Dr. Miller:
Sure.

Dr. Pradhan:
Okay. So I think you saw this from Dr. Cheeley's talk that every 40 milligram per deciliter reduction in LDL, irrespective of the drug type, at least the ones that we have so far in our armamentarium is associated with a 25% reduction in hard cardiovascular events. And you see that on the left from this meta-analysis of 25 statin trials, so you look right in the middle, and go across to the right-hand side where it says relative risk reduction, you get a 25% risk reduction for about a 40-milligram per deciliter difference in LDL.

And then on the right are the non-statin trials is well. It sort of replicates the same thing, whether you use ezetimibe, bile acids sequestrants, etc., etc., back calculate from the curve, and you still get that 25% risk reduction for 40 milligram per deciliter LDL reduction, but it's just a smaller increment in change that you get with these less potent agents. So that's why they're sort of second line on top of a statin.

Dr. Cheeley also mentioned that we've got different intensities of statins. She very nicely covered that. You know, for our higher risk patient, we're going to use a higher intensity statin, and less risk, we might use a less intensity - lower intensity statin. And that's important, because there are some risks that we haven't talked about with statin therapy that have been highly publicized. And certainly, your patients may also pick up on this. And that is - one of them is the risk of new onset diabetes. And it turns out that the risk of diabetes seems to correlate with the exposure to statin. So both the duration of how long - the longer you take it, the intensity as well as the dose, at least in observational data. And when we conducted the JUPITER trial, which is a trial of rosuvastatin, we found it heightened risk in that study with high-intensity rosuvastatin which is about 30% increase over the placebo in that group.

But the patients that went on to get diabetes, important to note, were patients who had - were obese, had hypertension, had insulin resistance, had all the things that you would imagine might predict diabetes anyway.

So again, it's all about risk benefit. You know, are they likely to get more of a benefit from the statin than, you know, an offset by the new onset diabetes. And again, talk to your patients about this.

So with this patient, we do put them on a high-intensity statin. There's no question, right? They've got polyvascular disease, you start them on statin, you get about a 50% reduction with high-intensity statin which translates into in the blue you see, going from 2 - from 170 to 85 milligram per deciliter of their LDL. That converts, if you again, look at the 40 milligram per deciliter and get your 25% risk reduction, this conversion allows you to estimate that you've taken down their MACE risk by 40%. And you'll see that the annual risk of cardiovascular disease goes from 5% to 3%. That's the 40% reduction with the high-intensity statin.

Okay, and you've also gotten some reduction in their triglycerides. So their pretreatment level was 280. And their triglyceride level has gone down by 7 to 30%, because we know all statins have some benefit in terms of triglyceride lowering as well.

So the question becomes, do we need more LDL lowering? What do you think? What do you guys think? Obvious, right? Yeah.

Dr. Miller:
I would say yes. Just getting started.

Dr. Pradhan:
Yeah, so their LDL is 85. Right? You know, really high-risk patients, one of those super high guys that we want to get down to at least less than 70. I went back one.

Step 2, so we've done the statin, now the next thing is going to be ezetimibe, right? So we add ezetimibe, that risk goes from 3% down to 2.8%, it's not much on the relative risks. You've added a new drug that they're now obligated to take. You have gotten their LDL down to 72. There's a reduction overall 43% from that initial spot you started them on. So not a huge benefit, but your numbers look better. You're at 72, you've added a new drug and you've gotten a little bit of a TG reduction as well. You've gone from 238 using a high-intensity statin alone down to 214 for the posttreatment value.

Okay, so then the question is, do we need more LDL lowering. The - right on the corner 72, 2.8% annual risk of MACE, cumulative risk over 10 years, you know, still way up there. So yeah, we go with more LDL lowering. So you add a PCSK9 inhibitor. With that, you take their 72 milligram per deciliter LDL down to 29. You've gotten a big, big change in their LDL. But what look at that 3-point MACE rate. You went from 2.8% annual risk of MACE, down to 2.3%. So there's still pretty high risk, you've really driven their LDL down and you've gotten a little bit of triglyceride reduction as well. So their triglycerides are at 184. So you might be happy with this. You've at least addressed their LDL, but you're leaving triglycerides back on the table. So you have to think about other choices.

And the other choice here really is off of this playbook. The current playbook is what's shown here, or at least before - the pre-reducing playbook was to start the statin, check their LDL, and then I'd remeasure it 1 to 3 months after you've initiated the statin, add ezetimibe if they're not at 70 for this high-risk patient. And if they're still not at 70, less than 70, go ahead and add a PCSK9 inhibitor. That sort of was what we were thinking in the past.

But now with REDUCE-IT, we actually have an option to treat specifically based on residual hypertriglyceridemia. And we've shown you a lot of data related to that. Let's see what happens in this patient if instead of adding PCSK9 inhibition, we just add icosapent ethyl. So their LDL really doesn't change much. This is stays at 72 or so. In this patient, we add icosapent ethyl, we take their triglycerides down by about 20% from 214 to 176. And you've actually reduced their MACE, if you do all the calculations, to 2.3%. So fairly good, you know, slightly better if not better than adding a PCSK9 inhibitor on this patient in terms of what their projected risk would be. So we - I think we'd all agree that this is sort of the calculus that you might want to do in this type of patient.

And that lipid profile, you know, yes, their LDL cholesterol is not way less than 50, but they've - the risk projected risk is just as good as if you added it PCSK9 inhibitor. That's with the addition of EPA.

Alright, so really the bifurcation in my mind is this difference between, you know, we have that near-goal patient, you've got in at least in this case scenario, near-goal patient, you've got residual high triglycerides, and you're deciding between PCSK9 inhibitor and icosapent ethyl.

Now, I'm not going to read through the rest of this, I want to give you guys a chance to go through some more cases. But this does illustrate some of the other features that you need to stay on this agent for a long period of time. We're talking about the treatment divergence occurring at around 1.5 to 2 years. So once you initiate therapy, encourage your patients to continue to get that benefit. Alright, I'm going to pass on the baton to you.

Dr. Miller:
Sure.

Dr. Pradhan:
Anything else?

Dr. Miller:
Yeah, I mean, I would just say that, as you pointed out, that ACC consensus statement, I was on the writing committee for that, we did move from an LDL centric to a triglyceride centric, once you got the LDL down under good control. So if you saw, obviously, the whole point is you're going to start with a statin, ezetimibe, PCSK9, but now once your LDL level goes down, and let's say below 70, and the triglycerides are still elevated, then it's clearly that it would be very reasonable to then consider icosapent ethyl in - as part of that algorithm.

Dr. Pradhan:
Yeah.

Dr. Miller:
So the nice thing about the consensus panel is it takes the best information from 2018 and then adds, with that, just that just little tweak there.

Dr. Pradhan:
Yeah.

Dr. Miller:
For those individuals.

Dr. Underberg:
The fascinating thing about this case, is trying to intersperse a risk-reducing agent into a lipid algorithm. Right? And, you know, in my mind, I think about the addition of EPA in this setting, similar to well, what if the patient were hypertensive, and you wanted to add an additional blood pressure lowering agent as opposed to a PCSK9 inhibitor? What would the added benefit be? And in particular, I wonder whether if you waited until you were on a PCSK9 inhibitor, and your LDL was 26, what the incremental benefit would be of then adding icosapent ethyl? Because we don't know.

Dr. Pradhan:
Yeah, you're right.

Dr. Underberg:
Because we haven't studied a population of patients treated, but we do know those patients who are at still high residual risk –

Dr. Pradhan:
Right.

Dr. Underberg:
Based on the data from FOURIER. So I'm almost concerned that doing one versus the other avoids the potential benefit of the additional intervention. And so I try to think of it almost as a different category, or a different corridor, you know, like the aspirin corridor, or the risk reducing corridor.

But it's a fascinating kind of demonstration of the fact that we have a host of risk-reducing agents now, including the diabetes medications, and colchicine in some setting, right? And so we've got this rather large kind of armamentarium now to choose from, and we don't have a lot of data on bundling them all together, right?

Dr. Pradhan:
Right.

Dr. Underberg:
And that's where I think the art of medicine comes in, right? I've never met a patient who didn't want to be put on fish oil. And I say fish oil, because I mean it generically. But people love this drug.

Dr. Pradhan:
Yeah.

Dr. Underberg:
They asked to be on it. There's nothing else I give people that people ask to be on. And so I think there's a real benefit there. Because if people want to take something, they're more likely to take it.

Dr. Pradhan:
Right.

Dr. Underberg:
That's just my thought, anyway.

Dr. Miller:
You know, the only other issue I wanted to mention was the issue of statins-induced diabetes. Because that comes up a lot. A lot of patients believe that statins cause diabetes and there have been books written about, you know, all the bad things about statins. But it did turns out that and – that you really very well, nicely pointed out, that statins don't take somebody who has no more fasting glucose and cause them to be diabetic. It's not like steroids in somebody who's placed on high-dose steroids that might happen to, or even niacin, for that matter that could do it. But what statins do is it just, on average, raises glucose somewhere between 2 to 5 milligrams per deciliter. So if you're in that camp, where you're already prediabetic and you have a fasting glucose of, let's say, 122 and have other things that statins could definitely put you over the edge for the biochemical diagnosis. The biochemical diagnosis, not necessarily the path of physiologic diagnosis.

Dr. Pradhan:
Right.

Dr. Miller:
So I try, when a patient comes up to me, you know, and says to me, you know, 'What about dia - I don't want to take a statin because it causes diabetes.' I'll try to go through that.

Dr. Pradhan:
Yeah, deconstruct that. Yeah.

Dr. Underberg:
I tell people they're going to become diabetic 6 weeks sooner, over the course of their lifetime, if they were going to become diabetic.

Dr. Pradhan
That's what the data shows, right?

Dr. Miller:
Yeah. They say, 'Oh, well forget about it.'

Dr. Pradhan:
True.

Dr. Miller:
So let's go to Miss P. She's 61 years old 2:55:02 and fairly well 9 months ago, smoker for 30 years hypertension, ARB minimal exercise, blood pressure 126/78, BMI 31, A1c 6.3 at the time of her MI. She wasn't on a statin. LDL 144, HDL 39, TG 167. She was started on atorvastatin, stopped due to severe bilateral thigh pain after 1 month. Subsequently tried and failed 2:55:30 rosuvastatin once a day and once a week, prava 40 milligrams every other day. So she's you know, falls into that camp of having some statin-associated muscle symptoms or SAMS. She's counseled on a heart healthy diet and exercise program and started a smoking cessation program. So she's doing all the right things from that vantage point. Able to tolerate ezetimibe at 10 milligrams per DL. Repeat LDL on ezetimibe is 10 milligrams was 120, started on evolocumab 140, she lost 8 pounds, stopped smoking. Wow, model patient. Walking 5 times a week. Doesn't tell you how much she's walking. Repeat labs, her LDL was 73, HDL 43, triglyceride 151, and a total cholesterol of 146. What – this is almost akin to what you just went through that exercise here?

Dr. Pradhan:
I – yeah.

Dr. Miller:
So what would be your next step? What would you do here? Would you obviously want to continue her lifestyle changes? And I mean, she's done pretty good therapy. LDL is close to that 70 marker. She's not in Europe, so we don't have to drive her down to 55.

Dr. Underberg:
You know, this is a good, I think demonstration of what does the evidence tells us, right? So there are other LDL-lowering agents out there you could give her if you felt that she was, you know, above her threshold for intervention of 70 milligrams per deciliter. You could give her bempedoic acid, you could combine it with ezetimibe, and give her fixed-dose combination to minimize her pill burden. But you don't yet have any data telling you that that intervention will improve her cardiovascular risk.

Dr. Miller:
Well, let's ask the audience because we have a few hundred people out here. By show of hands, how many would say bempedoic acid? We don't have any takers.

Dr. Underberg:
Okay, so where do we have data? We have data with adding icosapent ethyl, right? And her triglycerides are still elevated. She certainly meets the criteria. The only issue is that, as we discussed a little earlier, she's not on a statin. But I don't think that would stop me based on that information from adding a drug that I think probably has a better safety profile, with at least more concrete outcome data, and probably more likely to be adherent. That's just my thought. But I suspect there are even other things that one might consider doing here.

Dr. Miller:
Yeah, I mean, she would fall, I mean, with the exception of that you can't take a statin, she would have otherwise fallen into the REDUCE-IT criteria.

Dr. Underberg:
Right.

Dr. Miller:
You know, 150 is the approval, but patients got in with levels as low as 135 because of the 10% differential. So yeah, I mean, I think it would be a reasonable consideration.

Dr. Pradhan:
Yeah, I think I'd email one of you guys, and ask. I mean, this is when you ask for some additional help. If you're in the primary care setting, and you're not really sure you've gone down the algorithms, you got a patient that doesn't really quite fit, and there's some emerging other potential agents that could be used to treat the number, I'd do exactly. I mean, I'd call these guys and ask, you know, what would you suggest?

Dr. Underberg:
I also suggest is the perfect time to have that shared risk decision discussion, right, with the patient? You know, these are the options. These are the risks and the benefits of the drug. We don't know what her uric acid level is, if she has a history of gout, that might affect your ability to use bempedoic acid. But all of that

Dr. Miller:
And Niacin. I would not use niacin if she had gout.

Dr. Underberg:
Yeah.

Dr. Miller:
So that's a joke. We don't use niacin.

Dr. Underberg:
But when I come to these decision points, I find that if the patient buys into the decision, they're more likely to continue with it. And when I'm not 100% sure, that's when I lay it out. And I say, 'Look, these are our options. This is what I think. What do you think?' And you know, and then we come to a decision together and they're more likely, I think, to move forward with it and follow up so.

Dr. Miller:
And patients always appreciate when you kind of involve them in the decision-making process.

Dr. Underberg:
Yeah. And I always remind our trainees that shared decision-making doesn't mean the patient makes the decision without information.

Dr. Pradhan:
Right.

Dr. Underberg:
They still want to know what you think. That's why they're there. But they want to know that within the context of how it's going to impact them, and their lifestyle and what they're likely to do or not that.

Dr. Miller:
Okay, great. I think that that answers that question.

Let's meet Katherine. She's another 61-year-old woman with a history of CABG in in 2003, so she's now almost 20 years out. It was pretty good dyslipidemia, hypertension. I wonder if she had a LIMA and a RIMA. Dyslipidemia, hypertension, type 2 diabetes, and obesity presented in 14 with an abnormal CT angio. More recent left superficial femoral artery angioplasty, stent placement, good pedal pulse. She's here for the results of a nuclear stress test. She was experienced in recurring angina with exertion. So again, she had the bypass in 03 now, she's 15 years later, common for us, especially if they've had vein grafts. A whole bunch of medications here for blood pressure, for cholesterol, for diabetes. Her labs show a cholesterol of 184, HDL 50, LDL 82, triglyceride to 27, high LP little a 118. And this is a milligrams per deciliter, which is really quite high, right? Because the other way to measure it is nanomoles per liter, which would be 75, would be the cut point. But for milligrams per deciliter, anything above 30 is pretty high. BP 134/77, heart rate 86, and BMI is 37. What would be the next step to consider and Katherine's lipid management? A, stop. She's at goal. colesevelam 625 six times a day, evolocumab 140, aspirin 8? Please vote. We got about.

Dr. Underberg:
What were her triglycerides again?

Dr. Miller:
Her triglycerides. Let's go back.

Dr. Underberg:
I don't think we can.

Dr. Miller:
We can't go back. Her triglycerides were –

Dr. Underberg:
Were they about 200?

Dr. Pradhan:
I think they were. I was struck by them.

Dr. Miller:
Yeah, 220. Okay, 227. Okay, so they were a bit high. So we can go forward again.

And okay, so we have evolocumab and colesevelam. So colesevelam, which you know, is a bile acid resin, might in fact raise your triglycerides a bit more. So that would be my concern here.

We properly document that she's taken rosuva and ezetimibe, and evolocumab was added every 14 days. Let's see what happens. Katherine's angina is improving, but we are still concerned about her triglyceride levels. What happened to that nuclear test result? Just a slight little thing.

Dr. Underberg:
Must have been abnormal.

Dr. Miller:
We just treat the numbers we don't care about – yeah, no don't worry about that.

Based on Catherine's current lipid profile and very high risk, what would be the appropriate next step to manage your mixed dyslipidemia? What about the appropriate next step for managing a coronary disease? Start feno, icosapent ethyl, omega-3 ethyl esters, over-the-counter fish oil?

Dr. Underberg:
There’s no such thing as over-the-counter fish oil.

Dr. Miller:
That's right, that’s misnomer because over the counter is - means that it's regulated by the FDA. So these are all dietary supplements, not OTC.

Well, so we got, I mean, I would certainly want to see what's going on with her nuclear scan. And she might need some intervention. It's been 15 years. She probably needs that. But on top of that, when we come to here, I think this is reasonable.

Dr. Pradhan:
Yeah.

Dr. Miller:
Anybody disagree? So now she had an excellent response to the addition of - and now her angina is completely gone, amazingly enough. She's on these meds and these are her labs. Cholesterol 125, HDL 52, LDL 51, trigs 112, LP little a even went down 85. And that went down because of – why did her LP little a come – go down?

Dr. Underberg:
I’m going to guess she’s on the evolocumab.

Dr. Miller:
Yeah, but it's not listed on her medication list.

Dr. Underberg:
Yeah, because her LDL is now 51, so she has to be on it.

Dr. Miller:
She has to be on that, so that’s a misnomer. And things are looking better. She - her BMI is still a little bit on the high side. Okay, any comments from any additional thoughts about that case?

Dr. Underberg:
So, again, this is an example of kind of how far we can go, right? I mean, if you look, she was also on semaglutide. Right? So a diabetes drug has been shown to reduce the risk of cardiovascular events. She's on three LDL-lowering agents, all with evidence-based data. And now on icosapent ethyl on top of it. I was curious to the two cardiologists, there was the question about the aspirin.

Dr. Miller:
It wasn't showing aspirin?

Dr. Underberg:
Yeah. And should she be on aspirin?

Dr. Miller:
She has coronary disease.

Dr. Underberg:
Yeah. So she should, right?

Dr. Pradhan:
She's on clopidogrel, as well, right?

Dr. Underberg:
Was there a benefit to being on both?

Dr. Pradhan:
____ 3:05:52 platelet in this high-risk patient with – she had PAD, as well. Yeah.

Dr. Miller:
PAD, and I plus she's having anginal symptoms.

Dr. Underberg:
Yeah.

Dr. Miller:
So in all likelihood, she's going to be brought back to the cath lab and whether or not they open up one of her stents, presumably the saphenous. But - or needs a redo, I don't know. But I think she would benefit from aspirin.

Dr. Underberg:
But it's, I mean, just think, you know, 4 years ago, we wouldn't have been able to do a lot of this or wouldn't have had the evidence to do it.

Dr. Pradhan:
Yeah.

Dr. Underberg:
So she's really, you know, benefiting from, I think, an exciting time in cardiovascular risk management. I wouldn't call it lipid management, but risk management.

Dr. Miller:
Right. I mean, and so in closing, we're coming to the end of this superb session. So I wanted to thank Drs. Underberg, Dr. Pradhan, and Dr. Cheeley, did a really phenomenal job here. And I think you really expressed it well, both of you, that we've had pretty significant progress over the last 4 years, despite COVID.

There are - we've added to our armamentarium, we've added to risk reduction with proven therapies, and we've established that LDL lowering in and of itself is beneficial, so we're not going to throw the baby out with the bathwater. But on the other hand, there's more to the story than just LDL. And we have great therapies now available for not only the hypertriglyceridemic patient, as we talked about, but also for treating some of the other risks associated with these patients with established disease or with risk factors.

So with that, I think the story will continue. I'm looking forward to working and seeing you all again in the near future and with my colleagues to make more advances in this field. Thank you very much.

Dr. Pradhan:
Thank you.

Dr. Underberg:
Thanks.

Dr. Cheeley:
Thank you.